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Review

Lipocalin 2 as a link between ageing, risk factor conditions and age-related brain diseases

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ABSTRACT

Chronic (neuro)inflammation plays an important role in many age-related central nervous system (CNS) diseases, including Alzheimer's disease, Parkinson's disease and vascular dementia. Inflammation also characterizes many conditions that form a risk factor for these CNS disorders, such as physical inactivity, obesity and cardiovascular disease. Lipocalin 2 (Lcn2) is an inflammatory protein shown to be involved in different age-related CNS diseases, as well as risk factor conditions thereof. Lcn2 expression is increased in the periphery and the brain in different age-related CNS diseases and also their risk factor conditions. Experimental studies indicate that Lcn2 contributes to various neuropathophysiological processes of age-related CNS diseases, including exacerbated neuroinflammation, cell death and iron dysregulation, which may negatively impact cognitive function. We hypothesize that increased Lcn2 levels as a result of age-related risk factor conditions may sensitize the brain and increase the risk to develop age-related CNS diseases. In this review we first provide a comprehensive overview of the known functions of Lcn2, and its effects in the CNS. Subsequently, this review explores Lcn2 as a potential (neuro)inflammatory link between different risk factor conditions and the development of age-related CNS disorders. Altogether, evidence convincingly indicates Lcn2 as a key constituent in ageing and age-related brain diseases.

1. Introduction

With ageing comes an increased risk to develop age-related brain diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD) and vascular dementia (VaD). Although it is evident that ageing is the major risk factor for these central nervous system (CNS) conditions, the causal mechanisms behind these conditions remain incompletely understood. However, it is becoming increasingly clear that chronic neuroinflammatory processes play an important role in the pathogenesis of age-related CNS diseases (Akiyama et al., 2000; Heneka et al., 2015; Iadecola, 2013; Wang et al., 2015b).

Neuroinflammation is mediated by different cell types that reside in the brain, including microglia and astrocytes (Heneka et al., 2015) as well as certain infiltrating immune cells from the periphery (Kanashiro et al., 2020; Mammana et al., 2018). While neuroinflammatory processes can have essential neuroprotective functions, chronically elevated neuroinflammation can exert adverse effects on the functioning of brain. For example, activated microglia and astrocytes exert multiple protective functions, including the clearance of pathogens, cellular debris and harmful protein aggregates (Eikelenboom et al., 2006; Heneka et al., 2015). However, when chronically activated, microglia and astrocytes may lose some of their physiological functions. Instead, chronically activated microglia and astrocytes can provoke brain damage by persistently secreting pro-inflammatory cytokines, thereby sensitizing neurons to cell death and promoting formation of toxic protein aggregates (Frank-Cannon et al., 2009; Glass et al., 2010; He et al., 2007; Heneka et al., 2015, 2014; Meraz-Ríos et al., 2013; Venegas et al., 2017). Chronic neuroinflammation characterizes many

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age-related CNS diseases, and is fundamental in the development and progression of these pathologies (Heneka et al., 2014). Identification of inflammatory constituents and their associated mechanisms that are involved in chronic neuroinflammation is essential to improve our understanding of the pathology of age-related brain diseases, and ultimately to provide new therapeutic targets.

It is widely accepted that neuroinflammatory processes are already involved during the earliest stages of age-related brain diseases (Kwon and Koh, 2020; Watermeyer et al., 2018). Notably, ageing itself is accompanied by the gradual development of a chronic low-grade inflammatory state (termed inflammageing) (Cribbs et al., 2012; Franceschi and Campisi, 2014). Moreover, (neuro)inflammation is known to occur and to play a role in the aberrant physiological processes of several risk factor conditions (such as obesity and cardiovascular disease) for age-related brain diseases (Heneka et al., 2015). Therefore, inflammatory processes in the periphery and CNS may be a link between ageing, risk factor conditions, and development of age-related CNS diseases.

Lipocalin 2 (Lcn2) is an age-associated (neuro)inflammatory factor that appears to be involved in numerous age-related CNS disorders and their risk factor conditions. Systemic and CNS expression of Lcn2 was found to increase with age. The expression of Lcn2 is further increased in several age-related CNS diseases, as well as in different conditions that are risk factors for these age-related CNS disorders. Evidence suggests that Lcn2 can contribute to the pathophysiology of these risk factor conditions and age-related brain diseases, by affecting several (neuro) biological mechanisms such as inflammation, cell death/cell survival signaling, and iron metabolism (Ferreira et al., 2015; Jha et al., 2015) (also see Fig. 1). Hence, we hypothesize that chronically increased Lcn2 levels as a result of arising risk factor conditions (such as age-related chronic diseases and unhealthy lifestyles) primes and sensitizes the brain, rendering the brain more vulnerable to develop different age-related brain diseases.

In this review, we will discuss Lcn2 as a (neuro)inflammatory component linking ageing, risk factor conditions and the development of age-related brain diseases, including: AD, PD and VaD. Of note, Lcn2 is also known as neutrophil gelatinase-associated lipocalin (NGAL), 24p3, siderocalin, uterocalin, 24 kDa superinducible protein (SIP24), and neu-related lipocalin, and is generally referred to as Lcn2 or 24p3 in mice, and as NGAL in humans. For consistency, Lcn2 will be used as further reference throughout this review.

2. Biochemical characteristics and functions of Lcn2

2.1. Biochemical characteristics and binding partners of Lcn2

Lcn2 is a 25 kDa member of the lipocalin protein family, which comprises a group of more than 20 small secretory proteins that are involved in transport of hydrophobic ligands. Members of the lipocalin family are notably heterogeneous regarding amino acid sequence, with a sequence homology that can be lower than 20 % (Du et al., 2015; Flower, 1996; Flower et al., 2000). However, all lipocalins share one to three characteristic conserved sequence motifs, and present a comparable structural hallmark named the lipocalin fold. The lipocalin fold is formed by a single eight-stranded antiparallel β-sheet which closes on itself by hydrogen bonds to form a β-barrel (Flower, 1994). The internal cavity of this cup-shaped β-barrel, together with an external loop scaffold, presents the site where ligands can bind. The specific composition of this ligand-binding site varies between different lipocalin members, explaining the variation in ligands that different lipocalins can bind to and carry (Flower, 2000b, a; Flower, 1996; Flower et al., 2000). Lcn2 contains a shallower, broader and more polar binding cavity in comparison to other lipocalins, large enough to allow Lcn2 to bind small hydrophobic molecules as well as certain bigger soluble macromolecules (Bao et al., 2015b; Goetz et al., 2000, 2002).

2.1.1. Ligands of Lcn2

Different ligands have been identified for Lcn2 (also summarized in Table 1). As was anticipated for a lipocalin family member, different small hydrophobic ligands were reported to be bound by Lcn2. For example, Lcn2 was reported to bind to the hydrophobic molecules; cholesteryl oleate, retinol, linoleic acid, platelet-activating factor, leukotriene B4 and the chemotactic peptide N-formyl-Met-Leu-Phe (fMLP) (Bao et al., 2015b; Bratt et al., 1999; Chu et al., 1998; Song et al., 2014). Other mediators of inflammation have been proposed as potential ligands of Lcn2 as well, including lipopolysaccharide (LPS) (Goetz et al., 2000; Nielsen et al., 1996).

It was discovered by Goetz and colleagues in 2002 that Lcn2 can (indirectly) bind iron, by binding to the bacterial siderophore enterobactin (Bao et al., 2015b; Goetz et al., 2002). Siderophores can be secreted by several microbial species (including different bacteria and fungi) and are able to scavenge ferric iron (Fe^{3+}). Iron-bound siderophores transport iron into the pathogen, providing the pathogen with iron, which is essential for growth and survival of many microbes. The

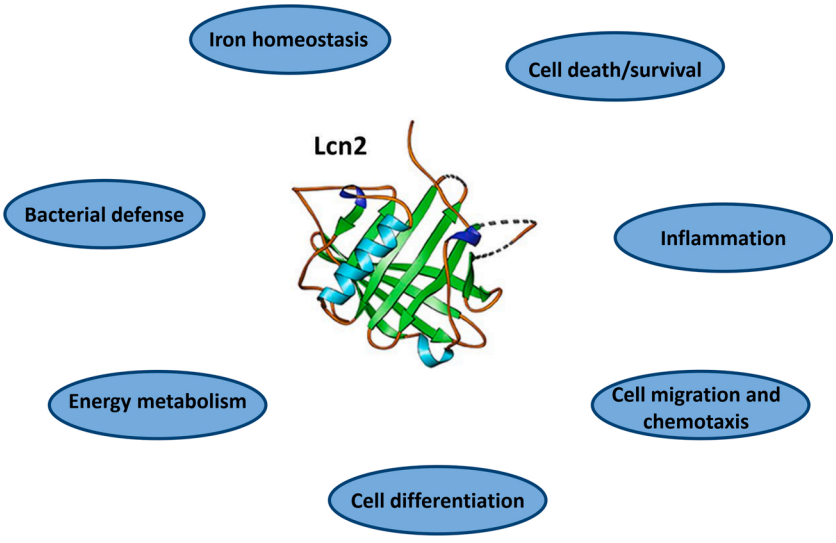

Fig. 1. The various roles of Lcn2. Lcn2 is involved in different processes, ranging from bacterial defense and iron regulation to inflammation and regulation of cell death/cell survival mechanisms. The illustration of the protein structure of human Lcn2 was adjusted from Fig. 1 by Asimakopoulou et al., 2016, with permission from the authors (Asimakopoulou et al., 2016).

Table 1
Ligands, other binding partners, receptors and post-translational modifications of Lcn2, and their effect on the functions/properties of Lcn2.

	Ligands, other binding partners, receptors and post-translational modifications of Lcn2	Effect on functions/properties of Lcn2	Ref.
Ligands/other binding partners	Bacterial siderophores (Fe^{3+}-free or Fe^{3+}-bound), such as enterobactin and carboxymycobactin	Equips Lcn2 with anti-bacterial effects.	(Bachman et al., 2012; Berger et al., 2006; Ferreira et al., 2015; Flo et al., 2004; Goetz et al., 2002; Guo et al., 2020; Holmes et al., 2005; Huang et al., 2020; Saiga et al., 2008; Wu et al., 2010)
	Mammalian siderophores (Fe^{3+}-free or Fe^{3+}-bound), including simple catechols, L-norepinephrine, 2,5-dihydroxybenzoic acid (2,5-DHBA) and certain green tea polyphenols	Allows Lcn2 to regulate mammalian iron homeostasis.	(Bao et al., 2010, 2015b, 2015a, 2013; Devireddy et al., 2010, 2005; Miethke and Skerra, 2010; Shields-Cutler et al., 2016, 2015; Yang et al., 2002; Zhang et al., 2018a,b,c)
	Small hydrophobic ligands, including cholesteryl oleate, retinol, linoleic acid, platelet-activating factor, leukotriene B4, N-formyl-Met-Leu-Phe (fMLP)	Lcn2 mediates transport of small hydrophobic ligands.	(Bao et al., 2015b; Bratt et al., 1999; Chu et al., 1998; Song et al., 2014)
	Lcn2 itself; forming homodimers and homotrimers	Dimeric Lcn2 is cleared less quickly from the body than monomeric Lcn2. Functional differences between the monomeric, homodimeric and homotrimeric state of Lcn2 are unknown.	(Axelsson et al., 1995; Cai et al., 2010; Haase-Fielitz et al., 2014; Kjeldsen et al., 1993; Li et al., 2019a,b; Mårtensson et al., 2012; Yan et al., 2001)
	Matrix metalloproteinase 9 (MMP-9)	Lcn2 may increase the stability and activity of human MMP-9. (Murine Lcn2 and MMP-9 do not bind.)	(Bouchet and Bauvois, 2014; Fernández et al., 2005; Kjeldsen et al., 1993; Kobara et al., 2013; Tschesche et al., 2001; Yabluchanskiy et al., 2013; Yan et al., 2001)
	Matrix metalloproteinase 2 (MMP-2)	Lcn2 may potentially increase the stability and activity of MMP-2.	(Catalán et al., 2009; Kiczak et al., 2013; Wu et al., 2014; Yang et al., 2012)
	Membrane phosphatidylethanolamine (PE)	Binding of Lcn2 to membrane PE on the sperm membrane resulted in stimulation of lipid raft movement and cholesterol efflux.	(Chu et al., 2000; Elangovan et al., 2004; Watanabe et al., 2014)
	Hepatocyte growth factor (HGF)	Lcn2 can bind to and partly inhibit the activity of HGF, and as such reduce HGF-stimulated cell branching in kidney tubular epithelial cells.	(Gwira et al., 2005)
	Dab2	Lcn2 can bind the endocytic adaptor protein Dab2, and may thereby modulate Dab2/integrin β1 signaling, promote neutrophil adhesion and transmigration into the retina.	(Ghosh et al., 2019)
	Epidermal growth factor receptor (EGFR)	Lcn2 binds to the intracellular domain of EGFR in late endosomal compartments. Lcn2 promotes cell surface localization and sustained activation of EGFR.	(Yammine et al., 2019)
	Neutrophil extracellular traps (NETs)	Lcn2 is a component of NETs and contributes to their antimicrobial properties.	(Li et al., 2018)
Receptors	24p3R (also known as SLC22A17, LCN2R, NGALR and brain type organic cation transporter (BOCT))	Lcn2 amongst others acts on iron homeostasis and cell death/survival, via 24p3R.	(Devireddy et al., 2005)
	Megalin (also known as Lrp2 and gp330)	Lcn2 may amongst others act on iron homeostasis, via megalin.	(Hvidberg et al., 2005)
	MC4R	Lcn2 acts on appetite, via MC4R.	(Mosialou et al., 2017)
	(MC1R, MC3R?)	Suggested receptors. Further confirmation and investigation is required.	(Mosialou et al., 2017)
Post-translational modifications	Phosphorylation	Phosphorylation of Lcn2 may affect its release from neutrophils.	(Lee et al., 2001; Weng et al., 2015)
	Amination	The amination state of Lcn2 affects the speed at which Lcn2 is cleared from the circulation.	(Song et al., 2014; Yang et al., 2017)
	Glycosylation	Different glycosylation patterns might affect the stability and solubility of Lcn2.	(Borkham-Kamphorst et al., 2018; Chu et al., 1996; Fujiwara et al., 2016; Lee et al., 2006; Miyamoto et al., 2011; Rudd et al., 1999)

Abbreviations: 2,5-DHBA; 2,5-dihydroxybenzoic acid, BOCT; brain type organic cation transporter, EGFR; epidermal growth factor receptor, fMLP; N-formyl-Met-Leu-Phe, HGF; hepatocyte growth factor, MC1R; melanocortin 1 receptor, MC3R; melanocortin 3 receptor, MC4R; melanocortin 4 receptor, MMP-2; matrix metalloproteinase 2, MMP-9; matrix metalloproteinase 9, NETs; neutrophil extracellular traps, PE; phosphatidylethanolamine.

work from Goetz et al. (2002) and Flo et al. (2004) provided the first evidence that Lcn2 aids in the defense against bacterial infections: Lcn2 binds to iron-loaded (and iron-free) bacterial siderophores, and as such interferes with siderophore-mediated bacterial iron acquisition (Flo et al., 2004; Goetz et al., 2002). It has become clear that Lcn2 is able to bind different types (e.g. catecholate-, carboxylate- and phenolate-type) of bacterial siderophores, thereby providing protection against bacteria that depend on these siderophore types, including for example *E. coli* and mycobacteria such as *M. tuberculosis* (Bachman et al., 2012; Berger et al., 2006; Ferreira et al., 2015; Flo et al., 2004; Goetz et al., 2002; Guo et al., 2020; Holmes et al., 2005; Huang et al., 2020; Saiga et al., 2008; Wu et al., 2010). Accordingly, Lcn2 is not able to interfere with the iron-thievery of microbes that use other types of siderophores (i.e. hydroxamate-type), or utilize siderophore-independent pathways to scavenge iron (Bachman et al., 2011; Bao et al., 2015b; Ferreira et al., 2014; Fischbach et al., 2006a, 2006b; Halaas et al., 2010; Liu et al., 2014b). In addition, bacteria may interfere with the antibacterial functions of Lcn2, for example by producing factors (such as cyclic diguanylate monophosphate (c-di-GMP)) that can strongly bind Lcn2, thereby competing with the binding between Lcn2 and bacterial siderophores (Li et al., 2015).

Importantly, it became clear that Lcn2 not only influences bacterial iron regulation, but may also play a role in physiological mammalian iron regulation (Devireddy et al., 2005; Yang et al., 2002). Indeed, mammalian siderophores were identified, enabling Lcn2 to bind to ferric iron under normal physiological conditions (Bao et al., 2015b).

Mammalian siderophores known so far include for example simple catechols (including catechol, 3-methylcatechol, 4-methylcatechol and pyrogallol), which are diet-derived metabolic products (Bao et al., 2010, 2015b, 2015a; Shields-Cutler et al., 2016, 2015). These simple catechols are abundantly present in e.g. the blood circulation and urine, and catechol-iron-Lcn2 complexes can for example be detected in human urine where they can influence Lcn2′s antimicrobial activity in the urinary tract (Bao et al., 2010; Shields-Cutler et al., 2016, 2015). In addition to these simple catechols, the neuroendocrine catecholamine L-norepinephrine and the iron-binding moiety 2,5-dihydroxybenzoic acid (2,5-DHBA) were both found to form a complex with iron and Lcn2 (Devireddy et al., 2010; Miethke and Skerra, 2010). By binding iron-loaded L-norepinephrine, Lcn2 could inhibit L-norepinephrine-mediated bacterial iron scavenging (Miethke and Skerra, 2010). Production of 2,5-DHBA (via synthesis by the enzyme 3-hydroxybutyrate dehydrogenase-2 (BDH2)) was shown to be required for normal iron metabolism (Liu et al., 2014b,a,c; Zhao et al., 2018). Finally, certain polyphenols present in green tea were reported to form a complex with Lcn2 and iron, representing another diet-derived type of Lcn2-binding siderophore in the body (Bao et al., 2013, 2015b; Zhang et al., 2018a).

Taken together, next to interfering with bacterial iron acquisition by sequestrating bacterial siderophores, Lcn2 may also play an important physiological role in mammalian iron homeostasis, via binding mammalian siderophores. Of interest, Lcn2 may also use siderophores to bind more exotic metal ions including radioactive plutonium and curium (Allred et al., 2015).

2.1.2. Other binding partners of Lcn2

Besides the small hydrophobic and siderophoric ligands described above, some additional binding partners of Lcn2 are known that may affect its biological functions (also see Table 1). Firstly, Lcn2 can covalently bind matrix metalloproteinase 9 (MMP-9), which is involved in extracellular matrix degradation and tissue remodeling (Bouchet and Bauvois, 2014; Kjeldsen et al., 1993; Yabluchanskiy et al., 2013; Yan et al., 2001). Lcn2 can protect MMP-9 against degradation, and as such may increase the stability and activity of MMP-9 (Fernández et al., 2005; Kobara et al., 2013; Tschesche et al., 2001; Yan et al., 2001). Of note, human Lcn2 has a cysteine residue at position 87 that allows a disulfide bond with MMP-9, whereas rodent Lcn2 is unable to form heterodimers with MMP-9 (Holmes et al., 2005). Secondly, Lcn2 was reported to bind to and possibly promote the stability and activity of matrix metalloproteinase 2 (MMP-2) (Catalán et al., 2009; Kiczak et al., 2013; Wu et al., 2014; Yang et al., 2012). Thirdly, it was reported that Lcn2 can bind to and partly inhibit the activity of hepatocyte growth factor (HGF), thereby reducing HGF-stimulated cell branching in kidney tubular epithelial cells (Gwira et al., 2005). Fourth, Lcn2 was found to attach to the sperm membrane by binding to membrane phosphatidylethanolamine (PE), which resulted in stimulation of lipid raft movement and cholesterol efflux (Chu et al., 2000; Elangovan et al., 2004; Watanabe et al., 2014). The mechanisms that underlie these Lcn2-mediated effects in the sperm membrane however are not clear yet (Watanabe et al., 2014). Fifth, Lcn2 was shown to interact with the endocytic adaptor protein Dab2 in neutrophils, which was even more pronounced in neutrophils that were activated with interferon-lambda (IFN-λ) (Ghosh et al., 2019). The interaction between Lcn2 and Dab2 – allowing Lcn2 to affect the Dab2/integrin β1 signaling axis – may be an important new mechanism via which Lcn2 promotes neutrophil adhesion and neutrophil transmigration into the retina, thereby contributing to retinal degeneration (Ghosh et al., 2019). Sixth, recent evidence indicated that Lcn2 binds to the intracellular domain of epidermal growth factor receptor (EGFR) in late endosomal compartments, in mouse and human kidney cell lines (Yammine et al., 2019). The exact mechanisms via which Lcn2 directly or indirectly binds EGFR require further elucidation. Nevertheless, it was apparent that Lcn2 could promote the sustained activation of EGFR, by inhibiting lysosomal degradation of EGFR and enhancing the localization/recycling of EGFR back to the cell membrane, in transforming growth factor α (TGF-α)-stimulated cells. The potentiating effects of Lcn2 on EGFR activity could contribute to kidney damage and diseases including chronic kidney disease (Yammine et al., 2019). Seventh, it was observed that Lcn2 can bind to/be present in neutrophil extracellular traps (NETs) (Li et al., 2018; Shao et al., 2019). NETs – web-like structures consisting of extracellular DNA, histones and antimicrobial proteins – can be released by neutrophils under various infectious and inflammatory conditions, and can significantly improve/worsen disease processes, depending on the condition (Papayannopoulos, 2018). It was reported that Lcn2, as a component of NETs, contributes to the antimicrobial properties of NETs (Li et al., 2018). The binding partners of Lcn2 within NETs require further identification. Finally, Lcn2 can bind itself: Lcn2 not only exists as a monomer, but may also form homodimers and homotrimers (Kjeldsen et al., 1993; Yan et al., 2001). While monomeric Lcn2 appears to be the most common form, certain cell types seem to be related with formation of homo-multimeric forms of Lcn2 (Cai et al., 2010; Haase-Fielitz et al., 2014; Li et al., 2019b; Mårtensson et al., 2012; Yan et al., 2001). It is unknown whether and how the functions of Lcn2 differ between its monomeric, homodimeric and homotrimeric state. Interestingly, the monomeric versus multimeric state of Lcn2 may influence the clearance rate of Lcn2 from the body. It was shown that monomeric Lcn2 was more rapidly cleared from the body than dimeric Lcn2 under healthy physiological conditions (Axelsson et al., 1995). It is certainly possible that Lcn2 has more binding partners, that have at this moment not been identified or validated yet. For example, a list of other potential binding partners was reported by Ghosh et al. (Ghosh et al., 2020, 2019), resulting from a human proteome array. It would be of great interest to further validate these and other potential binding partners of Lcn2, and to determine possible effects of these complexes.

2.1.3. Receptors for Lcn2

Lcn2 can bind to the multi-ligand receptors 24p3R and megalin, which were both shown to mediate internalization of Lcn2 into cells (Devireddy et al., 2005; Hvidberg et al., 2005). 24p3R (also known as SLC22A17, LCN2R, NGALR and brain type organic cation transporter (BOCT)) also binds albumin, metallothionein, phytochelatins and possibly transferrin, when not outcompeted by Lcn2 (Dizin et al., 2013; Langelueddecke et al., 2014, 2012). Other ligands for megalin (also known as Lrp2 and gp330) include albumin, insulin, insulin-like growth factor 1, MMP-9 and hemoglobin (Marzolo and Farfán, 2011; Van den Steen et al., 2006). Of note, different alternative splice variants were found for 24p3R, which all appeared to be functional receptors for Lcn2, yet possibly with different affinities for Lcn2 (Devireddy et al., 2005; Fang et al., 2007).

Furthermore, it was recently shown that Lcn2 can bind to and activate the melanocortin 4 receptor (MC4R) (Mosialou et al., 2017). In addition, it was suggested that MC1R and MC3R may be activated by Lcn2 (Mosialou et al., 2017). This adds Lcn2 to the list of melanocortin receptor ligands, which otherwise consists of melanocortins such as the agonistic α- and β-melanocyte-stimulating hormones (α-MSH and β-MSH) and adrenocorticotropic hormone (ACTH), and the antagonistic Agouti and Agouti-related peptide (Tao, 2010). The exact mechanisms for the binding between Lcn2 and MC4R/MC1R/MC3R are not known yet, although a first prediction of the potential binding site between Lcn2 and MC4R has been made (Heyder et al., 2019).

Altogether, at least three functional Lcn2 receptors are currently known (including 24p3R, megalin, MC4R and possibly MC1R and MC3R). The signaling mechanisms mediated by these receptors upon Lcn2 binding, and their potential differential affinities for different ligand-bound states of Lcn2, are incompletely understood and require further elucidation. For example, both 24p3R and megalin are able to take up iron-free Lcn2 (apo-Lcn2) as well as iron-bound Lcn2 (holo-Lcn2). However, while megalin does not appear to have a binding preference for either form, there is evidence that 24p3R does present a differential affinity for iron-free versus iron-bound ligands (Cabedo

Martinez et al., 2016; Devireddy et al., 2005; Hvidberg et al., 2005; Yang et al., 2002).

2.1.4. Post-translational modifications

Lcn2 can be subject to post-translational modifications (also see Table 1). Firstly, Lcn2 is a glycoprotein and may be secreted in at least two different glycosylation isoforms (glycoforms), due to different N-linked glycosylation patterns (Chu et al., 1996; Fujiwara et al., 2016; Lee et al., 2006; Miyamoto et al., 2011; Rudd et al., 1999). Different glycosylation patterns may relate to the tissue in which Lcn2 is produced and to the stimulus that induces its production, and might affect its stability and solubility (Borkham-Kamphorst et al., 2018; Fujiwara et al., 2016). Secondly, Lcn2 can be polyaminated, resulting in faster clearance of Lcn2 from the circulation (Song et al., 2014; Yang et al., 2017). On the other hand, deamidation (removal of polyamine groups) of Lcn2 in adipose tissue can delay its clearance and promote its detrimental accumulation in arteries (Song et al., 2014; Yang et al., 2017). Lastly, Lcn2 can also be phosphorylated (Lee et al., 2001; Weng et al., 2015). Protein kinase C delta (PKCδ) was shown to phosphorylate Lcn2, and to promote the release of Lcn2 from neutrophils (Weng et al., 2015). The underlying mechanisms for this remain to be explored.

In essence, Lcn2 can exist in different ligand-bound, complexed and post-translationally modified states, and is able to bind to different receptors. It has become clear that the iron-bound/iron-free state of Lcn2 controls certain effects of Lcn2 (e.g. on energy metabolism (Ishii et al., 2017), synaptic plasticity (Mucha et al., 2011), oxidative stress (Song et al., 2018) and cell survival/cell death (Devireddy et al., 2005; Rehwald et al., 2020)), and that the MMP-9-bound state of Lcn2 mediates certain cardiovascular effects of Lcn2 (Amersfoort et al., 2018; Eilenberg et al., 2019; Hemdahl et al., 2006). However, besides these insights (which are further described in Chapter 3.2 and Chapter 4), the understanding of the importance of specific ligand-bound, complexed and post-translationally modified states of Lcn2 in the healthy and diseased body and brain is very limited. As such, more research is required to clarify how the various states of Lcn2 may influence its functions and effects.

2.2. Expression and functions of Lcn2 and its receptors

Lcn2 is known to be involved in a wide range of physiological processes, including the defense against specific bacterial infections, regulation of mammalian iron homeostasis, anti- and pro-apoptotic signaling, anti- and pro-inflammatory responses, chemotaxis, cell migration, cell differentiation and energy metabolism (Fig. 1) (Ferreira et al., 2015; Jha et al., 2015; Mosialou et al., 2017). Abnormalities in these processes can affect the expression levels of Lcn2 and its receptors and *vice versa*.

2.2.1. Lcn2 and its receptors in the periphery

Under physiological conditions in adults, expression of Lcn2 is low and limited to specific cell types. Constitutive low expression of Lcn2 under healthy circumstances is found in neutrophils, bone marrow, bone osteoblast cells, adipose tissue, heart, blood vessels, uterus, prostate and salivary gland, as well as in tissues that are normally exposed to microorganisms, including epithelial cells in most parts of the respiratory, urinary and gastrointestinal tracts (Borregaard and Cowland, 2006; Cowland and Borregaard, 1997; Devarajan, 2007; Hvidberg et al., 2005; Mosialou et al., 2017; Wang et al., 2007; Yndestad et al., 2009; Zhang et al., 2012). Continuous Lcn2 expression in these epithelial cell types and constitutive Lcn2 storage in neutrophils are likely related to the readiness of these cell types to respond to pathogenic, inflammatory and tissue damage-related stimuli. Basal Lcn2 expression in tissues such as bone and adipose tissue plays a role in metabolic regulation (including glucose and insulin homeostasis, appetite and food intake) (Abella et al., 2015; Mosialou et al., 2017). Moreover, basic Lcn2 levels may be involved in maintaining iron homeostasis (Nairz et al., 2009). The known receptors for Lcn2 (including megalin and 24p3R) are widely expressed throughout the body (Chia et al., 2015; Devireddy et al., 2005; Hvidberg et al., 2005; Jha et al., 2015), indicating that many tissues may be sensitive for and able to respond to Lcn2. MC4R on the other hand seems to be expressed primarily in the CNS (Tao, 2010).

While Lcn2 expression is low and limited to specific cell-types under healthy conditions, it can increase manifold in various cell types upon different acute and chronic challenges. Lcn2 is an acute-phase protein, and is rapidly produced in response to pathogen exposure, tissue injury and inflammatory stimuli (Borregaard and Cowland, 2006; Ferreira et al., 2015; Flo et al., 2004). In addition, Lcn2 levels are significantly increased in various chronic conditions, such as in different types of cancer, metabolic diseases (including obesity and diabetes), heart failure, arthritic diseases and chronic kidney disease (Abella et al., 2015; Candido et al., 2016; Ferreira et al., 2015; Marques et al., 2017; Viau et al., 2010; Yang et al., 2017; Yndestad et al., 2009). Depending on the condition, Lcn2 production can be induced in many different cell types and tissues, including for example: neutrophils, macrophages, adipose tissue, cardiomyocytes, epithelial cells in the respiratory tract, gut, peritoneum, kidney, liver and vascular endothelium (Abella et al., 2015; Cramer et al., 2017; Ferreira et al., 2015; Flo et al., 2004; Li and Chan, 2011; Li et al., 2018; Marques et al., 2017; Viau et al., 2010; Xu et al., 2015; Yndestad et al., 2009). Lcn2 was shown to play an important role in several acute and chronic conditions, for example via its effects on iron homeostasis, cell survival and cell death, cell proliferation and inflammation (Ferreira et al., 2015; Jha et al., 2015; Li and Chan, 2011; Marques et al., 2017; Sung et al., 2017; Viau et al., 2010). In conditions in which microbial infections are involved, the antibacterial functions of Lcn2 (via hijacking bacterial iron acquisition as well as promoting neutrophil functioning) can play an essential part as well (Berger et al., 2006; Flo et al., 2004; Liu et al., 2013; Wang et al., 2019b; Zhao et al., 2012).

2.2.2. Lcn2 and its receptors in the CNS

Lcn2′s expression and functions in the CNS have only been explored more recently. Studies in mice and rats illustrated that Lcn2 mRNA and protein expression in the brain is low during normal physiological conditions (Chia et al., 2011; Dekens et al., 2018; Gouweleeuw et al., 2016; Hovens et al., 2016; Ip et al., 2011; Mucha et al., 2011; Noçon et al., 2014; Ranjbar Taklimie et al., 2019; Zamanian et al., 2012). Similarly, in the human brain low Lcn2 protein expression levels were observed in post mortem brain tissue from healthy controls, when compared for example to patients with gliomas, AD and VaD (Cowland and Borregaard, 1997; Liu et al., 2011b; Llorens et al., 2020; Naudé et al., 2012). Although not much Lcn2 protein is detected in the healthy brain, it has appeared that Lcn2 in the healthy brain may be mostly localized to blood vessels, and resting microglia (Llorens et al., 2020). Of note, it is likely that the basal levels of Lcn2 in the brain originate not only from the brain itself but also from the blood (Ferreira et al., 2018a). Indeed, a recent study showed that intravenous injected radiolabeled human Lcn2 crossed the blood brain barrier (BBB) and localized to the hypothalamus in primates (Petropoulou et al., 2020). Moreover, intraperitoneally injected Lcn2 was confirmed to accumulate in the brain in Lcn2 knockout (KO) mice (Mosialou et al., 2017), providing further support that peripherally produced Lcn2 can enter and accumulate in the brain. The low basal levels of Lcn2 in the brain are involved in different physiological processes, including maintenance of normal brain iron homeostasis, adult neurogenesis and synaptic activity/plasticity (Dekens et al., 2018; Ferreira et al., 2013, 2018a; Mucha et al., 2011; Skrzypiec et al., 2013). Moreover, basal Lcn2 levels play a role in behavioral and cognitive functioning (Dekens et al., 2018; Ferreira et al., 2013, 2015; Ferreira et al., 2018a). The effects of Lcn2 in the brain are likely largely mediated via its receptors, which indeed are known to be expressed throughout the brain. Megalin is primarily present in the choroid plexus, ependymal cells of the lateral ventricles, and brain capillaries (Carro et al., 2005; Chun et al., 1999; Gajera et al., 2010).

Megalin expression on astrocytes and neurons has also been described (Alvira-Botero et al., 2010; Bento-Abreu et al., 2008; Fleming et al., 2009). Anatomical localization of 24p3R in the brain with *in situ* hybridization in mice showed that it is widely distributed throughout the gray matter regions, including cortex, thalamus and neurons in the granule layer of the cerebellum (Ip et al., 2011). The highest expression levels were found in the choroid plexus, dentate gyrus and pyramidal cells of the hippocampus (Chia et al., 2015; Ip et al., 2011). Furthermore, 24p3R can be expressed by neurons, microglia, astrocytes and endothelial cells (Ip et al., 2011; Jin et al., 2014b; Kim et al., 2017). MC4R is widely expressed throughout the brain as well, with expression found in various brain regions including the hypothalamus, thalamus, hippocampus, cortex, amygdala, brain stem and spinal cord (Tao, 2010). Cellular MC4R expression was found in neurons, astrocytes, microglia and oligodendrocytes (Lisak and Benjamins, 2017; Tao, 2010). Considering the widespread expression of Lcn2 and its receptors in the brain, it can be hypothesized that Lcn2 may exert effects on different brain cell types and in multiple brain regions, in the healthy brain.

Similar to many other tissues in the body, the mRNA expression and protein production of Lcn2 in the brain have been found to increase significantly upon various acute stimuli and chronic pathologies. For example, Lcn2 expression in the brain was found to be increased in different animal models of acute neuronal injury (Chia et al., 2011; Rathore et al., 2011), as well as in mice that received peripheral or central injection with LPS (Ferreira et al., 2015; Hamzic et al., 2013; Ip et al., 2011; Jha et al., 2015). Microarray analyses from several studies have identified Lcn2 as one of the highest upregulated genes in the brain and brain cells upon acute pro-inflammatory stimuli and neuronal damage (Almeida-Suhett et al., 2014; Hamzic et al., 2013; Marques et al., 2012, 2008; Naudé et al., 2012; Zamanian et al., 2012). Increased brain Lcn2 levels are also present in different chronic CNS diseases, including multiple sclerosis (MS) and neurodegenerative conditions such as AD, PD and VaD (Berard et al., 2012; Dekens et al., 2017; Ferreira et al., 2015; Jha et al., 2015; Kim et al., 2016; Llorens et al., 2020; Naudé et al., 2012). In most of the studied pathological CNS conditions, astrocytes appeared to be the major producers of Lcn2 (Bi et al., 2013; Dekens et al., 2017; Kim et al., 2016, 2017). Indeed, Lcn2 expression was found to be highly upregulated in astrocytes in response to different types of brain injury, and was suggested to be a pan-reactive astrocyte marker as its upregulation was found in both 'A1′ and 'A2′ reactive astrocytes (Liddelow et al., 2017; Zamanian et al., 2012). However, increased Lcn2 may also be produced and/or taken up by other cell types, including choroid plexus epithelial cells, brain endothelial cells, neurons, infiltrating neutrophils and microglia (Jin et al., 2014a, 2014b; Llorens et al., 2020; Marques et al., 2008; Mesquita et al., 2014; Mondal et al., 2020; Mucha et al., 2011; Naudé et al., 2012; Ni et al., 2015; Paratore et al., 2006; Wang et al., 2015a; Xing et al., 2014). The cell type (s) that produce Lcn2 may depend on the specific disease and disease stage. As described (and as will be described in more detail in Chapter 3), Lcn2 expression is increased in different acute and chronic CNS conditions. This likely results from (combinations of) different pathological events/hallmarks, including for example acute/chronic inflammation, hypoxia, protein aggregation and neuronal damage. The exact molecular mechanisms that underlie the overexpression of Lcn2 remain to be explored more fully. Different factors and signaling pathways have been identified as potent triggers of Lcn2 expression, as will also be discussed in Chapter 5.1. For example, signaling of tumor necrosis factor alpha (TNF-α) via tumor necrosis factor receptor 1 (TNFR1), and activation of multiple toll-like receptors (TLRs) by – for instance – LPS, have appeared to be important pathways in the induction of Lcn2. More research is needed to elucidate which specific (combinations of) triggers and signaling mechanisms are responsible for the overexpression of Lcn2, in different CNS conditions.

Taken together, Lcn2 expression can be induced in many different cell types throughout the body and brain, in both acute and chronic conditions. By affecting multiple processes such as inflammation and iron regulation, Lcn2 may play a significant role in the pathophysiology of various diseases in the periphery and CNS. However, it is important to note that the effects of Lcn2 in many disorders are not fully understood yet. Lcn2 has been found to exert contrasting effects, including anti- and pro-apoptotic signaling, and anti- and pro-inflammatory responses. The effects exerted by Lcn2 may depend on a complex combination of several factors, including the pathology that is studied, the cell types that are involved, the states in which Lcn2 is present (e.g. iron-free or iron-bound), the relative expression of the different receptors for Lcn2 and the chronicity of Lcn2 exposure. In the next chapter of this review, we will address these points in the context of different age-related brain conditions (including AD, PD and VaD), and will summarize the neurotoxic and neuroprotective effects that have been reported for Lcn2.

3. The expression and effects of Lcn2 in age-related CNS diseases

3.1. Lcn2 expression and effects in human and animal studies of AD, PD and VaD

Evidence from existing human and animal studies indicates that Lcn2 is involved in the disease processes of AD, PD and VaD (also see Table 2). Altered Lcn2 levels have been found in human brain tissues of AD, PD and VaD patients. In human post-mortem brain tissue of AD patients, elevated Lcn2 mRNA and protein levels were detected in multiple brain regions that are affected by AD pathology, such as the hippocampus, entorhinal cortex and prefrontal cortex (Czapski et al., 2020; Dekens et al., 2017; Llorens et al., 2020; Naudé et al., 2012). An increase in plasma Lcn2 levels was observed in preclinical AD (Eruysal et al., 2019). Yet, at a later disease stage, no differences in serum Lcn2 levels were found between AD patients and healthy controls (Choi et al., 2011; Dekens et al., 2017; Naudé et al., 2012; Rosén et al., 2011). Notably, Lcn2 levels in cerebrospinal fluid (CSF) were significantly decreased in AD patients as compared to healthy age-matched control subjects (Dekens et al., 2017; Naudé et al., 2012), mimicking the characteristically decreased CSF amyloid-β (Aβ) concentrations in AD (Galasko et al., 1998; Sancesario et al., 2012; Sunderland et al., 2003). Hypothetically, the decreased CSF levels of Lcn2 and Aβ in AD may be associated with lower protein expression of megalin in the choroid plexus in AD patients. Namely, both Lcn2 and Aβ can be transported by megalin, and therefore lower megalin levels might result in lower clearance of Lcn2 and Aβ from the brain into the CSF (Alvira-Botero and Carro, 2010; Dietrich et al., 2008; Hammad et al., 1997; Zlokovic, 1996; Zlokovic et al., 1996). Of note, while the studies by Llorens et al., 2020 (Llorens et al., 2020) and Rosén et al., 2011 (Rosén et al., 2011) also appear to indicate lower CSF Lcn2 levels in AD, these changes were not significant. In post-mortem brain tissue of PD patients, increased Lcn2 levels were measured in the substantia nigra (Kim et al., 2016). In addition, increased serum Lcn2 levels were found in PD patients, and Lcn2 levels in the CSF were shown to be positively correlated with CSF α-synuclein as well as $A\beta_{40}$ levels (Eidson et al., 2017). Regarding VaD, immunohistochemical stainings of post-mortem brain tissue revealed that Lcn2 protein expression is highly increased in multi-infarct dementia patients, as compared to both control and AD patients (Llorens et al., 2020). Furthermore, increased Lcn2 levels were found in both plasma and CSF in VaD patients (Kim et al., 2017; Llorens et al., 2020). In the study by Rosén and colleagues no significant differences in plasma and CSF Lcn2 levels were detected in control subjects versus VaD patients (Rosén et al., 2011). However, higher CSF Lcn2 levels were found in AD patients that presented cerebrovascular pathology (mixed dementia) as compared to 'pure' AD patients, indicating that vascular pathology in AD is associated with increased CSF Lcn2 levels (Rosén et al., 2011).

Corresponding to the upregulated Lcn2 expression seen in patients, Lcn2 levels were also found to be significantly elevated in cell culture and animal models of AD, PD and VaD (Table 2) (Dekens et al., 2018; Kim et al., 2016, 2017; Mesquita et al., 2014; Steeland et al., 2018). Importantly, from these cell culture and animal studies it appeared that

Table 2
Expression and effects of Lcn2 in AD, PD and VaD.

CNS condition	Model	Expression /effects of Lcn2	Cell types in which increased Lcn2 expression was found	Ref.
AD	Human AD patients	Increased Lcn2 mRNA and protein levels in affected brain regions (including hippocampus, prefrontal cortex, amygdala, anterior cingulate cortex). Decreased Lcn2 levels in CSF, compared to healthy age-matched controls. Note: this decrease was not significant, in studies by Llorens et al. (2020) and Rosén et al. (2011). No difference in serum Lcn2 levels. Plasma levels of an 'inflammatory factor' (including Lcn2 and four other inflammatory, neutrophil-related markers) were predictive of a decline in executive function.	Astrocytes, brain capillaries, neurons, microglia.	(Bawa et al., 2020; Czapski et al., 2020; Dekens et al., 2017; Llorens et al., 2020; Naudé et al., 2012; Rosén et al., 2011)
	Human patients with pre-clinical/ prodromal AD	Increased plasma Lcn2 levels in preclinical and prodromal AD. Increased plasma Lcn2 levels were associated with impaired executive function. Plasma Lcn2 levels were inversely correlated with CSF $A\beta_{42}$ levels. CSF Lcn2 levels were lower in people with MCI compared to healthy controls.	N.D.	(Choi et al., 2011; Eruysal et al., 2019; Naudé et al., 2012)
	AD mouse models	Increased brain Lcn2 protein levels in the J20 AD mouse model (12 months old). Increased brain Lcn2 mRNA expression in hippocampus and choroid plexus in APP/PS1 mice (~12 wk old), and WT mice that received i.c.v. oligomeric Aβ injection. Increased Lcn2 mRNA levels in brain of young (2 mo.) but not older (12 mo.) Tg2576/PS-1$^{P264L/P264L}$ AD mice. Increased Lcn2 mRNA expression in the colon of 3 months old APP/PS1 and App^{NL-G-F} mice. Knockout of Lcn2 in J20 AD mice did not significantly affect AD-like behavioral changes, cognitive impairment, plaque load and glial activation, but did affect brain iron accumulation (J20 x Lcn2 KO mice, 12 months old).	Astrocytes, choroid plexus cells.	(Dekens et al., 2018; Manocha et al., 2019; Steeland et al., 2018; Wu et al., 2006)
	Cultured primary brain cells	Increased Lcn2 production in astrocytes and choroid plexus epithelial cells upon $A\beta_{1-42}$ exposure. Treatment with Lcn2 sensitized astrocytes and neurons to Aβ- and glutamate-induced cell death.	Astrocytes, choroid plexus epithelial cells.	(Dekens et al., 2020; Mesquita et al., 2014; Naudé et al., 2012)
PD	Human PD patients	Increased Lcn2 protein levels in the substantia nigra of PD patients. Increased Lcn2 levels in serum of PD patients. Positive relations between CSF Lcn2 and CSF α-synuclein, and between CSF Lcn2 and CSF $A\beta_{40}$ levels, were found.	N.D.	(Eidson et al., 2017; Kim et al., 2016)
	PD mouse models (MPTP and 6-OHDA models)	Increased Lcn2 mRNA and protein expression in the substantia nigra and striatum in two neurotoxin mouse models of PD. Lcn2 promoted neuronal death and neuroinflammation, thereby contributing to disruption of the nigrostriatal dopaminergic pathway and disturbance of locomotor behavior.	Mostly astrocytes, microglia.	(Kim et al., 2016)
	Cultured primary brain cells	Increased Lcn2 production in cultured glia upon treatment with conditioned medium from differentiated 1-methyl-4-phenylpyridinium (MPP^+)-pretreated SH-SY5Y neurons. Astrocyte-derived Lcn2 promoted neurotoxicity of MPP^+, in co-cultures of mesencephalic neurons and astrocytes.	Astrocytes.	(Kim et al., 2016)

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Table 2 (*continued*)

CNS condition	Model	Expression /effects of Lcn2	Cell types in which increased Lcn2 expression was found	Ref.
VaD	Human VaD patients	Increased Lcn2 protein levels in cortex of multi-infarct dementia patients as compared to control and AD patients. Increased Lcn2 levels in plasma and CSF. Of note, Rosén et al. (2011) found no difference in plasma and CSF Lcn2 levels between controls and VaD patients. However, CSF Lcn2 levels were found to be increased in AD patients with cerebrovascular pathology (AD + VaD or mixed dementia), as compared to 'pure' AD patients.	Brain capillaries, astrocytes, microglia, macrophages.	(Kim et al., 2017; Llorens et al., 2020; Rosén et al., 2011)
	VaD mouse model (tBCCAo and cUCCAo models)	Increased hippocampal Lcn2 levels in two mouse models of VaD. Lcn2 contributed to neuronal loss, neuroinflammation, white matter damage, BBB disruption and cognitive impairment, as shown in WT vs Lcn2 KO VaD mice.	Astrocytes.	(Kim et al., 2017)
	Cultured primary brain cells	Increased Lcn2 production in primary astrocytes, upon chemically induced hypoxia by $CoCl_2$. The upregulation of Lcn2 was dependent on HIF-1α. Recombinant Lcn2 reduced the viability of cultured hippocampal neurons. Lcn2 treatment induced production of NO, IL-1β, and TNF-α by primary microglia. Lcn2 promoted microglia-mediated neurotoxicity.	Astrocytes.	(Kim et al., 2017)

Abbreviations: Aβ; Amyloid-β, AD; Alzheimer's disease, BBB; blood-brain barrier, $CoCl_2$; cobalt chloride, CSF; cerebrospinal fluid, cUCCAo; chronic unilateral common carotid artery occlusion, HIF-1α; hypoxia-inducible factor 1 alpha, i.c.v.; intracerebroventricular, IL-1β; interleukin 1 beta, Lcn2; Lipocalin 2, Lcn2 KO; Lipocalin 2 knock-out, MCI; mild cognitive impairment, MPTP; 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, N.D.; not determined, NO; nitric oxide, 6−OHDA; 6-hydroxydopamine, PD; Parkinson's disease, tBCCAo; transient bilateral common carotid artery occlusion, TNF-α; tumor necrosis factor alpha, VaD; vascular dementia, WT; wildtype.

Lcn2 is associated with neuropathological processes, such as neuroinflammation, cell death and dysregulated iron metabolism, depending on the experimental model. As such, it is possible that increased Lcn2 levels play an important role in the pathophysiology of AD, PD and VaD.

However, the evidence for the involvement of Lcn2 in these age-related CNS diseases is still limited. Moreover, the overall understanding of the functions and effects of Lcn2 in the healthy and diseased brain is limited. To gain more insight into the potential effects of Lcn2 in neurodegenerative and neuroprotective conditions, we will summarize the reported findings of Lcn2′s functions in the healthy and unhealthy brain. In this regard, we will not only discuss findings from cell culture and animal models of AD, PD and VaD, but also from other CNS conditions in which Lcn2 may play a role, such as stroke, MS and spinal cord injury (also see Table 3). Even though the latter CNS conditions may not be linked with older age or may not be neurodegenerative in nature, different neuropathological processes that contribute to these conditions may overlap with those in AD, PD and VaD. For example, neuroinflammation, iron dysregulation, white matter damage and BBB disruption are neuropathological processes that are shared between many CNS disorders. Nevertheless, it should be kept in mind that effects found for Lcn2 in one specific tested condition may not translate to similar effects in another condition. For example, contradictory (e.g. neurotoxic versus neuroprotective) effects of Lcn2 in certain conditions have been found, as will be described below. These contrasting findings are intriguing and crucial to consider, as they point out that the functions and effects of Lcn2 are not completely understood yet and are difficult to predict at this moment. Therefore, it is important to note that the effects of Lcn2 may depend on a complex combination of factors, including: the specific disease, disease stage, age, sex, involved tissues/cell types, the neuropathological environment, and the acute versus chronic nature of the disease that is studied.

3.2. *The neurobiological functions of Lcn2 in the healthy and diseased brain*

Lcn2 was suggested to play a role in different neuro(patho)physiological processes, which will be discussed here (also see Fig. 2).

3.2.1. *Neuroinflammation*

Neuroinflammation is an important player in many if not all CNS conditions. Many studies – as performed for example in models of AD, VaD, PD, amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), stroke, MS, diabetic encephalopathy, spinal cord injury and LPS-induced sepsis – have found that Lcn2 promotes pro-inflammatory activation of glia, and may in certain conditions enhance infiltration of neutrophils and macrophages into the brain (Behrens et al., 2021; Bhusal et al., 2019a; Jang et al., 2013a, 2013b; Jeon et al., 2013; Jha et al., 2013, 2014; Jin et al., 2014b, 2014a; Kim et al., 2016, 2017; Lee et al., 2007, 2009, 2011; Mike et al., 2019; Nam et al., 2014; Ni et al., 2015; Ojeda-Juárez et al., 2020; Rathore et al., 2011; Shin et al., 2021; Shishido et al., 2016; Wang et al., 2015a; Wang et al., 2020; Xing et al., 2014; Zhang et al., 2021; Zhao et al., 2019). Most of these studies were performed by comparing WT and Lcn2 KO mice, in different disease models. Interestingly, a recent study in mice that received intracerebral peroxiredoxin-2 injections (mouse model for intracerebral hemorrhage) showed reduced brain swelling, neutrophil infiltration, microglia activation and neuronal death in heterozygous and homozygous Lcn2 KO mice (Zhang et al., 2021). Although Lcn2 expression levels in the heterogenous Lcn2 KO mice were not shown in the study by Zhang et al., the results indicate that partial inhibition of Lcn2 is sufficient in reducing neuroinflammation after brain injury.

Some contradictory findings – also obtained from comparing WT and Lcn2 KO mice – should be mentioned. Firstly, no differences in glial activation were found in 12 months old 'J20′ transgenic AD mice in which Lcn2 was either present or knocked out (Dekens et al., 2018). Also, while an effect on microglia activation was observed, Lcn2 did not

Table 3
Expression and effects of Lcn2 in other CNS conditions.

CNS condition	Model	Expression/effects of Lcn2	Cell types in which increased Lcn2 expression was found	Ref.
AD in Down syndrome (DS)	Human individuals with DS with or without AD dementia	Increased serum Lcn2 levels in DS individuals compared to non-DS individuals. Serum Lcn2 levels correlated positively with rising age. Serum Lcn2 levels were not associated with clinical dementia symptoms in DS. Serum Lcn2 levels associated with distinct Aβ species, depending on the progression to dementia (DS without AD vs. DS with AD at baseline, vs. DS with conversion to AD).	N.D.	(Naudé et al., 2015a; Dogliotti et al., 2010)
Hemorrhagic stroke	Human hemorrhagic stroke patients	Increased serum Lcn2 levels in hemorrhagic stroke patients, when compared to healthy controls and ischemic stroke patients (pilot study).	N.D.	(Weng and Chou, 2014)
	Mouse and rat models of hemorrhagic stroke	Increased Lcn2 production in the brain upon hemorrhagic stroke. Lcn2 contributed to brain injury and neurological deficits after hemorrhagic stroke (including increased neuroinflammation, BBB disruption and neuronal death).	Astrocytes (most clearly), neurons, microglia and endothelial cells.	(Chou et al., 2015; Dong et al., 2013; Egashira et al., 2016, 2014; Mao et al., 2016; Ni et al., 2015; Shishido et al., 2016; Toyota et al., 2019; Wang et al., 2021)
Ischemic stroke	Human ischemic stroke patients	Increased Lcn2 levels in human brain tissue and blood after ischemic stroke. Higher plasma levels of Lcn2 in the first week after ischemic stroke associated with worse clinical outcome at 90 days, higher cardiovascular mortality in 4 years after stroke, and with the presence of post-stroke infections.	Neurons.	(Anwaar et al., 1998; Chou et al., 2015; Elneihoum et al., 1996; Falke et al., 2000; Hochmeister et al., 2016; Xia et al., 2017; Xing et al., 2014; Zhou et al., 2017)
	Mouse and rat models of ischemic stroke (ischemia-reperfusion injury)	Increased Lcn2 production in the brain upon ischemia-reperfusion injury. Increased Lcn2 levels were detected in the blood. Lcn2 contributed significantly to ischemia-reperfusion injury in the brain (including increased neuroinflammation, BBB disruption and neurotoxicity) and worsened neurological deficits.	Astrocytes, endothelial cells, macrophages/ microglia, infiltrating neutrophils (23 h after stroke, mouse). Neurons (3 days after stroke, rat).	(Du et al., 2019; Hochmeister et al., 2016; Jin et al., 2014b; Liu et al., 2018; MacManus et al., 2004; Peng et al., 2020; Ranjbar Taklimie et al., 2019; Wang et al., 2015a; Xing et al., 2014; Zamanian et al., 2012; Zhao et al., 2019)
	Cultured primary brain cells	Lcn2 stimulated glia to adopt a 'pro-recovery' phenotype, thereby providing neuronal protection against oxygen-glucose deprivation.	Neurons.	(Xing et al., 2014)
FTLD/ALS	Human FTLD patients	Upregulated Lcn2 expression in brain tissue of FTLD patients.	Astrocytes.	(Bi et al., 2013; Ngo et al., 2015)
	Human ALS patients	Increased Lcn2 levels in the motor cortex and spinal cord of ALS patients. Increased Lcn2 plasma protein levels in ALS patients.	Neurons, astrocytes, microglia.	(Ngo et al., 2015; Petrozziello et al., 2020)
	Transgenic rat models of FTLD/ALS	Increased Lcn2 levels in brain tissue of transgenic rats expressing mutant TDP-43, FUS or SOD1. Lcn2 levels in CSF increased with disease progression in mutant TDP-43 expressing rats.	Astrocytes.	(Bi et al., 2013; Tong et al., 2013)
	Cultured primary brain cells	Lcn2 induced neurotoxic effects in WT neurons. Moreover, primary neurons expressing ALS-related mutant TDP-43 or FUS displayed a further increased sensitivity to Lcn2-induced cell death compared to WT neurons.	N.D.	(Bi et al., 2013)
	Progranulin-deficient mice	Increased Lcn2 expression in the brain of progranulin-deficient mice, in which features of FTLD are mimicked.	N.D.	(Tanaka et al., 2014)
MS	Human MS patients	Increased Lcn2 protein expression around plaques in the brain of MS patients. Increased Lcn2 levels in plasma and CSF of (especially progressive) MS patients. However, in early stages of MS, Lcn2 levels in plasma and CSF may be decreased. Higher CSF Lcn2 levels associated with conversion to clinically definite MS, in clinically isolated syndrome patients.	Monocyte/macrophages and granulocytes, in the blood vessel lumen and perivascular cuffs of active plaques.	(Al Nimer et al., 2016; Al-Temaimi et al., 2017; Berard et al., 2012; Khalil et al., 2016; Marques et al., 2012)
	Mouse model of MS (EAE)	Increased Lcn2 mRNA and protein expressions in spinal cord and choroid plexus in the EAE mouse model. Lcn2 levels were also increased in the CSF and	Infiltrating neutrophils (choroid plexus), astrocytes (brain parenchyma and spinal cord),	(Berard et al., 2012; Ebrahimi-Kalan et al., 2014; Marques et al., 2012; Nam et al., 2014)

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Table 3 (*continued*)

CNS condition	Model	Expression/effects of Lcn2	Cell types in which increased Lcn2 expression was found	Ref.
		correspond with active disease phases. Lcn2 significantly affected EAE severity. Notably, both detrimental and beneficial effects have been reported.	microglia and monocytes (spinal cord).	
HIV-associated neurocognitive disorders	Human HIV patients	Increased Lcn2 mRNA and protein expression in brain tissue of HIV patients with brain pathology. Lcn2 mRNA expression in the brain correlated with HIV RNA load in the CSF and HIV DNA levels in the frontal neocortex. Increased Lcn2 levels in blood of HIV patients. Higher plasma Lcn2 levels associated with reduced thickness of the bilateral orbitofrontal cortex in HIV-positive participants. Increased plasma Lcn2 levels associated with worse motor function, which was mediated by cortical thickness of the bilateral orbitofrontal region. Additionally, higher blood Lcn2 levels were associated with worse psychomotor processing speed.	N.D.	(Morieri et al., 2018; Ojeda-Juárez et al., 2020; Williams et al., 2020, 2019)
	Mouse model of HIV	Lcn2 contributed to behavioral impairment, neuronal damage and microglial activity, an interfered with neuroprotective mechanisms in a HIV mouse model.	Lcn2 mRNA co-localizes with GFAP. Cellular localization of Lcn2 protein was not determined.	(Ojeda-Juárez et al., 2020)
Traumatic brain injury (TBI)	Human TBI patients	Increased Lcn2 levels in brain and serum of TBI patients. Increased serum Lcn2 levels associated with trauma severity and were a predictor of mortality after head trauma.	Neurons.	(Shen et al., 2017; Zhao et al., 2016a)
	Mouse and rat models of TBI	Increased Lcn2 mRNA and protein expression in the brain after TBI.	Astrocytes.	(Almeida-Suhett et al., 2014; Huang et al., 2016; Zhao et al., 2016b)
Spinal cord injury	Mouse model of spinal cord contusion injury	Increased Lcn2 protein levels in spinal cord after spinal cord contusion injury. Increased Lcn2 expression was also found in the brain and liver after spinal cord contusion. Lcn2 worsened locomotor recovery, and increased neuroinflammation, neuronal loss, myelin loss and tissue damage after spinal cord contusion injury.	Astrocytes, neurons and infiltrating neutrophils in the spinal cord. Brain endothelial cells in the brain.	(Behrens et al., 2021; Rathore et al., 2011)

Abbreviations: ALS; amyotrophic lateral sclerosis, BBB; blood-brain barrier, CSF; cerebrospinal fluid, DS; Down syndrome, EAE; experimental autoimmune encephalomyelitis, FTLD; frontotemporal lobar degeneration, FUS; fused in sarcoma, Lcn2; Lipocalin 2, MS; Multiple Sclerosis, N.D.; not determined, SOD1; superoxide dismutase 1, TBI; traumatic brain injury, TDP-43; TAR DNA-binding protein 43, WT; wildtype.

affect astrocyte activation in a mouse model of systemic lupus erythematosus (SLE) (Mike et al., 2019). Further, the presence/absence of Lcn2 did not influence neuroinflammation in mice with West Nile virus encephalitis (Noçon et al., 2014), nor did it affect neuroinflammation in a mouse model of cerebellar degeneration (Lattke et al., 2017). Moreover, while the majority of research indicate that Lcn2 aggravates LPS-induced neuroinflammation (modelling sepsis) (Jang et al., 2013a, 2013b; Jin et al., 2014a; Lee et al., 2011), a few studies showed no effect of Lcn2 on glial activation/neuroinflammation upon LPS stimulation (Gasterich et al., 2021; Ip et al., 2011; Vichaya et al., 2019), and another study reported opposite, anti-inflammatory, effects of Lcn2 (Kang et al., 2018). In addition, while one group found significant pro-inflammatory effects of Lcn2 in the spinal cord in the experimental autoimmune encephalomyelitis (EAE) mouse model of MS (Nam et al., 2014), another group found that Lcn2 induced anti-inflammatory effects in this model (Berard et al., 2012). The reasons behind these contradictory findings on effects of Lcn2 on neuroinflammation are not clear. Various factors may be responsible for the conflicting results, including: the specific CNS condition that was modeled, the exact experimental set-up that was used, the disease stage, the involved cell types, the chronicity of Lcn2 overexpression and the age and sex of the animals. More work is required to clarify the conditions that determine whether Lcn2 may exert e.g. pro- or anti-inflammatory effects. Moreover, the exact mechanisms underlying the potential immunomodulatory effects of Lcn2 warrant further investigation. Lcn2 is able to induce classical activation of both astrocytes and microglia (Jang et al., 2013a, 2013b; Lee et al., 2015). In addition, Lcn2 can act as a chemokine inducer, thereby enhancing the migration of cells within the brain (e.g. astrocytes and microglia) (Lee et al., 2011), and possibly also contributing to infiltration of peripheral immune cells into the brain (e.g. neutrophils). Upregulation of the chemokine CXCL10 via modulation of JAK2/STAT3 and IKK/NF-κB signaling pathways in astrocytes was implicated to be one important mechanism behind the chemokine-inducing effects of Lcn2 (Lee et al., 2011). Besides this and other identified signaling pathways via which Lcn2 may exert its effects on neuroinflammation, it seems certain that additional signaling pathways of Lcn2 are waiting to be discovered. For instance, Lcn2 was recently shown to induce activation of the NLRP3 (nucleotide-binding oligomerization domain-, leucine-rich repeat- and pyrin domain-containing 3) inflammasome in cardiac fibroblasts, resulting in caspase-1 activation and interleukin 1 beta (IL-1β) production (Song et al., 2017). It would be of interest to assess whether Lcn2 may also influence glial activity via this mechanism. A recent study by Mondal et al. provides the first indirect support that this may indeed be the case (Mondal et al., 2020). Firstly, Lcn2 levels and NLPR3 activation were both found to be increased in the brain of a non-alcoholic steatohepatitis mouse model. Subsequently, a link between the two factors was suggested by cell culture studies, by showing that Lcn2 induced high mobility group box 1 (HMGB1) secretion from brain endothelial cells. Since HMGB1 has previously been found to induce NLRP3 activation, it is possible that Lcn2 may indirectly promote NLRP3 activation via inducing HMGB1 (Mondal et al., 2020). This potential mechanism requires further direct confirmation in future studies.

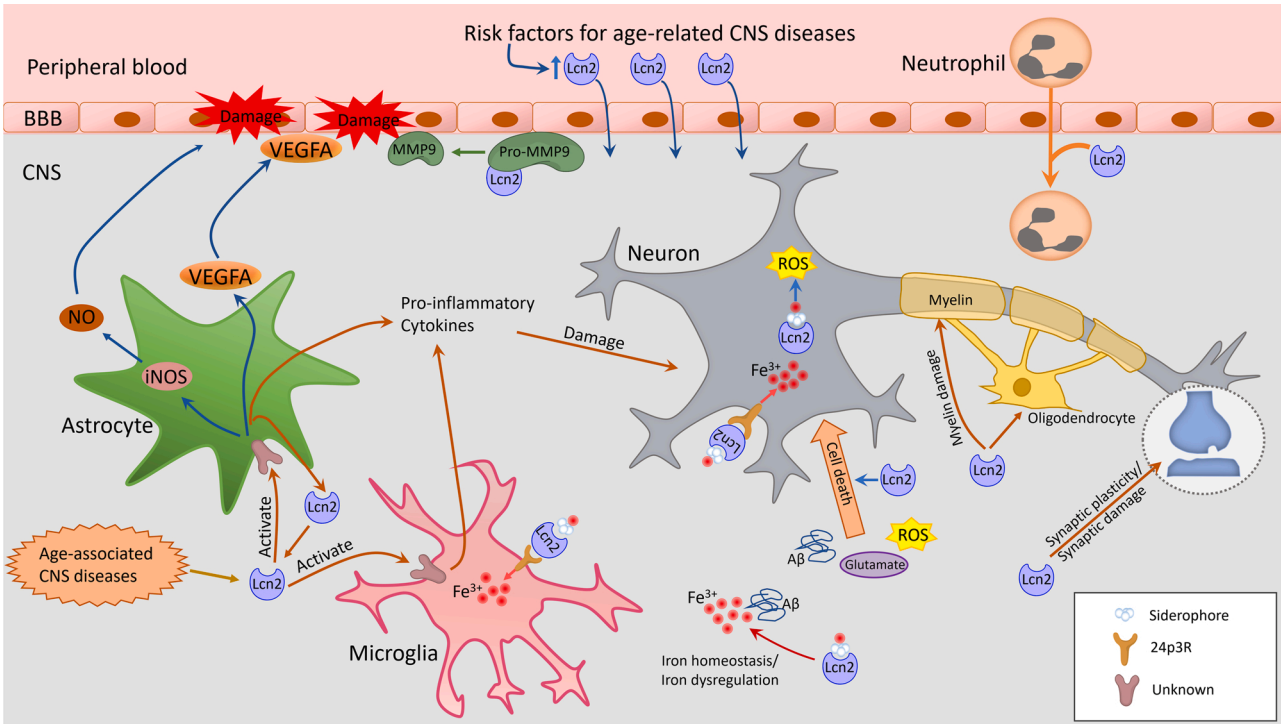

Fig. 2. The neurobiological functions of Lcn2. Lcn2 may exert various neurotoxic and neuroprotective effects in the brain, which may depend on the specific CNS disease and disease stage that is studied. The effects of Lcn2 on e.g. neuronal survival/death, neuroinflammation, neutrophil infiltration, brain iron metabolism, blood-brain barrier (BBB) disruption and white matter damage (and additional effects as described in Chapter 3 of this review) may play a role in multiple CNS disorders, such as AD, PD, VaD, stroke-induced brain injury, FTLD, ALS and MS. It is important to note that of all the different pathological processes in which Lcn2 can be involved, many are interconnected. For example, iron metabolism, neuroinflammation and oxidative stress are intertwined processes. As such, it is likely that effects of Lcn2 on one process may be accompanied by changes in other processes as well. In addition, it may be likely that Lcn2-induced cell damage and cell death are often the result of multiple actions of Lcn2 combined (e.g. a combination of Lcn2-induced iron dysregulation, neuroinflammation and oxidative stress).

3.2.2. Cell death

Death of brain cells occurs in neurodegenerative diseases, as well as in CNS injury. Lcn2 sensitizes different brain cell types (including neurons, astrocytes and microglia, and possibly infiltrating cell types such as neutrophils) to cell death (Bhusal et al., 2019a; Bi et al., 2013; Chen et al., 2020; Jang et al., 2013a, 2013b; Jin et al., 2014b, 2014a; Kim et al., 2016, 2017; Lee et al., 2007, 2012; Liu et al., 2011d; Mao et al., 2016; Mesquita et al., 2014; Mike et al., 2019; Naudé et al., 2012; Ni et al., 2015; Ojeda-Juárez et al., 2020; Peng et al., 2020; Petrozziello et al., 2020; Rathore et al., 2011; Shin et al., 2021; Wang et al., 2015a; Zhang et al., 2021). Lcn2 may reduce the survival of at least certain cell types when iron-free Lcn2 is taken up by (24p3R expressing) cells, after which Lcn2 binds intracellular iron and mediates the export of iron from the cell (Devireddy et al., 2005). This Lcn2-mediated cellular iron deprivation was found to induce expression of the pro-apoptotic protein BCL2-interacting mediator of cell death (BIM) in different cell types (including astrocytes, neurons and hematopoietic cell types), leading to apoptotic cell death (Devireddy et al., 2005, 2001; Lee et al., 2012, 2009). However, other studies indicated that induction of BIM is not always required for Lcn2-mediated cell death (Lee et al., 2007; Naudé et al., 2012). As such, it is likely that Lcn2 may mediate sensitization to cell death in multiple ways. For example, besides inducing cellular iron deprivation, Lcn2 may also affect cell viability by promoting pro-inflammatory glial activation and secretion of pro-inflammatory cytokines, and via inhibiting certain protective signaling pathways (such as signaling via tumor necrosis factor receptor 2 (TNFR2) (Naudé et al., 2012)). Moreover, while Lcn2 may induce apoptosis in certain cell types by exporting iron, Lcn2 may also promote cell death in certain cells types by inducing cellular iron accumulation (Ni et al., 2015; Xu et al., 2012).

Interestingly, some contradictory findings have been reported regarding the pro-apoptotic effects of Lcn2 on brain cells. Firstly, disagreement exists whether Lcn2 is able to induce cell death by itself, or whether Lcn2 only sensitizes cells to cell death in the presence of other inflammatory or toxic stimuli, such as TNF-α, glutamate, nitric oxide, hydrogen peroxide or Aβ. While different studies suggest the latter (Lee et al., 2012, 2009, 2007; Mesquita et al., 2014; Naudé et al., 2012), Lcn2 was found to induce significant toxic effects on its own in other studies (Bi et al., 2013; Kim et al., 2016, 2017; Wang et al., 2015a). Secondly, some inconsistent findings have been reported concerning the brain cell types that are sensitive to Lcn2-mediated toxicity. One study concluded that Lcn2 affects the viability of neurons and not that of glia (Bi et al., 2013), while other studies found that Lcn2 can also sensitize astrocytes and microglia to cell death (Lee et al., 2009, 2007; Mesquita et al., 2014; Mike et al., 2019). These differences might depend on whether studies were performed *in vitro* or *in vivo*, and on the specific toxic factors that were present (e.g. TAR DNA-binding protein 43 (TDP-43) or Aβ). Lastly, while most studies indicate that Lcn2 exerts cytotoxic effects, one study reported that Lcn2 may be secreted by endangered neurons as a 'help-me' signal upon oxygen-glucose deprivation. Increased Lcn2 levels subsequently stimulate glia to adopt a pro-recovery phenotype, resulting in neuroprotection and a decrease in neuronal cell death (Xing et al., 2014). Hence, it should be taken into account that Lcn2 may induce neuroprotective effects in certain situations. Lcn2 may also not exert toxic or protective effects: no effect of Lcn2 on cell death was found in a mouse model of neuroinflammation-induced cerebellar degeneration (Lattke et al., 2017).

3.2.3. Iron dysregulation

Dysregulation and accumulation of iron is found in many neurodegenerative diseases and types of CNS damage and may significantly contribute to CNS injury. For example, free iron can increase oxidative

stress (via the Fenton reaction), induce ferroptosis and promote aggregation of pathogenic proteins such as Aβ (Belaidi and Bush, 2016; Golts et al., 2002; Hagemeier et al., 2012; Li et al., 2010; Liu et al., 2011a; Petrova et al., 2016; Stockwell et al., 2017; Telling et al., 2017). Lcn2 is involved in the regulation of iron homeostasis, and is able to mediate both import and export of iron into and out of cells (Devireddy et al., 2005). Absence of Lcn2 in healthy unchallenged Lcn2 KO mice appeared to cause intracellular iron accumulation in certain cell types, including macrophages, hippocampal neurons and neural stem cells (Dekens et al., 2018; Ferreira et al., 2018a; Nairz et al., 2009, 2015). Thus, the complete absence of Lcn2 may induce accumulation of intracellular iron in certain cell types. On the other hand, elevated Lcn2 levels in different CNS conditions may promote iron accumulation as well. For example, it was suggested that Lcn2 contributes to kainic acid-induced hippocampal iron accumulation in mice (Shin et al., 2021). In addition, we recently found increased hippocampal iron accumulation (especially in plaques and hippocampal pyramidal and granular neurons) in a transgenic AD mouse model as compared to wildtype (WT) mice, while the lack of Lcn2 significantly decreased this AD-related hippocampal iron accumulation (Dekens et al., 2018). This finding also seems to correspond with *in vitro* data, in which WT astrocytes presented increased ferritin mRNA expression upon Aβ-treatment (indicating elevated iron storage facilities, possibly resulting in iron accumulation), whereas Lcn2 KO astrocytes did not (Mesquita et al., 2014). However, it was reported that these effects of Lcn2 on astrocytic ferritin mRNA expression may not translate to the protein level (Dekens et al., 2020). This indicates that Lcn2 might not mediate significant iron accumulation in astrocytes, but preferably in other brain cell types (possibly including neurons and microglia) and structures such as Aβ plaques. Further support for Lcn2-mediated brain iron accumulation under pathological CNS conditions comes from findings in a mouse model of intracerebral hemorrhage. In this mouse model, the upregulation of ferritin upon hemorrhage was lower in Lcn2 KO mice as compared to WT mice, indicating less iron accumulation in Lcn2 KO mice (Ni et al., 2015). Moreover, intranigral iron administration aggravated Lcn2-induced loss of dopaminergic neurons in the substantia nigra, while administration of an iron chelator reduced Lcn2-induced cell death (Kim et al., 2016). These findings support the possibility that intracellular iron accumulation is an important mechanism involved in Lcn2-mediated loss of dopaminergic neurons (Kim et al., 2016). In addition, in a mouse model of ischemic stroke, increasing Lcn2 levels in the brain were paralleled by cellular iron accumulation, which appeared to occur mostly in macrophages/microglia (Hochmeister et al., 2016). Another notable finding is that CSF Lcn2 levels were found to correlate with CSF transferrin levels and with iron accumulation in the basal ganglia in clinically stable MS patients (Khalil et al., 2016).

In summary, it appears that iron dysregulation might occur both when Lcn2 is completely absent (in Lcn2 KO mice) and when Lcn2 production is increased, as is the case in several CNS conditions. While several findings indicate that high Lcn2 levels may increase cellular iron accumulation, it is important to note that this effect may be cell type- and disease-specific. It is possible that Lcn2 promotes pathological iron accumulation in certain cell types, and at the same time mediates iron export and iron deprivation in other cell types (which might e.g. depend on the relative expression of Lcn2 receptors). Both iron accumulation and iron deficiency in cells can have significant pathological effects, including induction of inflammatory changes, oxidative stress and cell death. Thus, Lcn2-mediated iron dysregulation may have profound effects on cellular health and viability, potentially via promoting both cellular iron accumulation and iron deprivation, depending on the specific cell type (Devireddy et al., 2005; Ferreira et al., 2018a; Kim et al., 2016; Lee et al., 2009; Ni et al., 2015; Xu et al., 2012).

3.2.4. Blood-brain barrier (BBB) disruption

BBB disruption may play an important role in different CNS injuries and diseases including AD and PD (Carvey et al., 2009; Sweeney et al., 2018). Lcn2 was found to aggravate BBB disruption in mouse models of ischemic and hemorrhagic stroke (Egashira et al., 2016; Jin et al., 2014b; Kim et al., 2017; Mao et al., 2016; Ni et al., 2015; Toyota et al., 2019). Moreover, neutralization of Lcn2 with a monoclonal antibody against Lcn2 reduced BBB leakage in a mouse model of stroke reperfusion injury (Wang et al., 2020). Lcn2 was also found to contribute to kainic acid-induced BBB leakage in the hippocampus (Shin et al., 2021). The mechanisms underlying this effect of Lcn2 may include Lcn2-mediated induction of vascular endothelial growth factor A (VEGFA) (Kim et al., 2017), which has been implicated in BBB disruption. Another possibility is that the interaction of Lcn2 with MMP-9 is involved in Lcn2-mediated BBB damage. Namely, MMP-9 can contribute significantly to BBB damage in several CNS conditions (Rempe et al., 2016; Turner and Sharp, 2016; Weekman and Wilcock, 2016). Lcn2 may enhance MMP9′ s damaging effect to the BBB since Lcn2 protects MMP-9 from degradation and may prolong its activity (Weng and Chou, 2014). In addition, Lcn2 was shown to reduce the levels of the tight junction proteins claudin-5 and zonula occludens-1 in cultured brain endothelial cells (Mondal et al., 2020). As such, this may present another pathway via which Lcn2 could impair BBB integrity. Contrastingly, in another recent study with brain endothelial cells, treatment with TNF-α caused increased endothelial permeability, which was rescued by Lcn2 (Du et al., 2019). Moreover, Lcn2 was found to restore the membrane distribution of zonula occludens-1 and the adherens junction protein VE-cadherin (Du et al., 2019). The reasons for these conflicting cell culture experimental results remain to be clarified.

3.2.5. Induction of inducible nitric oxide synthase (iNOS) and nitric oxide (NO)

Lcn2 was found to promote synthesis of inducible nitric oxide synthase (iNOS) and nitric oxide (NO) upon LPS injection and spinal cord injury in mice, and in LPS-stimulated astrocyte cultures (Jang et al., 2013b, 2013a; Lee et al., 2009; Rathore et al., 2011). Lcn2-mediated induction of iNOS and NO may be a potential mechanism via which Lcn2 can contribute to both neuroinflammatory and pro- and anti-apoptotic signaling pathways (and possibly BBB disruption) (Calabrese et al., 2007; Olivera et al., 2016; Parathath et al., 2006; Yuste et al., 2015).

3.2.6. White matter damage

White matter damage occurs in many brain disorders and is known to play a significant role in cognitive decline and dementia (Mascalchi, 2005; Wang et al., 2016; Zhang et al., 2009). In mouse models of ischemic and hemorrhagic stroke, spinal cord injury and MS, Lcn2 was found to significantly aggravate the myelin loss that occurs in these models (Egashira et al., 2016, 2014; Kim et al., 2017; Nam et al., 2014; Rathore et al., 2011; Toyota et al., 2019). Accordingly, Lcn2 was reported to exacerbate axonal damage after subarachnoid hemorrhage, possibly due to loss of protective myelin (Egashira et al., 2014). In addition, Lcn2 inhibited myelination in neuroglial co-cultures (Al Nimer et al., 2016). The importance Lcn2′s role in white matter damage was further shown in a study with mouse models of subarachnoid hemorrhage and MS. Inhibition of Lcn2 using small interfering RNA resulted in increased oligodendrocyte differentiation and remyelination of the damaged white matter (Li et al., 2020).

3.2.7. Synaptic impairment

Synaptic impairment occurs early on in different CNS conditions (Forner et al., 2017; Hofmeijer and van Putten, 2012; Schirinzi et al., 2016; Stein et al., 2015), and it is possible that increased Lcn2 levels may affect synaptic and neuronal functioning. Lcn2 was proposed to act as a 'help-me' signal upon oxygen-glucose deprivation in a study by Xing et al., 2014 (Xing et al., 2014). In this study, conditioned media of Lcn2-treated glia had protective effects on neurons, and induced the neuronal expression of different synaptic markers (including synaptotagmin, synaptophysin and post-synaptic density 95) (Xing et al., 2014).

This finding may indicate that Lcn2 activates astrocyte derived factors with a protective effect on synapses. However, findings from Staurenghi and colleagues (Staurenghi et al., 2020) showed that increased Lcn2 in conditioned media from oxysterol treated astrocytes, mediated a reduction in the number of dendritic spines, complexity of neurites and post-synaptic density in primary neurons. Also, in a mouse model of HIV-associated brain injury, absence of Lcn2 protected to a large extent against loss of dendrites and presynaptic terminals in the cortex and hippocampus, indicating that Lcn2 may contribute to synaptic impairment (Ojeda-Juárez et al., 2020). Furthermore, exposure of cultured hippocampal neurons to Lcn2 reduced the mobility of actin in dendritic spines, caused retraction of mushroom spines, and inhibited spine maturation (Mucha et al., 2011). Interestingly, it appeared that iron-free Lcn2 (rather than iron-bound Lcn2) was especially potent in inducing these effects (Mucha et al., 2011). Accordingly, it was shown that Lcn2 KO mice had a higher spine density in the hippocampus and basolateral amygdala as compared to WT control mice, in a mouse model of psychological stress (which induced Lcn2 upregulation in the brains of WT mice). Corresponding with this higher spine density, neurons from the hippocampus and amygdala of Lcn2 KO mice were more excitable and fired more action potentials than WT neurons (Mucha et al., 2011; Skrzypiec et al., 2013). These findings indicate that Lcn2 may play an important physiological role in spine elimination in the hippocampus and amygdala. As such, Lcn2 is potentially involved in controlling and adapting behavior (including anxiety) under basic physiological conditions and in response to stimuli such as psychological stress (Mucha et al., 2011; Skrzypiec et al., 2013). Of note, it was reported that healthy unchallenged Lcn2 KO mice present reduced long-term potentiation in the dorsal hippocampus (Ferreira et al., 2013). In addition, it was suggested that abnormally low Lcn2 levels may impair synaptic function in the hippocampus, which could be resolved by normalization of Lcn2 expression levels (Noh et al., 2019). The potential protective (e.g. via promoting specific glial pro-recovery phenotypes) and/or damaging (e.g. via excessive spine elimination) effects on synapses by increased Lcn2 levels in different CNS conditions should be explored further in future studies.

3.2.8. Defects in neurogenesis

Adult neurogenesis is impaired in different CNS conditions including AD and PD (Rodríguez and Verkhratsky, 2011; Tobin et al., 2014; Winner and Winkler, 2015). Studies have investigated the role of Lcn2 in adult neurogenesis in WT and Lcn2 KO mice under basal physiological conditions. Firstly, it was found that absence of Lcn2 in Lcn2 KO mice caused a G0/G1 cell cycle arrest in neural stem cells, resulting in deficits in the proliferation, differentiation and maturation of neural stem/-progenitor cells (Ferreira et al., 2018a). The cell cycle arrest in Lcn2 KO neural stem cells was likely due to intracellular iron accumulation and oxidative stress (Ferreira et al., 2018a). Secondly, it was recently found that neurogenesis is impaired in neuronal growth regulator 1 (Negr1) deficient mice. These mice present significantly decreased basal hippocampal Lcn2 expression levels, as compared to WT mice (Noh et al., 2019). Notably, adeno-associated viral vector-mediated normalization of hippocampal Lcn2 expression levels rescued the problems in hippocampal neurogenesis in these mice (Noh et al., 2019). The results from these studies indicate that normal physiological levels of Lcn2 are important for successful adult neurogenesis (Ferreira et al., 2018a;b). Interestingly, a recent report confirmed the previous findings, and in addition indicated that voluntary running could rescue the impaired neurogenesis seen in Lcn2 KO mice, by stimulating the generation, proliferation and survival of newborn neurons (Ferreira et al., 2019). Whether increased (as against absent/abnormally low) Lcn2 levels in CNS disorders may (positively or negatively) affect adult neurogenesis as well requires further investigation.

3.2.9. Oxidative stress

Oxidative stress plays a common role in many CNS conditions (Kim et al., 2015; Rodrigo et al., 2013). Emerging evidence suggests that Lcn2 may be involved in processes related to oxidative stress. It was shown that reactive iron accumulated in neural stem cells in Lcn2 KO mice, causing an increase in oxidative stress (Ferreira et al., 2018a;b). Besides absence of Lcn2, it is plausible to speculate that increased Lcn2 levels (as observed in different CNS conditions) can contribute to oxidative stress as well, for example via promoting iron accumulation. Indeed, Lcn2 appeared to be involved in the induction of oxidative stress, in the hippocampus of kainic acid-treated mice (Shin et al., 2021). Interestingly, in rat primary cardiomyocytes it was found that iron-bound Lcn2 increased generation of mitochondrial reactive oxygen species (ROS), which relied strongly on the siderophore component present in iron-bound Lcn2 and not on Lcn2 alone (Song et al., 2018). Conversely, Lcn2 was found to have significant anti-oxidant properties in the liver of LPS-treated mice and in different peripheral cell lines, potentially in part by inducing the expression of heme oxygenase 1 (HO-1) (Bahmani et al., 2010; Mesquita et al., 2014; Roudkenar et al., 2011, 2008; Srinivasan et al., 2012; Yamada et al., 2016). Hence, it appears that Lcn2 may exert both anti- and pro-oxidant effects in the periphery, which might also be the case in the CNS. A recent study showed that the interaction between Lcn2 and its iron-loaded siderophores caused a conformational shift of the protein structure towards an unfolded state, which facilitated cellular accumulation of ROS (Huang et al., 2020). Therefore, changes to the protein structure of Lcn2 may in part contribute to its effects on ROS generation.

3.2.10. Other effects: Mitochondrial dysfunction, defects in autophagy and insulin resistance

Results from studies with non-CNS tissue suggest that Lcn2 may be involved in other important mechanisms, which may also play an important role in different CNS disorders. For example, it has been suggested that Lcn2 affects mitochondrial functioning, autophagy and insulin sensitivity. Dysregulation in all these processes play a role in various neurodegenerative diseases and CNS injury (Aviles-Olmos et al., 2013; Chen et al., 2014b; de la Monte et al., 2009; Deng et al., 2017; Hroudová et al., 2014; Johri and Beal, 2012; Li and Gao, 2017; Wong and Cuervo, 2010). Also here differential effects of Lcn2 have been observed: evidence exists for both protective and detrimental effects of Lcn2 on mitochondrial function (Asimakopoulou et al., 2017, 2016; Chella Krishnan et al., 2019; Song et al., 2018; Xu et al., 2012; Zhang et al., 2014) and autophagy (Chan et al., 2016; Jin et al., 2011; Qiu et al., 2018; Sung et al., 2017; Toyonaga et al., 2016; Zhang et al., 2018c). Similarly, differential effects of Lcn2 have been reported with regard to energy metabolism. Several studies have reported that Lcn2 can dysregulate energy metabolism, for instance by promoting insulin resistance and decreasing glucose tolerance (Chan et al., 2016; Chella Krishnan et al., 2019; Ishii et al., 2017; Kamble et al., 2016; Law et al., 2010; Moschen et al., 2017; Principi et al., 2018; Yan et al., 2007). However, other investigations showed beneficial effects of Lcn2 on insulin sensitivity and glucose tolerance (Deis et al., 2019; Guo et al., 2010; Mosialou et al., 2017), and yet other studies did not observe a significant role for Lcn2 in metabolic disturbances (Feng et al., 2019; Jun et al., 2011; Liu et al., 2011c; Wallenius et al., 2011).

3.2.11. Neurobiological effects of Lcn2 on cognitive, behavioral and neuropsychiatric changes

Considering the various neurobiological functions of Lcn2 described above, it could be expected that the effects of Lcn2 at the molecular/cellular level may ultimately give rise to changes at the functional level. Indeed, data shows that the effects of Lcn2 reach up to the level of cognition and behavior: both absence and excess of Lcn2 have been linked with cognitive, behavioral and neuropsychiatric changes. Regarding cognitive functioning, elevated Lcn2 levels were found to correlate with the exacerbation of memory impairment in mouse models of VaD, sepsis, diabetes/diabetic encephalopathy and SLE (Bhusal et al., 2019a; Jang et al., 2013b; Kim et al., 2017; Mike et al., 2019;

Pinyopornpanish et al., 2019), and were correlated with impaired cognitive functioning in other studies (Bawa et al., 2020; Choi et al., 2011; Eruysal et al., 2019; Gouweleeuw et al., 2016, 2017; Naudé et al., 2014a). However, no differences in working memory and long-term hippocampus-dependent memory functioning were found between AD mice and Lcn2-deficient AD mice (Dekens et al., 2018). Of note, while increased Lcn2 levels may promote memory impairment in at least certain models of CNS disorders, it has appeared that – under basal physiological conditions – complete absence of Lcn2 may disturb memory as well. It was shown that unchallenged Lcn2 KO mice under basal physiological conditions may present mild memory problems (Dekens et al., 2018; Ferreira et al., 2018a, 2013). However, other studies showed that unchallenged WT and Lcn2 KO mice performed at the same level (Dekens et al., 2018; Jang et al., 2013b; Kim et al., 2017). These differences in outcome may amongst others, depend on the specific cognitive tests that were used, and the age of the studied mice; as we suggested recently, it might be that cognitive problems in (unchallenged) younger Lcn2 KO mice may diminish with age (Dekens et al., 2018). In addition, the housing conditions (e.g. access to a running wheel) may be of influence herein: voluntary running was described to rescue cognitive and behavioral problems observed in Lcn2 KO mice (Ferreira et al., 2019).

Lcn2 can also affect neuropsychiatric changes that often accompany CNS disorders, such as anxiety and depression (Cerejeira et al., 2012; Gallagher and Schrag, 2012). Lcn2 KO mice were shown to display anxiety-like behavior under unchallenged control conditions as well as upon psychological stress (Ferreira et al., 2019, 2013; Kang et al., 2018; Mucha et al., 2011; Skrzypiec et al., 2013). This may be due to a lack in Lcn2-mediated spine deletion in Lcn2 KO mice (resulting in a higher spine density and increased neuronal excitability) in the hippocampus and amygdala (Ferreira et al., 2019, 2013; Mucha et al., 2011; Skrzypiec et al., 2013). Lcn2 KO mice were also found to have increased basal circulating corticosterone levels (Ferreira et al., 2013). Interestingly, although young Lcn2 KO mice (2–3 months old) were reported to present anxiety-like behavior under control conditions, no anxiety-like behavior was found in older Lcn2 KO mice (12 months old) (Dekens et al., 2018; Ferreira et al., 2019, 2013). This finding poses the possibility that behavioral differences in unchallenged Lcn2 KO mice may normalize with increasing age (Dekens et al., 2018). Notably, anxiety-like behavior was also found in young (2–3 months old) Negr1 deficient mice, which present strongly decreased basal hippocampal Lcn2 expression levels, as compared to WT mice (Noh et al., 2019). Adeno-associated viral vector-mediated normalization of hippocampal Lcn2 expression levels rescued the anxiety-like behavior in Negr1 deficient mice, indicating that abnormally low Lcn2 expression is causally involved in anxiety-like behavior under basic, unchallenged conditions (at least in young mice) (Noh et al., 2019). Besides anxiety-like behavior, low/absent Lcn2 levels have also been linked to depressive-like behavior. Lcn2 KO mice at 2–3 months of age were reported to display depressive-like behavior, when tested in the forced-swim test (Ferreira et al., 2013). Correspondingly, 2–3-month-old Negr1 deficient mice (in which hippocampal Lcn2 levels are significantly reduced as compared to WT mice) presented depressive-like behavior in the forced-swim test and tail suspension test, which could be rescued by normalization of hippocampal Lcn2 expression levels (Noh et al., 2019). In contrast, Lcn2 KO mice of 7 months old that were tested in the saccharin-preference test did not show a decreased preference for saccharin water, indicating no depressive-like anhedonia in Lcn2 KO mice as compared to WT mice (Mike et al., 2019). Additionally, another recent study found a minimal, non-significant increase in depressive-like behavior in unchallenged and LPS challenged adult Lcn2 KO mice as compared to WT mice (adult, exact age unknown) (Vichaya et al., 2019). Altogether, it might again be possible that young and older Lcn2 KO mice may differ in behavior, with depressive-like behavior subsiding with increasing age. However, to confirm this it would be essential to test young and old Lcn2 KO mice simultaneously, in exactly the same experimental set-ups. While the absence of Lcn2 may affect depressive-like behavior, increased Lcn2 levels have been associated with depression as well (Gouweleeuw et al., 2016; Mike et al., 2019; Naudé et al., 2015a,b, 2013; Naudé et al., 2014b). In humans, increased Lcn2 levels in serum and plasma have been associated with symptoms of depression (Naudé et al., 2015a,b, 2013; Naudé et al., 2014b). Also, it was found that hippocampal Lcn2 levels are significantly increased in AD patients with co-existing depression as compared to AD patients without depression (Dekens et al., 2017).

The effects of Lcn2 can also reach up to the level of locomotor functioning. Increased Lcn2 levels were associated with abnormal locomotor behavior (including disturbed locomotor activity and coordination) in a mouse model of PD, as well as in a mouse model of SLE (Kim et al., 2016; Mike et al., 2019).

The effects of Lcn2 found at the cognitive and behavioral level are likely the result of various neurobiological effects of Lcn2, which combined together can culminate into effects that reach up to the functional level. In this regard, it is important to note that although different neurobiological functions of Lcn2 were described separately in this chapter, many of the described functions are intertwined. For example, neuroinflammation and iron metabolism are known to be interconnected processes. As such, it is possible that certain effects of Lcn2 on iron metabolism may indirectly affect neuroinflammation as well, and vice versa. Similarly, the effects of Lcn2 on cell death may often not be due to a single effect of Lcn2 (e.g. solely iron metabolism), but may rather be the consequence of various interconnected effects of Lcn2 (e.g. iron metabolism, oxidative stress and neuroinflammation).

The absence as well as overexpression of Lcn2 may induce changes in different mechanisms (such as energy metabolism and iron metabolism), thereby affecting behavior and cognition. Thus, it appears that certain physiological processes depend on Lcn2 levels following an inverted U-shaped curve, with both absence and overexpression of Lcn2 resulting in the disruption of these processes. This characteristic of Lcn2 is comparable to other known inflammatory cytokines, including IL-1β, TNF-α and interleukin 6 (IL-6) (Gouweleeuw et al., 2015; McAfoose and Baune, 2009; Pollmächer et al., 2002).

In conclusion, Lcn2 production is upregulated in different CNS diseases and injuries, in human patients as well as in animal models for these CNS conditions. *in vitro* and animal studies have shown that Lcn2 may strongly influence several pathological processes (including neuroinflammation and cell death). Moreover, the effects of Lcn2 may reach up to the level of overall disease outcome/prognosis, behavior and cognition. Although the functions and effects of Lcn2 in the healthy and diseased brain are not fully understood or predictable yet, it is clear that elevated levels of Lcn2 may significantly contribute to neuropathological processes in different age-related CNS conditions, including AD, PD and VaD.

4. The expression and effects of Lcn2 in risk factor conditions for age-related CNS diseases – could Lcn2 be a link between risk conditions and CNS disease?

Besides the increased Lcn2 production in multiple age-related CNS diseases, mounting evidence shows that Lcn2 levels are also increased in several risk factor conditions (including for example ageing, unhealthy lifestyle and chronic inflammatory diseases) for age-related CNS diseases. This chapter explores the possibility that Lcn2 is a biological link between risk factor conditions and the development of different age-related CNS disorders, such as AD, PD and VaD. To this end, we discuss several risk factor conditions in which Lcn2 may play a role (Fig. 3). It should be noted that direct evidence for Lcn2 as a link between risk factor conditions and pathogenesis of age-related CNS diseases is lacking, which will also be emphasized in Chapter 4.2.

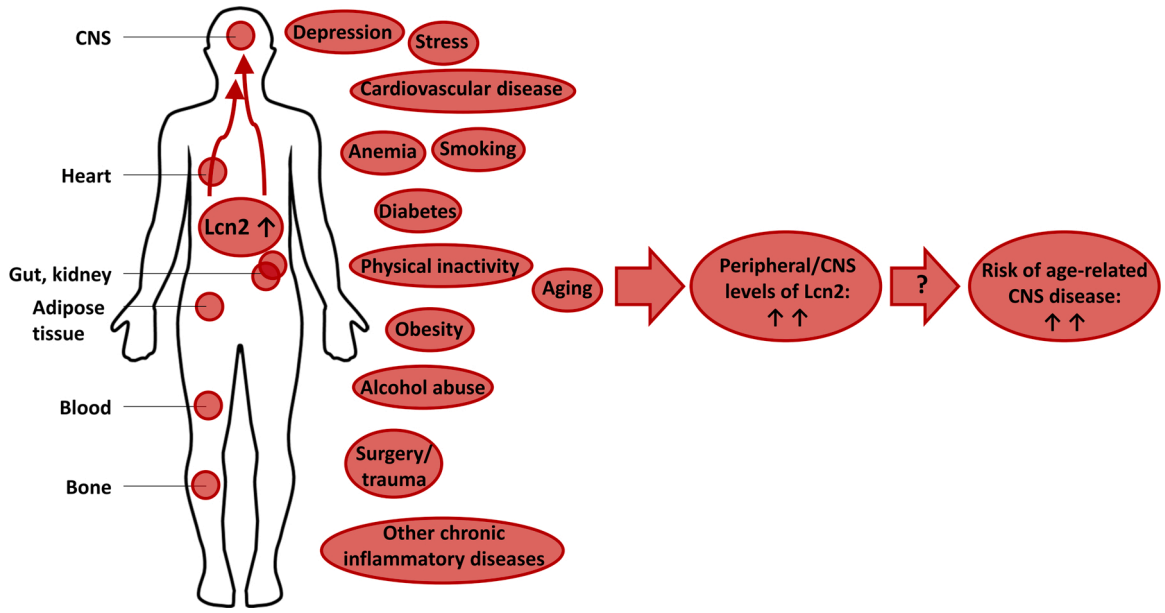

Fig. 3. Increasing Lcn2 levels during ageing and risk factor conditions as potential contributor to the development of age-related brain diseases. Lcn2 levels increase in the periphery and CNS during ageing and several other risk factor conditions for age-related CNS disorders. These risk factor conditions include for example physical inactivity and other unhealthy lifestyle factors, and different chronic inflammatory and metabolic diseases such as diabetes and obesity. Lcn2 levels can be expressed in various peripheral tissues such as bone, adipose tissue, kidneys, gut, heart, blood vessels and the blood, depending on the present risk factor condition(s). Moreover, CNS Lcn2 levels were also found to increase in certain risk factor conditions, such as depression, chronic stress, unhealthy diet, obesity and surgery. Findings from studies indicate that increased CNS Lcn2 levels in risk factor conditions may originate both from peripherally produced Lcn2 that crosses the BBB, as well as from *de novo* Lcn2 production in the CNS itself. We hypothesize that rising/chronically elevated Lcn2 levels in the periphery and brain during ageing and risk factor conditions may gradually drive the brain into a primed inflammatory and sensitive state, which may contribute to the development of different age-related CNS diseases, such as AD, PD and VaD.

4.1. The expression and effects of Lcn2 in risk factor conditions for age-related CNS diseases

4.1.1. Ageing

Ageing is the major risk factor for the CNS conditions discussed here (Livingston et al., 2017; Reeve et al., 2014). Ageing is characterized by a chronic low-grade inflammatory state, termed inflammageing (Franceschi and Campisi, 2014). Interestingly, in accordance with the phenomenon of inflammageing, Lcn2 levels in blood were found to increase with age in different human cohorts (Giaginis et al., 2010; Lim et al., 2015; Naudé et al., 2013; Wang et al., 2007; Wu et al., 2014a; Xiao et al., 2013). In mice, serum Lcn2 levels were reported to increase significantly when comparing 2 months versus 12 months old mice (Meyers et al., 2020). Notably, in the mouse brain, Lcn2 mRNA expression levels were found to rise with age (when comparing 4.5 months versus 26.5 months old mice) (Sharman et al., 2007). In addition, Lcn2 mRNA and protein levels increased in the rat midbrain with advancing age (when comparing 2, 6, 18 and 28 months old rats) (Wang et al., 2019a). Further studies are required to confirm age-related upregulation of Lcn2 mRNA and protein levels in the body and brain. This age-related rise in Lcn2 expression levels would correspond with the chronic low-grade inflammatory state that gradually develops with increasing age.

4.1.2. Depression

Depression is a risk factor for many CNS conditions including AD, PD and VaD (Diniz et al., 2013; Fang et al., 2010; Gustafsson et al., 2015; Livingston et al., 2017; Ownby et al., 2006; Schuurman et al., 2002; Wang et al., 2018). Increased Lcn2 levels in plasma were found to be associated with depression in older persons ($\geq$ 60 years of age), independent of age, sex, use of anti-inflammatory drugs and lifestyle factors (Naudé et al., 2013). People with a recurrent depression had higher plasma Lcn2 levels than subjects with a first episode (Naudé et al., 2013), and Lcn2 levels were especially increased in depressed persons with a higher waist circumference (Marijnissen et al., 2014). Notably, higher plasma Lcn2 concentrations in depressed subjects were associated with the sex-specific impairment of specific cognitive functions (Naudé et al., 2014a). In women, higher Lcn2 levels were associated with impaired verbal memory and lower processing speed. In men, higher Lcn2 levels were associated with worse interference control (Naudé et al., 2014a). Plasma Lcn2 levels in male rats were also associated with depressive-like behavior and cognitive dysfunction (Gouweleeuw et al., 2016). Of note, depression is a frequently observed co-morbidity in other diseases such as heart failure and AD, and is known to worsen the prognosis of these diseases (Byers and Yaffe, 2011; Gouweleeuw et al., 2015; Hsiao and Teng, 2013; Muliyala and Varghese, 2010). In this regard, interestingly, depression and depression scores in heart failure patients were associated with increased serum Lcn2 levels (Gouweleeuw et al., 2015; Naudé et al., 2015a,b; Naudé et al., 2014b). Moreover, depression in AD patients was related with increased Lcn2 levels in the hippocampus (and, intriguingly, with decreased Lcn2 levels in certain other brain regions, such as the prefrontal cortex) (Dekens et al., 2017). Hippocampal Lcn2 levels were positively correlated with severity of depressive symptoms in AD patients (Dekens et al., 2017). It remains to be investigated whether Lcn2 levels in the brain are also increased in depressed persons that do not suffer from AD, and whether Lcn2 may play a role in development of depressive symptoms. Studies in mice have suggested that both absence and overexpression of Lcn2 might contribute to development of depressive-like symptoms (Ferreira et al., 2013; Mike et al., 2019). Although other brain regions may be involved as well, the hippocampus has been implicated to play an important role in depression, as well as in the effects of Lcn2 on depressive symptoms. Indeed, Lcn2′s actions in the hippocampus have been previously reported to be involved in depressive and anxiety-like symptoms, in studies comparing WT and Lcn2 KO mice (Ferreira et al., 2018a, 2019; Mucha et al., 2011).

4.1.3. Physical inactivity and osteoporosis

Physical inactivity is associated with an increased risk to develop

age-related CNS disorders including AD, PD and VaD (Livingston et al., 2017; Paillard et al., 2015; Schmidt et al., 2013). Of interest, sedentary behavior was correlated with increased blood Lcn2 levels in humans (Arts et al., 2015; Lim et al., 2015; Naudé et al., 2013; Rucci et al., 2015). For instance, in healthy human participants, bed rest was associated with a time-dependent rise in blood Lcn2 levels (Rucci et al., 2015). Accordingly, exercise (e.g. resistance and endurance training) was associated with decreased plasma Lcn2 concentrations in young men and elderly women (Lim et al., 2015; Moghadasi and Mohammadi Domieh, 2014; Ward et al., 2020). Of note, two clinical studies did not detect an effect of exercise intervention on plasma Lcn2 levels (Choi et al., 2009; Nakai et al., 2021). It appears that the efficacy of exercise interventions may depend strongly on the exact content (e.g. resistance versus endurance training, exercise intensity and frequency) and duration, as well as the characteristics of the participants. In mice it was shown that Lcn2 is a mechanoresponsive protein, with strong induction in bone osteoblasts by mechanical unloading (e.g. by simulated microgravity, tail suspension or muscle paralysis), and lowered expression upon exercise (Capulli et al., 2009; Rucci et al., 2015; Villalvilla et al., 2016). Thus, osteoblasts may be a significant source of Lcn2 in physically inactive persons, due to low mechanical forces on the skeleton. Notably, increased Lcn2 levels in bone may contribute to bone fragility and damage in osteoporotic joints, for instance via reducing osteoblast and chondrocyte viability, interfering with osteoblast differentiation and promoting cartilage breakdown through extending MMP-9 activity (Costa et al., 2013; Gupta et al., 2007; Villalvilla et al., 2016). Moreover, elevated Lcn2 levels are associated with an increased risk of osteoporotic fracture-related hospitalization in elderly women (Lim et al., 2015). Interestingly, physical inactivity is a risk factor for osteoporosis, and osteoporosis – like physical inactivity – has been suggested as a risk factor for dementia (Chang et al., 2014; Chen and Lo, 2017; Downey et al., 2017). All in all, an inactive lifestyle may add to increased production of Lcn2, which may contribute to osteoporosis, and possibly to an increased risk to develop age-related brain disorders.

4.1.4. Obesity and diabetes

Obesity and diabetes increase the risk for many age-related CNS conditions, including AD (which has also been termed type 3 diabetes), PD and VaD (Craft, 2009; de la Monte and Wands, 2008; Zhang and Tian, 2014). Lcn2 has been identified as an adipokine, and a higher body mass index, increased waist circumference and higher body fat content correlate with its elevated blood levels (Auguet et al., 2011; Lee et al., 2010; Lim et al., 2015; Luo et al., 2016; Marijnissen et al., 2014; Moschen et al., 2017; Naudé et al., 2013; Xu et al., 2018). Moreover, increased Lcn2 levels were found in blood and different peripheral tissues (including adipose tissue and liver) of patients with obesity, metabolic syndrome and type 2 diabetes, as well as in animal models thereof (Auguet et al., 2011; Cakal et al., 2011; Catalán et al., 2013, 2009; De Sousa Rodrigues et al., 2019; Elkhidir et al., 2017; Huang et al., 2012; Koiou et al., 2012; Law et al., 2010; Moreno-Navarrete et al., 2010; Moschen et al., 2017; Ni et al., 2013; Song and Kim, 2018; Wang et al., 2007; Wu et al., 2014b; Yan et al., 2007; Yang et al., 2017) (also reviewed by Bhusal et al., 2019 (Bhusal et al., 2019b)). Interestingly, a positive correlation between serum Lcn2 levels and insulin resistance was found in two human studies (Cakal et al., 2011; Wang et al., 2007). Mouse and cell culture studies showed that increased Lcn2 levels could worsen metabolic health, for example by impairing insulin sensitivity and glucose tolerance, promoting inflammation, increasing visceral fat mass, inhibiting brown adipose tissue activity and stimulating appetite (Capulli et al., 2018; Chella Krishnan et al., 2019; Ishii et al., 2017; Kamble et al., 2016; Law et al., 2010; Moschen et al., 2017; Principi et al., 2018; Yan et al., 2007). However, contradictorily, other studies reported beneficial effects of Lcn2 including improved insulin sensitivity and glucose tolerance, improved brown adipose tissue activity and suppressed inflammation, appetite and weight gain (Capulli et al., 2018; Deis et al., 2019; Guo et al., 2010; Meyers et al., 2020; Mosialou et al., 2017; Petropoulou et al., 2020; Zhang et al., 2008, 2014). Moreover, two other studies found no/minimal effects of Lcn2 on metabolic disturbances in obese mice (Feng et al., 2019; Jun et al., 2011). The discrepancy between these study results is not understood yet, but may involve differences in mouse strain, age, sex and diet. The harmful versus beneficial effects of Lcn2 in obesity and diabetes require further elucidation. In case Lcn2 would aggravate insulin resistance and weight gain, this may be a potential important mechanism via which Lcn2 could contribute to the development of age-related CNS conditions. However, also if Lcn2 does not significantly promote obesity and diabetes, its elevated levels in these conditions might still provoke other pathological processes, which could contribute to the elevated risk to develop CNS disorders. Of interest, Lcn2 expression was also found to be increased in the hippocampus, in mouse models of obesity, mice that were fed a high-fat high-fructose diet, and different mouse models of diabetes (Bhusal et al., 2019a; de Sousa Rodrigues et al., 2017; Jeon et al., 2016; Jin et al., 2020; Kim et al., 2018). In one mouse model for diabetes, Lcn2 was shown to contribute significantly to multiple aspects of diabetic encephalopathy, including neuroinflammation and neuron loss in the hippocampus, and cognitive decline (Bhusal et al., 2019a). Obesity and diabetes may thus trigger neuroinflammatory processes in the brain including upregulation of Lcn2, and thereby allow Lcn2 to prime the brain.

4.1.5. Cardiovascular diseases

Cardiovascular diseases, including for example myocardial infarction and heart failure, are age-related conditions, and increase the risk of different age-related CNS disorders (including AD and VaD) (de Bruijn and Ikram, 2014; Gorelick, 2004; North and Sinclair, 2012). Lcn2 levels were found to be increased in blood and myocardial tissue after acute myocardial infarction, as well as in patients with various other cardiovascular diseases (Choi et al., 2008; Eilenberg et al., 2019, 2017; Gouweleeuw et al., 2015; Li et al., 2019a; Marques et al., 2017; Peng et al., 2019; Sivalingam et al., 2017; Wong et al., 2018; Wu et al., 2014a; Xiao et al., 2013; Yang et al., 2017; Yndestad et al., 2009). Of interest, plasma Lcn2 levels were shown to be valuable for predicting 28-day mortality as well as neurological outcome after cardiac arrest (Lee et al., 2019). Corresponding to clinical findings, elevated Lcn2 levels were observed in animal models of cardiovascular disease (Gouweleeuw et al., 2015; Marques et al., 2017; Martínez-Martínez et al., 2017). Although there are many factors that can trigger Lcn2 expression, its induction by mineralocorticoid receptor activation may be of particular interest in this regard, since mineralocorticoid receptor activation is well-known to provoke deleterious effects on the cardiovascular system (Latouche et al., 2012; Tarjus et al., 2015). Mouse and human studies suggest that Lcn2 exacerbates cardiac damage in cardiovascular diseases, for example by promoting cardiomyocyte apoptosis, vascular inflammation, atherosclerosis, vascular fibrosis, cardiac hypertrophy and diastolic dysfunction (Buonafine et al., 2018; Gouweleeuw et al., 2015; Liu et al., 2012; Marques et al., 2017; Martínez-Martínez et al., 2017; Shibata et al., 2020; Song et al., 2017; Sung et al., 2017; Tarjus et al., 2015; Xu et al., 2012; Yang et al., 2016). Moreover, Lcn2 and the Lcn2/MMP-9 complex were suggested to contribute to the instability of atherosclerotic plaques (in part via promoting MMP-9 activity), which increases the risk of cardiovascular events such as coronary thrombosis and myocardial infarction (Amersfoort et al., 2018; Bentzon et al., 2014; Chan et al., 2012; Cheng et al., 2014; Eilenberg et al., 2017; Hemdahl et al., 2006). All in all, Lcn2 levels are increased in cardiovascular diseases and may contribute to cardiovascular pathology, and thereby possibly to the development of several age-related CNS conditions.

4.1.6. Other lifestyle factors

Besides physical inactivity, other lifestyle factors such as smoking, alcohol use and chronic psychological stress have been associated with a higher risk of age-related CNS conditions including AD and VaD (Hemmerle et al., 2012; Livingston et al., 2017; Machado et al., 2014;

Peters et al., 2013; Zhong et al., 2015). All of these factors have also been linked to increased levels of Lcn2 in the circulation (Bchir et al., 2017; Budzynska et al., 2017; Mucha et al., 2011; Naudé et al., 2013; Pereira et al., 2016; Skrzypiec et al., 2013; Stankiewicz et al., 2015; Wang et al., 2017, 2007). Moreover, increased Lcn2 levels were detected in the brain and adipose tissue, upon psychological stress in mice (Mucha et al., 2011; Pereira et al., 2016; Skrzypiec et al., 2013; Stankiewicz et al., 2015; Wang et al., 2007). Of note, while excessive alcohol use has been linked with an increased risk to develop dementia and with increased Lcn2 levels (Bykov et al., 2007; Cai et al., 2016; Sabia et al., 2018; Wieser et al., 2016), moderate alcohol consumption has been associated with a decreased risk to develop dementia and lower Lcn2 levels (Sabia et al., 2018; Wallenius et al., 2011). Thus, several unhealthy lifestyles have been linked with increased Lcn2 levels, which might contribute to an increased risk for age-related CNS diseases.

4.1.7. Other chronic inflammatory diseases and anemia

There are many chronic inflammatory diseases which are known to increase the risk to develop different age-related brain diseases. For example, conditions such as chronic kidney disease and inflammatory bowel disease (including Crohn's disease and ulcerative colitis) have been linked to an increased chance to develop dementia and PD (Chen et al., 2016; Cheng et al., 2012; Cherng et al., 2018; Etgen, 2015; Villumsen et al., 2018; Weimers et al., 2018). Local and circulating Lcn2 levels are increased in these diseases, and can have harmful or protective effects (Bolignano et al., 2009; Lu et al., 2019; Østvik et al., 2013; Stallhofer et al., 2015; Viau et al., 2010). While Lcn2 may aggravate kidney damage in chronic kidney disease, Lcn2 has important protective effects in the gut in inflammatory bowel disease, by reducing mucosal inflammation and promoting bacterial clearance by macrophages (El Karoui et al., 2016; Moschen et al., 2016; Singh et al., 2016; Toyonaga et al., 2016; Viau et al., 2010). Nevertheless, in both cases the local and circulating levels of Lcn2 are increased, which hypothetically may contribute to an increased risk to develop age-related CNS conditions. Of note, at least in certain chronic inflammatory diseases, elevated circulating Lcn2 levels may originate both from local tissues and from circulating neutrophils with upregulated Lcn2 synthesis (Shao et al., 2016).

Interestingly, chronic inflammatory diseases are often accompanied by anemia (Nemeth and Ganz, 2014; Yanoff et al., 2007), which may relate to the general iron-retentive response of the body under inflammatory conditions, known as the anemia of inflammation. It has been suggested that anemia can increase the risk of age-related brain diseases including dementia and PD (Hong et al., 2013, 2016; Kaiafa et al., 2015). Lcn2 may contribute to anemia, by facilitating inflammatory anemic responses (Srinivasan et al., 2012; Xiao et al., 2016, 2017b).

In addition, different chronic inflammatory conditions (as well as ageing, diet, infections and other factors) have been linked with microbiome changes (Alkasir et al., 2017; Sochocka et al., 2018; Vogt et al., 2017). It is becoming increasingly clear that changes in the gut microbiome (as well as changes in the blood and oral cavity microbiomes) may play a role in the risk to develop age-related neurodegenerative diseases, including AD and PD (Kell and Pretorius, 2018; Megur et al., 2020; Potgieter et al., 2015; Pritchard et al., 2017; Sochocka et al., 2018; Ticinesi et al., 2018; Vogt et al., 2017). In Lcn2 knockout mice it was determined that Lcn2 may play an important role in the homeostasis of the gut microbiota (Singh et al., 2016). A subsequent study by this group in ageing Lcn2 knockout mice showed that Lcn2 is essential in maintaining gut bacterial homeostasis and markers of metabolic syndrome (Singh et al., 2020). More research is needed to determine whether chronically increased Lcn2 levels may play a role in pathological and/or protective microbiome changes. Considering the antibacterial and iron-trafficking functions of Lcn2, it can be hypothesized that in increased expression of Lcn2 (in the gut) may be induced upon certain gut bacterial alterations, and that Lcn2 itself may contribute to changes of the gut microbiome. These chronic changes in turn may contribute to risk factors in the development of age-related neurodegenerative diseases.

4.1.8. Surgery, sepsis, traumatic brain injury, others

More acute conditions including surgery, sepsis and traumatic brain injury also have been suggested to induce an increased risk to develop certain age-related brain diseases, including AD and other dementias (Chen et al., 2014a; Chou et al., 2017; Dams-O'Connor et al., 2016; Djordjevic et al., 2016; Vanderweyde et al., 2010). Increased Lcn2 levels in blood and brain were found in animal models of these risk factor conditions (Gouweleeuw et al., 2017, 2016; Hovens et al., 2016; Ip et al., 2011; Jang et al., 2013b; Jin et al., 2014a; Kang et al., 2018; Marques et al., 2008; Russell et al., 2019; Shen et al., 2017; Zhao et al., 2016a,b). Notably, increased Lcn2 levels upon thoracic and abdominal surgery were associated with post-operative cognitive decline (POCD) in rats (Gouweleeuw et al., 2017, 2016). Similarly, increased Lcn2 levels upon LPS-injection (a model of sepsis) in mice were associated with cognitive impairment (Jang et al., 2013b).

It is worth mentioning two additional risk conditions: firstly, individuals with schizophrenia were found to have a higher risk to develop dementia (Ribe et al., 2015), and to have higher plasma Lcn2 levels as compared to controls (Wei et al., 2018). Secondly, chronic use of benzodiazepines has been related to an increased risk to develop AD (Billioti de Gage et al., 2014; Tapiainen et al., 2018). Interestingly, chronic use of the benzodiazepine diazepam in mice was found to induce chronic Lcn2 expression in the brain (including cerebral cortex, amygdala and hippocampus) (Furukawa et al., 2017).

Taken together, different factors such as surgery and drug use may add to the risk to develop dementia. Hypothetically, the increased circulating and brain levels of Lcn2 in these risk conditions may contribute to cognitive changes and possibly to an increased risk to develop dementia.

4.1.9. Sex-related differences in the expression and effects of Lcn2

Many diseases show an unequal prevalence of age-associated CNS disorders in men versus women. For example, AD is more prevalent in women, while PD, stroke and VaD are more common in men (Di Carlo et al., 2002; Hanamsagar and Bilbo, 2016; Podcasy and Epperson, 2016). Interestingly, it has appeared that there are sex-related differences in the expression as well as the effects of Lcn2. From multiple studies it has become clear that circulating Lcn2 levels are generally higher in men than in women, which seems to be the case for human subjects as well as other animals (Gouweleeuw et al., 2016; Naudé et al., 2013; Ni et al., 2013; Wang et al., 2007; Wu et al., 2014a). Moreover, higher Lcn2 levels were associated with different outcomes in men and women (Chella Krishnan et al., 2019; Gouweleeuw et al., 2016; Hamzic et al., 2013; Jun et al., 2011; Naudé et al., 2014a). For example, in older people with late-life depression, higher plasma Lcn2 levels were associated with impaired verbal memory in females but lower processing speed in males (Naudé et al., 2014a). Furthermore, Lcn2 was associated with depressive-like symptoms and cognitive decline in male but not female rats after coronary artery ligation (Gouweleeuw et al., 2016), and Lcn2 affected obesity-induced metabolic disturbances differently in male versus female mice (Chella Krishnan et al., 2019; Jun et al., 2011). These sex-dependent differences in expression and effects of Lcn2 may in part be regulated via estrogen signaling. Estrogens are known to affect Lcn2 expression, and *vice versa* Lcn2 is able to modulate the production and effects of estrogens (Chella Krishnan et al., 2019; Drew et al., 2015; Fried and Greenberg, 2012; Fuentes et al., 2019; Guo et al., 2012; Kamble et al., 2019, 2018; Liu et al., 2020). Altogether, it seems that the expression of Lcn2 as well as its effects on certain pathological processes may differ between men and women. Lcn2 may play a role in the differential disease prevalence between men and women, for certain diseases.

In conclusion, Lcn2 levels are increased in a wide variety of conditions that form a risk factor for different age-related brain diseases such

as AD, PD and VaD. Of note, while we discussed most risk conditions separately, it is likely that multiple risk factors may frequently co-occur since they share underlying pathological mechanisms (such as inflammation) and may promote each other's development (e.g. physical inactivity is also a risk factor for cardiovascular disease, osteoporosis, cognitive dysfunction, depression and diabetes (van Nimwegen et al., 2011)).

4.2. Lcn2 as a link between risk factor conditions and development of age-related CNS diseases: is there any direct evidence?

We hypothesize that Lcn2 may form a link between ageing, risk factor conditions and age-related CNS diseases. This hypothesis is based on the following evidence (as has been described in Chapters 3 and 4):

1 Peripheral/blood Lcn2 levels were found to rise with increasing age, and many other risk factor conditions for age-related CNS diseases (Chapter 4.1).
2 In certain risk factor/peripheral conditions (ageing, diabetes, surgery, sepsis, SLE and nonalcoholic steatohepatitis (Chapter 4.1, (Mike et al., 2019; Mondal et al., 2020)), Lcn2 levels were not only increased in the periphery/blood, but also in the brain. This supports the notion that risk factor conditions that affect the periphery, are able to affect Lcn2 levels in the CNS.
3 Increased Lcn2 levels in certain risk conditions (including diabetes, surgery, sepsis, SLE and depression (Chapter 3, Chapter 4.1)) were causative of/associated with significant neuroinflammatory, cognitive and behavioral changes. This indicates that increased peripheral Lcn2 levels – and/or increased CNS Lcn2 levels, provoked by peripheral risk conditions – can indeed exert significant effects on the brain, at the molecular/cellular as well as functional level.

By taking into account the evidence above, and by considering the various neurobiological and neuropathological effects that have been implicated for Lcn2, we propose the following hypothetical model: 1) During ageing and different risk factor conditions, Lcn2 levels increase in the periphery. 2) These risk factor conditions, and increasing peripheral Lcn2 levels, are accompanied by rising Lcn2 levels in the CNS. This is possible via two ways. Firstly, certain peripheral risk factor conditions are highly potent in provoking Lcn2 expression in the CNS. Increased brain Lcn2 levels may therefore to a large extent result from upregulated local Lcn2 expression in the brain, induced by certain risk factor/peripheral conditions. Secondly, Lcn2 is able to readily pass the BBB (Mosialou et al., 2017; Petropoulou et al., 2020). As such, Lcn2 in the CNS may in part also originate from the periphery. 3) The rise in peripheral and brain Lcn2 levels – which may exacerbate with aging and comorbid risk factor conditions – may impact the brain significantly, considering the known effects of Lcn2 on neuroinflammation, iron metabolism and others (Chapter 3). Over time, the ongoing and increasing presence of Lcn2 in the brain during ageing and risk factor conditions may render the brain more vulnerable to develop age-related CNS diseases, potentially by (amongst others) provoking iron dysregulation, neuroinflammation, and sensitization of brain cells to toxic stimuli.

Since no direct evidence is available yet, future studies are needed to determine the potential role of Lcn2 in linking risk factor conditions, aging and the development of age-related CNS diseases.

5. Discussion and future considerations

Lcn2 is involved in various physiological processes, including the defense against bacterial infections by disturbing bacterial iron acquisition, the regulation of mammalian iron metabolism, pro-and anti-inflammatory responses and pro-and anti-apoptotic signaling. Under healthy conditions, Lcn2 is constitutively expressed by a limited selection of cell types, which results in well-detectable basal Lcn2 levels in the blood, but very low Lcn2 levels in the brain (Chia et al., 2015; Ferreira et al., 2018a; Ip et al., 2011). However, upon stimulation by pathogenic threats, inflammation and tissue injury, Lcn2 expression increases rapidly and substantially, resulting in increased local and circulating Lcn2 levels.

Lcn2 expression is significantly upregulated in a wide variety of CNS conditions. Although some conflicting findings remain to be resolved, the majority of the results from animal and cell culture studies presented here suggest that Lcn2 might contribute to the pathology of different CNS diseases. For example, by promoting pro-inflammatory signaling, dysregulating brain iron homeostasis, sensitizing neurons and other brain cell types to cell death, aggravating white matter damage and worsening BBB disruption.

Moreover, Lcn2 potentially drives the development of certain age-related brain diseases, by being upregulated and involved in several risk factor conditions for these brain diseases. The literature presented in this review collectively shows that circulating and CNS Lcn2 levels are elevated in many conditions that are known risk factors for the development of age-related CNS diseases including AD, PD and VaD. Moreover, elevated levels of Lcn2 in some risk factor conditions were associated with cognitive impairments. We therefore hypothesize that chronically increased Lcn2 levels during ageing and other risk factor conditions may contribute to detrimental neurobiological pathways involved in the pathophysiology of age-related CNS diseases. Nevertheless, direct evidence for this possibility is lacking, and at this moment thus remains speculative. Future studies should further explore whether Lcn2 may indeed form an inflammatory link between risk factor conditions and the development of age-related brain diseases, including AD, PD and VaD.

The regulation and effects of Lcn2 in the periphery and CNS are not completely understood yet. This is emphasized by the contradictory findings regarding beneficial versus harmful actions of Lcn2 in the body as well as in the brain, which were found for example in investigations of obesity, insulin resistance, LPS-induced neuroinflammation and MS. These variable outcomes may likely depend on the biological environment in which Lcn2 functions. Therefore, it may be of great importance to take a number of factors into account in future studies, including: the specific disease that is studied and the tissues/cell types that are involved, the acute versus chronic nature of the disease, the used experimental model, the chronicity of Lcn2 exposure, age, sex, the presence of a bacterial threat, diet, the abundance of iron and siderophores, the abundance of other Lcn2 ligands and receptors, and the post-translationally modified states in which Lcn2 is present.

For example, it seems that the effects of Lcn2 may depend strongly on whether it is bound to iron and its ability to transport iron (Devireddy et al., 2005; Huang et al., 2020; Ishii et al., 2017; Kim et al., 2016; Lee et al., 2009; Mucha et al., 2011; Rehwald et al., 2020; Song et al., 2018; Wang et al., 2020). As such, its actions may rely heavily on the regional availability of iron. Moreover, since Lcn2 can only bind iron in the presence of siderophores, also the local abundance of bacterial and/or mammalian siderophores is important. It may be of interest to analyze local levels of siderophores and iron in humans and animal models of CNS disorders, to determine whether they may relate to potential protective or damaging effects of Lcn2. With regard to mammalian siderophores (e.g. 2,5-DHBA and norepinephrine), it would be valuable to understand how their expression (and e.g. the enzymatic activity of BDH2, responsible for the synthesis of the siderophore 2,5-DHBA (Devireddy et al., 2010; Liu et al., 2014b)) is regulated in different CNS disorders. Concerning norepinephrine as mammalian siderophore, it is interesting to note that degeneration of noradrenergic neurons is seen in AD and PD (Delaville et al., 2011; Gannon et al., 2015; Vazey and Aston-Jones, 2012). Potentially, this may affect iron and Lcn2-mediated iron metabolism. Lastly, simple catechols and certain green tea polyphenols have been identified as Lcn2-binding siderophores as well (Bao et al., 2010, 2013, 2015b, 2015a; Ben Lagha et al., 2017; Shields-Cutler et al., 2015, 2016; Zhang et al., 2018a). These siderophores are derived

from the diet. Therefore, diet composition might influence the availability of siderophores in the body (Xiao et al., 2017a), and thereby the effects of Lcn2.

Furthermore, the acute versus chronic nature of the studied disease should be taken into account since Lcn2 might exert different effects in acute and chronic disease states, and since the duration of Lcn2 upregulation may be key in determining its positive or negative effects. For example, Lcn2 can exert significant protective effects on the kidneys in acute kidney injury, but overall worsens tissue damage in chronic kidney disease (An et al., 2013; El Karoui et al., 2016; Schmidt-Ott et al., 2007; Viau et al., 2010; Zhang et al., 2018c). Possibly, effects of Lcn2 also differ in acute versus chronic brain conditions. It is important to note in this regard that, while age-related brain diseases such as AD and PD are chronic diseases, many animal studies were performed in more acute models of these diseases. Interestingly, it was shown that Lcn2 mRNA expression levels were manifold higher in the hippocampus and choroid plexus in an acute mouse model of AD (i.c.v. injection with oligomeric Aβ) as compared to a chronic AD mouse model (APP/PS1 mice) (Steeland et al., 2018). Thus, the expression of Lcn2 may be generally dampened in chronic versus acute conditions. As such, studying chronic CNS diseases by using acute models may be problematic, since short-term highly increased Lcn2 levels in acute models might induce different effects than long-term moderately increased Lcn2 levels in chronic models of CNS diseases. In addition, the aspect of ageing is not taken into account in many animal studies that aim to investigate age-related CNS conditions. Many animal studies are performed in young adult (instead of aged) mice, in acute (instead of chronic) models of CNS disorders. Yet, it is possible that the effects of Lcn2 change with age, since the aged brain and aged neuroimmune system might respond differently to Lcn2 than the young healthy brain. Therefore, it may be essential to study aged mice in chronic models of age-related CNS conditions, in order to obtain results that are translatable to the human condition. In this regard, it may also be important to compare the expression levels of Lcn2 between the human and mouse brain. Possibly, Lcn2 levels reach higher concentrations in the human brain than in the brain of chronic mouse models, since neurodegenerative processes in chronic mouse models may not always reach the same severity as those in the human condition (Birch et al., 2014).

Finally, two more general notes may be pointed out with regard to Lcn2-related research. Firstly, Lcn2 KO mice are of great value in Lcn2 research. However, although healthy unchallenged Lcn2 KO mice at first sight appear rather similar to WT mice, differences in energy metabolism, iron metabolism, synaptic functioning, neurogenesis, anxiety-like behavior, depressive-like behavior and cognition have been reported (as described in Chapter 3 and 4). These phenotypes in Lcn2 KO mice under basal physiological conditions should be considered, as they might also confound the phenotype of challenged/diseased Lcn2 KO mice. Therefore, it may be of interest to study mice in which Lcn2 is conditionally overexpressed or knocked-out starting from e.g. early adulthood or early disease state to circumvent any potential developmental problems in these mice.

Secondly, it should be noted that the amino acid sequence of Lcn2 between species differ. For example, murine Lcn2 is 62 % identical to human Lcn2 on the amino acid level (Kjeldsen et al., 2000). Although basic structural and biological properties (such as antimicrobial effects and ligand specificity (Clifton et al., 2019; Flo et al., 2004; Goetz et al., 2002)) may be comparable between species, it is possible that certain functions of Lcn2 in mice will not translate to humans, and *vice versa*. For example, murine Lcn2 is unable to form heterodimers with MMP-9 and is possibly only produced in its monomeric form (Cramer et al., 2012; Holmes et al., 2005).

5.1. The therapeutic potential of Lcn2

Lcn2 may present a promising therapeutic target, via which the development and progression of age-related brain diseases might be modulated. Considering the essential functions of Lcn2 in maintaining normal brain functioning, complete blockage or clearance of Lcn2 may be expected to potentially introduce side-effects. Rather, normalization of Lcn2 levels could be an optimal therapeutic strategy.

Potential modulators of Lcn2 expression may be identified from signaling pathways and transcriptional regulators known to be involved in Lcn2 expression, as reviewed previously (Ferreira et al., 2015; Jha et al., 2015; Suk, 2016). Depending on the disease and involved tissue type, Lcn2 overexpression may for example be induced via activation of TNFR1 and multiple types of TLRs (Flo et al., 2004; Gómez et al., 2013; Naudé et al., 2012; Østvik et al., 2013; Yndestad et al., 2009). Accordingly, blocking these receptors may help to normalize Lcn2 expression. Promising compounds that were shown to reduce Lcn2 expression and to exert neuroprotective effects include for example TNFR1 antagonists, iron chelators such as deferoxamine, and dendritic polyglycerol sulfates (Dong et al., 2013; Furukawa et al., 2017; Maysinger et al., 2018; Steeland et al., 2018; Zhao et al., 2016a,b). More work on important triggers of Lcn2 expression, and involved signalling pathways, will help to identify other potential therapeutic targets that could be used to normalize aberrant Lcn2 expression. Interestingly, different herbal compounds such as ginkgo biloba, curcumin and MS14 were also found to reduce Lcn2 expression in the inflamed CNS and atherosclerotic lesions (Ebrahimi-Kalan et al., 2014; Wan et al., 2016; Wu et al., 2017; Zhang et al., 2018b). Furthermore, Lcn2 expression may be decreased by certain lifestyle interventions, including physical exercise, caloric restriction and – possibly – weight loss (An et al., 2020; An and Roh, 2020; Choi et al., 2009; Corripio et al., 2010; Jeon et al., 2016; Koiou et al., 2012; Lim et al., 2015; Moghadasi and Mohammadi Domieh, 2014; Park et al., 2019; Rucci et al., 2015; Ward et al., 2020). In addition to normalizing Lcn2 expression, other interesting strategies may include the neutralization of excessive Lcn2. Indeed, it was recently described that reperfusion injury after stroke was significantly reduced, when a monoclonal antibody against Lcn2 was administered via intraperitoneal injection shortly after stroke (Wang et al., 2020). The findings from the study by Wang et al. (2020) suggest that peripheral neutralization of Lcn2 may have positive outcomes in the brain. Furthermore, other potential strategies might include blocking the release of Lcn2 from Lcn2-producing cells, interfering with the receptor-binding of Lcn2, or targeting specific ligand-bound (e.g. iron-bound), complexed (e.g. with MMP-9) or post-translationally modified (e.g. deamidated) states of Lcn2.

5.2. The diagnostic potential of Lcn2

Blood and CSF Lcn2 levels are altered in a wide range of conditions, which in general makes Lcn2 a rather unspecific biomarker. However, Lcn2 concentrations in peripheral blood and CSF may be of additional value in the diagnosis of specific CNS diseases, when combined with other disease markers. For example, a pilot study indicated that serum Lcn2 may be a valuable biomarker to distinguish between hemorrhagic and ischemic stroke patients (Weng and Chou, 2014). CSF Lcn2 levels may be a useful marker to distinguish VaD from AD patients; (Llorens et al., 2020). Additionally, CSF Lcn2 levels might be of value in the early diagnosis of AD, since CSF Lcn2 levels were found to be significantly decreased in AD as well as in MCI patients as compared to controls (Naudé et al., 2012). The biomarker potential of Lcn2 for these and other CNS diseases (such as MS and PD (Eidson et al., 2017; Marques et al., 2012), also see Tables 2,3) requires further exploration in well characterized longitudinal cohorts. A beneficial characteristic of Lcn2 in this regard is its good storage stability (Han et al., 2009; Pedersen et al., 2010; Strong et al., 1998). Another advantageous property of Lcn2 may be its stable circadian expression in elderly persons. No significant fluctuations were found in blood and CSF Lcn2 concentrations during the day in healthy elderly subjects and PD patients (Eidson et al., 2017; Naudé et al., 2017). However, in young individuals Lcn2 levels may present significant fluctuations over the day, indicating that obtaining

samples at a standard time of day may be important in younger persons (Scheer et al., 2010). Additionally, in future studies it would be of great interest to investigate whether specific ligand-bound or modified states of Lcn2 (e.g. dimeric Lcn2, iron-bound Lcn2, Lcn2 in complex with MMP-9, deamidated Lcn2), and Lcn2 levels in other tissues or biofluids/feces besides blood and CSF, may be of additional value for the diagnosis of specific diseases.

6. Conclusions

Lcn2 levels are increased in the brain in many age-related brain diseases, including AD, PD and VaD. Although some contradictory findings are reported, the growing consensus is that Lcn2 may exacerbate neurodegenerative processes in many CNS conditions, and as such might play an important role in different CNS diseases. Interestingly, circulating Lcn2 levels increase with age and rise further in various risk factor conditions for different age-related CNS diseases. In addition, increased Lcn2 levels were found in the brain in multiple risk factor conditions, and higher Lcn2 levels were associated with cognitive decline. Altogether, it can be hypothesized that increased peripheral and CNS Lcn2 levels in risk factor conditions may contribute to the risk to develop different age-related CNS diseases, for example by gradually driving the brain into a primed inflammatory state, dysregulating iron metabolism and sensitizing brain cells to toxic stimuli. However, at this moment, direct evidence for this possibility is lacking. Therefore, future studies are required to explore whether – and via which mechanisms – Lcn2 may indeed act as a link between risk factor conditions and the development of age-related CNS diseases. Furthermore, contradicting findings with regard to the effects of Lcn2 emphasize that the functions and effects of Lcn2 are complex and are not fully understood. The effects of Lcn2 may depend on a complex combination of factors, including for example age, sex, the specific disease that is studied, the chronic versus acute nature of the disease, involved cell types, the specific ligands to which Lcn2 is bound, and the post-translationally modified states in which Lcn2 is present. Further research is necessary to improve our understanding of the role of Lcn2 in age-related brain diseases and risk factor conditions thereof, and to clarify the value of Lcn2 as a diagnostic and therapeutic target for these age-related diseases. Lcn2 is an interesting factor to take into account in the field of geroscience (Kennedy et al., 2014), which focuses on elucidating the biological mechanisms of aging that enable the development of age-related chronic diseases.

Wu et al. (2014b)

Declaration of Competing Interest

The authors declare no conflict of interest.

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