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The role of neutrophil gelatinase associated lipocalin (NGAL) as biological constituent linking depression and cardiovascular disease

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ABSTRACT

Depression is more common in patients with cardiovascular disease than in the general population. Conversely, depression is a risk factor for developing cardiovascular disease. Comorbidity of these two pathologies worsens prognosis. Several mechanisms have been indicated in the link between cardiovascular disease and depression, including inflammation. Systemic inflammation can have long-lasting effects on the central nervous system, which could be associated with depression. NGAL is an inflammatory marker and elevated plasma levels are associated with both cardiovascular disease and depression. While patients with depression show elevated NGAL levels, in patients with comorbid heart failure, NGAL levels are significantly higher and associated with depression scores. Systemic inflammation evokes NGAL expression in the brain. This is considered a proinflammatory effect as it is involved in microglia activation and reactive astrocytosis. Animal studies support a direct link between NGAL and depression/anxiety associated behavior. In this review we focus on the role of NGAL in linking depression and cardiovascular disease.

1. Introduction

Cardiovascular disease and major depression are two of the most prevalent illnesses in the western world, affecting a large part of the population and leading to a high economic burden. Cardiovascular disease is the leading cause of death world-wide, with more than 1 out of 3 American adults suffering from at least one type of CVD (Writing Group Members et al., 2010), while anti-depressant medication is one of the most prescribed types of drugs. Around 60% of patients with depression report severe or very severe impairment in their daily life, which includes social interactions and work (Kessler et al., 2003). The comorbidity of cardiovascular disease and depression is associated with worse prognosis compared with either cardiovascular disease or depression alone. In recent years there has been more interest in the link between cardiovascular disease and depression. It is reported that patients with cardiovascular disease, including heart failure and acute myocardial infarction (AMI), have an increased risk of developing depression. On the other hand, patients suffering from depression are more likely to develop cardiovascular disease, including a myocardial infarction. Mechanistically it is still unclear what links these distinct pathologies, although inflammation has been mentioned as a possible mechanism. Cardiovascular disease and depression share an increased expression of pro-inflammatory cytokines. For some of these, a relationship with both depression and heart disease is reported in the literature (Pasic et al., 2003). Recently, it was found that neutrophil gelatinase associated lipocalin (NGAL), also referred to as lipocalin-2 (Lcn-2), has characteristics of a (neuro)inflammatory constituent. Subsequently, it was suggested that NGAL fulfills a possible role in both, cardiovascular disease and depression. Furthermore, NGAL is reported an independent predictor of mortality in heart failure (van Deursen et al., 2014). We recently showed that NGAL is elevated in relation to late life depression (Naude et al., 2013). Moreover, NGAL is associated with depression scores in heart failure patients, independent of measures for cardiac- or renal dysfunction (Naude et al., 2014). This review focusses on the putative mutual interaction between cardiovascular disease and depression and the potential coupling role of NGAL.

1.1. Cardiovascular disease increases the prevalence of depression

Patients suffering from heart failure commonly have other comorbidities. Depression is a comorbid illness in heart disease, which is of particular interest because of its negative impact on the quality of life and prognosis. Up to 65% of patients recovering

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from myocardial infarction show symptoms associated with depression (Carney et al., 1997), and 15–22% of myocardial infarction patients can be categorized as having major depression (Hance et al., 1996; Frasure-Smith et al., 1993; Schleifer et al., 1989). Both clinical depression and elevated levels of subclinical depressive symptoms are common in the weeks following acute coronary syndrome (Thombs et al., 2006) and predict recurrent cardiac events and cardiovascular mortality (Meijer et al., 2011).

However, not only the acute phases of cardiovascular disease, also chronic heart failure is associated with an increased prevalence of depression; with up to 40% of heart failure patients experiencing symptoms of depression (Shimizu et al., 2013; Sherwood et al., 2007; Rutledge et al., 2006).

It is important to recognize the heterogenic characteristics of depression. General depression can be categorized as somatic/affective (with symptoms including fatigue and psychomotor problems) or cognitive/affective (with symptoms including depressed mood and feelings of worthlessness or guilt). It is worth mentioning that compared to depressed patients without heart disease, depressed patients with heart disease suffer from somatic/affective-rather than from cognitive/affective symptoms of depression (Holzapfel et al., 2008). Moreover, in heart failure patients, inflammation is associated with somatic symptoms of depression, but not with cognitive/affective symptoms (Kupper et al., 2012).

Depression in heart failure patients often goes unrecognized, because of overlapping symptoms of depression and heart failure, and is regarded as the "natural" response to a life threatening condition. Nevertheless, comorbid depression in heart failure patients jeopardizes quality of life, adherence to therapy and life style advises, and hence cardiovascular prognosis.

1.2. Depression increases the prevalence of cardiovascular disease

Major depression is a common disorder with an estimated lifetime prevalence of 8.3–16.2% in the United States (Kessler et al., 2003; Bourdon et al., 1992). Data from epidemiological studies clearly suggest that depression is an independent risk factor for acute myocardial infarction and heart diseases in general. Patients with depression have a greater risk of mortality due to cardiovascular related conditions up to 10 years after the diagnosis (Barefoot and Schroll, 1996). This finding holds for mild- as well as major depression (Penninx et al., 2001).

In addition, prospective studies with depressed individuals show that a history of major depressive episodes is associated with a higher risk of myocardial infarction, even after correction for major coronary risk factors (Pereira et al., 2013). A systemic review calculated a pooled relative risk of 1.64 for developing coronary heart disease in patients with major depression (Rugulies, 2002). The relative risk for patients with major depression for the development of ischemic heart disease was 1.56 (Charlson et al., 2013). A recent follow-up study of a large population-based study also found depression to be a risk factor for the development of heart failure (Gustad et al., 2014). Furthermore, depressed patients that adhere to their medication regimen have a 26% lower risk of hospitalizations for coronary artery disease than depressed patients that do not adhere to their treatment (Cooper et al., 2014).

1.3. The influence of depression on prognosis in patients with CVD

In the past years, the co-morbidity of heart disease and depression has been thoroughly investigated. Numerous studies have reported worsened prognosis in patients with cardiovascular disease when depression is present.

In patients who already have developed congestive heart disease (CHD), the impact of depression is of great importance. A prospective population-based cohort study, investigated age- and sex-adjusted hazard ratios for death from all causes. Results from this study show that patients with both depression and CHD have a higher mortality than patients with either depression or CHD alone (Nabi et al., 2010). This is in concordance with the study by Sherwood et al., showing that heart failure patients with depression display 2–3 times higher mortality when compared with heart failure patients without depression (Sherwood et al., 2007).

As mentioned earlier, depression can be classified into cognitive/affective depression and somatic/affective depression. The type of depression experienced by patients with cardiovascular disease was reported to affect prognosis. In patients with stable coronary heart disease, somatic symptoms of depression are associated with cardiac events, while there is no significant association of cognitive symptoms of depression with cardiac prognosis (Hoen et al., 2010). Later the same results were found for somatic symptoms of depression in patients that suffered acute myocardial infarction (Roest et al., 2013). Additionally, in chronic heart failure somatic symptoms of depression are associated with all-cause mortality, while cognitive symptoms of depression are not (Schiffer et al., 2009). In accordance, a very recent meta-analysis, including more than 11,000 subjects, showed that in fully adjusted analyses only somatic/affective symptoms are significantly associated with adverse prognosis (de Miranda Azevedo et al., 2014).

While optimal treatment of cardiovascular disease usually has no major effects on depression, treatment of depression in these patients, though associated with modest improvement in depressive symptoms, does not improve cardiac outcome (Thombs et al., 2008). This may indicate a common denominator rather than a causal relationship for cardiovascular disease and depression.

1.4. Inflammation as a link between depression and cardiovascular disease

Different putative mechanisms have been proposed as common denominator to link cardiovascular disease to depression. Besides psychological factors and behavioral factors (Whooley et al., 2008; Ziegelstein et al., 2000), endothelial dysfunction (Celano and Huffman, 2011; Pizzi et al., 2009), increased platelet activity (Celano and Huffman, 2011; Schins et al., 2004), autonomic nervous system dysfunction (Dao et al., 2010; Kop et al., 2010) and inflammation are possible factors having a role in the interaction between cardiovascular disease and depression. For this review we will focus on inflammation. In Fig. 1 the role of inflammation as a common factor between cardiovascular disease and depression is depicted (Fig. 1).

An increase in circulating pro-inflammatory cytokines has been detected in patients with cardiovascular disease as well as patients with major depression. In AMI patients, an inflammatory response is required for proper scar formation and is initiated immediately after the event (Frangogiannis, 2006). As early as 1978 it was reported that C-reactive protein levels in the plasma are elevated hours after myocardial infarction (Kushner et al., 1978). Other cytokines that were found to be raised in the plasma of acute MI patients are TNF-a, IL-2, IL-10, IL-6 and IL-1β (Mizia-Stec et al., 2003; Blum et al., 1994; Basaran et al., 1993; Ikeda et al., 1992). Elevated levels of plasma cytokines are, however, not restricted to acute coronary syndromes. In chronic heart failure patients, cytokines including TNF-α and IL-6 (Munger et al., 1996; Levine et al., 1990) are also elevated.

With regard to depression, an increase in circulating cytokines is observed in clinical studies. The cytokines that were most consistently found to be elevated across different studies with depressed patients are TNF-α, IL-6, IL-1β, IL-2 and IFN-γ (Dowlati et al., 2010; Simon et al., 2008; Pavon et al., 2006; Brambilla and Maggioni, 1998).

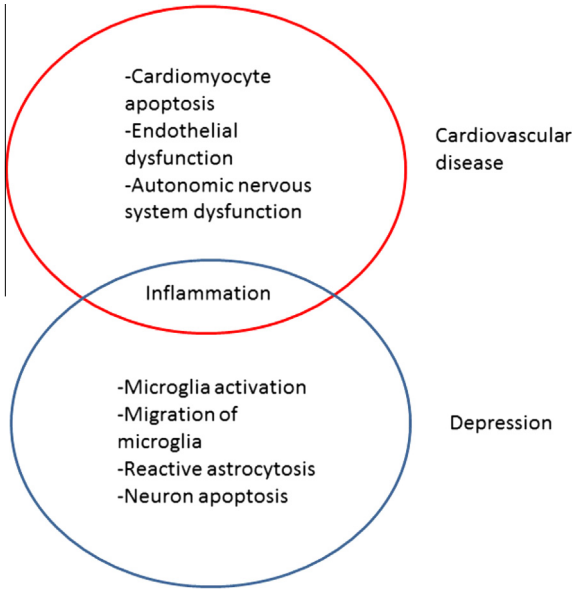

Fig. 1. Pathophysiological factors in cardiovascular disease and depression. Inflammation has been described as a factor in both cardiovascular disease as well as depression.

What stands out in these findings is that there seems to be an overlap in cytokines elevated in cardiovascular disease and depression, as reviewed by Pasic et al. (2003). Several studies have also investigated cytokine expression profiles in patients that have both cardiovascular disease and depression. In heart failure patients IL-6 and CRP levels are associated with depression (Johansson et al., 2011). TNF-α levels are associated with depression score in heart failure patients as well (Ferketich et al., 2005). Additionally, in patients admitted for MI higher TNF-α levels were found in those who were depressed compared to non-depressed MI patients (Shang et al., 2014).

Animal studies show depressive symptoms weeks after experimental myocardial infarction (Frey et al., 2014; Grippo et al., 2003; Schoemaker and Smits, 1994) that can be blocked by the TNF-α blocker Etanercept (Grippo et al., 2003).

Several publications advocate the importance of inflammation in the interaction between cardiovascular disease and depression (Kupper et al., 2012; Kop et al., 2010; Andrei et al., 2007). In brief, following an AMI, inflammation in the brain was demonstrated, especially in the paraventricular nucleus of the hypothalamus (PVN), a region involved in control of the sympathetic nervous system and the expression of the hormones vasopressin and oxytocin. Also, the PVN is important in cardiovascular homeostasis (Li and Patel, 2003). The cytokines TNF-α and IL1-beta were increased in the hypothalamus of rats, both at mRNA and protein level, after MI (Francis et al., 2004). Moreover, MI in rats induces focal leakage of the BBB (Van der Werf et al., 1995), which can be mimicked by intravenous TNF-α infusion in an experimental setting (Ter Horst et al., 1997). Hence, peripheral inflammatory mediators may facilitate entry of inflammatory mediators through leakage of the endothelium lining the BBB, and subsequently induce neuroinflammation (Liu et al., 2013; Abbott et al., 2010). TNF-α, by influencing the permeability of the BBB, induces leakage of the BBB and neuroinflammation. The neuroinflammatory reaction may cause depression, both by affecting monoamines, tryptophan and kynurenine production as well as by affecting the HPA axis, which is thought to contribute to depression (Jones and Thomsen, 2013; Raison et al., 2006). Indeed, TNF-α infusion can induce depressive-like behavior in mice (Kaster et al., 2012).

In the rat, TNF-α expression in the heart, at mRNA as well as protein level, peaked at 7 days after MI and subsequently declined. Cells expressing this TNF-α were primarily inflammatory cells involved in the repairing of cardiac tissue (Lu et al., 2004). Interestingly, plasma TNF-α levels remained elevated, at least up to 4 weeks after MI (Kang et al., 2009). This finding indicates that the elevated plasma TNF-α levels seen in heart failure (after MI) may not originate from the inflamed infarcted heart. Moreover, an MI in rats leads to an increase in microglia activation in the PVN (Dworak et al., 2012; Badoer, 2010; Rana et al., 2010). Microglia activation, although slightly higher at 1 week, was substantially and persistently increased up to 16 weeks after MI (Dworak et al., 2012). Comparing the time course of TNF-α levels and microglia activation, it seems that the cytokine-induced neuroinflammatory response in the brain induces structurally altered activated microglia. In a recent review, Quan (2014) thoroughly described the above process of an initially local inflammatory response progressing into systemic inflammation as well as neuroinflammation, eventually leading to neuronal damage and psychological disorders (Quan, 2014).

2. Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Neutrophil Gelatinase-Associated Lipocalin (NGAL), also known in humans as lipocalin-2 (Lcn-2), uterocalin, siderocalin and in the mouse as 24p3, is a 25 kDa glycoprotein originally purified from human neutrophils (Kjeldsen et al., 2000; Kjeldsen et al., 1993). NGAL was found constitutively synthesized during a narrow window of maturation in the granulocyte precursors in the bone marrow, and is stored in specific granules of mature neutrophils in complex with gelatinase (Kjeldsen et al., 1994), but has since been described in a variety of cell-types. Other cells known to produce NGAL are renal cells (Langelueddecke et al., 2012), endothelial cells (Hamzic et al., 2013), hepatic cells (Borkham-Kamphorst et al., 2011), cardiomyocytes (Yndestad et al., 2009) and neurons (Naude et al., 2012). NGAL is involved in anti-microbial defense by sequestering iron; *in vitro* studies have demonstrated that NGAL has a bacteriostatic effect via the binding of siderophore molecules, thereby restricting the availability of iron to bacteria (Goetz et al., 2002). A study using NGAL knock-out mice supports this effect, as these mice showed a much higher susceptibility to bacterial infections than wild-type (WT) controls (Berger et al., 2006). More recently, NGAL was identified as a biomarker for acute kidney injury, since, NGAL is released rapidly in response to kidney tubular damage (Di Grande et al., 2009; Parikh and Devarajan, 2008). In respect to research about NGAL as a biomarker for renal injury, raised NGAL levels are also thought to predict renal failure in patients with heart failure (Mortara et al., 2013; Yndestad et al., 2009). NGAL was also associated with mortality in heart failure patients, with or without renal disease (van Deursen et al., 2014). In animal experiments, NGAL production is increased in spared myocytes after MI. This augmented NGAL production persists at least for 6 weeks (Yndestad et al., 2009). They also found that in isolated rat cardiomyocytes NGAL production increases following stimulation with various inflammation-associated agents, including endothelin-1, interleuking-1β and TNF-α (Yndestad et al., 2009).

More recently, our group reported that increased circulating NGAL levels are significantly associated with depression in the elderly (Naude et al., 2013), as well as symptoms of depression in heart failure patients (Naude et al., 2014).

The effects of NGAL are mediated by two putative receptors: 24p3R and megalin, with distinct functions.

2.1. Receptors for NGAL

2.1.1. 24p3R

The 24p3R is one of the known receptors for NGAL. Immunoblot analysis on a panel of murine tissues revealed that 24p3R was

widely expressed in different organs, including the heart and brain (Devireddy et al., 2005). The 24p3R is widely expressed throughout the heart, but particularly on the surface of cardiomyocytes (Ding et al., 2010). This finding is of special interest because cardiomyocytes are also considered as the most important source for NGAL in both experimental and clinical HF, as previously discussed (Yndestad et al., 2009). Expression of 24p3R in mice (Ip et al., 2011) revealed high expression levels of the receptor in the brain under physiological conditions, with the highest levels in the choroid plexus and the dentate gyrus of the hippocampus. By combining in situ hybridization with immunohistochemistry that allowed for the identification of neurons (NeuN), astrocytes (GFAP), microglia (IBA-1) and endothelium (lectin), cellular sources of NGAL and 24p3R RNA transcripts were determined. Whereas no NGAL RNA signal was detectable in neurons, 24p3R RNA was expressed almost exclusively in neurons in the brain, specifically and extensively expressed in cortical neurons, hippocampal dentate gyrus, granule neurons and Purkinje neurons of the cerebellum. Furthermore, high levels of 24p3R RNA are present in the choroid plexus. Besides expression on neurons, 24p3R also seems to be expressed on the surface of microglia (Lee et al., 2007). High NGAL RNA hybridization signal was found in cells in close proximity to neurons, presumably microglial cells, as well as vascular endothelium (Ip et al., 2011). Lee et al., also found mRNA expression of 24p3R and megalin, the other known receptor for NGAL (see below), in neuronal cell cultures (Lee et al., 2012).

In contrast to the observed increase in NGAL, which expression is increased upon LPS administration, expression of 24p3R was not altered by LPS (Lee et al., 2012; Ip et al., 2011). Functioning of NGAL via 24p3R is dependent on whether iron is bound to NGAL or not. In the case of iron-lacking NGAL, binding to 24p3R results in the uptake of NGAL and subsequent decrease of intracellular iron levels, followed by an upregulation of the protein Bcl-2-interacting mediator of cell death (BIM), which is a potent inducer of apoptosis. When NGAL is bound to iron (Apo-NGAL), binding to 24p3R will increase intracellular iron levels without inducing apoptosis (Devireddy et al., 2005). In neurons, NGAL and 24p3R are important for dendritic spine maturation and influenced by iron, with pertubation of dendritic spine maturation in absence of iron (Mucha et al., 2011). This is in concordance with indications that neurodegenerative diseases are often associated with disturbances of brain iron metabolism (Crichton et al., 2011). However, a recent study showed that iron and transferrin did not produce an effect on NGAL toxicity to primary cortical neurons (Bi et al., 2013). Therefore, the mechanisms of NGAL via 24p3R in neuronal cells are still unclear.

2.1.2. Megalin

The other known receptor for NGAL is megalin (which is also known as low-density lipoprotein receptor-related protein 2: LRP2). Megalin is a multi-ligand endocytosis receptor, expressed on a variety of epithelia; primarily epithelia possessing a high absorptive capacity, such as tubular epithelial cells of kidneys, ileum, choroid plexus, and yolk sac (Moestrup and Verroust, 2001). Megalin has also been detected in cardiomyocytes cultured *in vitro* (Van Dijk et al., 2010). Megalin belongs to the low density lipoprotein receptor family (Saito et al., 1994) and has been shown to bind a variety of (mouse) lipocalins (Flower, 2000; Leheste et al., 1999). Hvidberg and coworkers (Hvidberg et al., 2005) investigated whether NGAL also binds to megalin. Results indicate that apo-NGAL (NGAL not bound to iron) binds to megalin with a high affinity. Similar affinity was found with siderophore-bound NGAL. To confirm that megalin is responsible for the cellular uptake of NGAL a sheep polyclonal anti-megalin antibody was used. This antibody completely prevented cellular uptake of NGAL, indicating the important role of megalin in mediating the cellular uptake of NGAL (Hvidberg et al., 2005). Expression of the megalin receptor has been detected in neuronal cell cultures (Lee et al., 2012), indicating that megalin may have a function in the uptake of NGAL in the brain. Miharada et al., (2008) found high levels of megalin mRNA in $CD3^+$ T lymphoid cells and the next highest in $CD71^{++}$ erythroid cells (Miharada et al., 2008). $CD15^+$ granulocytic cells, $CD14^+$ monocyte/macrophage lineage cells, and $CD19^+$ B lymphoid cells also expressed megalin mRNA, albeit at lower levels than in $CD3^+$ or $CD71^{++}$ cells. Expression of megalin on T- as well as B-lymphocytes may indicate a function for NGAL in the immune system but this needs to be further investigated.

In the brain megalin in the endothelium lining of the BBB was reported as important for transport of ligands across the BBB (Pan et al., 2004). Recently a role for megalin was described in Alzheimer's disease using an endothelial specific megalin knockout mouse model. The investigators showed that mice lacking the megalin receptor in the endothelium were more prone to neurodegeneration. The mice also showed behavioral characteristics associated with Alzheimer's disease, including anxiety and cognitive impairment (Dietrich et al., 2014).

Presently, molecular mechanisms induced by NGAL binding to megalin are still unknown.

2.2. NGAL and inflammation

As previously mentioned, NGAL was first described in neutrophils (Kjeldsen et al., 1993). Later NGAL has also been observed in other cells of the immune system including macrophages and dendritic cells (Jha et al., 2014; Flo et al., 2004). Upregulation of NGAL can be induced by various stimulants including lipopolysaccharide (Zhang et al., 2008), IL-1β (Borkham-Kamphorst et al., 2011; Yndestad et al., 2009; Cowland et al., 2003), IL-6 (Hamzic et al., 2013), IFN-γ (Zhao et al., 2014), and TNF-α (Zhao et al., 2014; Naude et al., 2012; Yndestad et al., 2009), depending on cell-type.

Multiple studies have investigated the function of NGAL in the immune system (Han et al., 2012; Ip et al., 2011). As discussed earlier, NGAL is involved in anti-microbial defense by sequestering iron (Goetz et al., 2002). The role of NGAL in the innate immune system has been extensively reviewed (Borregaard and Cowland, 2006) and is beyond the scope of this review.

In a recent report NGAL was demonstrated to have chemotactic properties, as neutrophils were shown to migrate along increasing concentrations of NGAL. Neutrophils of NGAL-/- mice showed a decreased neutrophil adherence, which was associated with lower CXCR2 expression (Schroll et al., 2012).

Besides its functions in the innate immune response, NGAL was also reported to be involved in chronic inflammation and autoimmune diseases. In a study of NGAL in a healthy population, NGAL was associated with other markers of inflammation, including C-reactive protein and neutrophil count (Lindberg et al., 2014). NGAL levels are upregulated in different autoimmune disorders (Shashidharamurthy et al., 2013; Rubinstein et al., 2008). Inflammation in autoimmune disorders has been studied in NGAL-/- mice. Chronic skin inflammation was reduced by 50% in NGAL-/- mice. This effect was abolished when NGAL was administrated to the NGAL-/- mice (Shashidharamurthy et al., 2013). The complexity of the role of NGAL in immune responses is further evidenced by a study where NGAL was evaluated in two different inflammation models. NGAL-/- mice were partially protected against inflammation induced by the reverse passive Arthus (RPA) reaction. To initiate this type of inflammation animals were injected with rabbit IgG anti-ovalbumin, and thereafter with ovalbumin to provoke an immune response. In the same article, the authors discussed NGAL in a model of serum induced arthritis (SIA). They demonstrate NGAL-/- mice to have a more extreme, rather than a damp-

ened, inflammatory response. When the inflammatory infiltrated tissues of these mice were compared, the investigators found primarily neutrophils in the infiltrates from WT mice, whereas in the NGAL-/- mice, macrophages were more abundant. This suggests that NGAL is important for the recruitment of neutrophils, and that without NGAL other immune cells like macrophages mediate the SIA response (Shashidharamurthy et al., 2013).

To summarize, NGAL has been associated with a wide range of immune responses, ranging from anti-microbial defense to chronic inflammation in auto-immune disorders.

2.3. Function of NGAL in the central nervous system

Under physiological conditions NGAL concentrations in the CNS are very low, with mRNA levels undetectable (Ip et al., 2011; Flo et al., 2004). Very little is known about physiological functions of NGAL in the brain. Under inflammatory conditions, NGAL is increased and has pleiotropic effects of different cell-types within the CNS. These effects are hypothesized to lead to behavioral changes and are depicted in Fig. 2.

Interestingly, NGAL production is strongly induced in the CNS by peripheral lipopolysaccharide (LPS) administration (Marques et al., 2008; Flo et al., 2004), meaning peripheral inflammation leads to an upregulation of NGAL in the brain. It is also known that NGAL can be produced in different cell types in the CNS, including neurons, astrocytes and microglia, and that its expression is increased after stimulation with TNF-α (Naude et al., 2012). This appeared to be mediated by the proinflammatory TNFR1 receptor rather than the cytoprotective TNFR2 receptor. It was suggested that the TNFR1 mediated NGAL subsequently inhibits the TNFR2 signaling pathway, hence, further promoting a proinflammatory TNF-α response. Additionally, it was shown that NGAL is taken up by neurons, suggesting neurons may be a target for the actions of NGAL.

In the CNS, microglia form a first line of defense protecting the CNS from pathogens and other harmful conditions. In addition to these physiological functions, glial cells also participate in chronic neuroinflammation under pathological conditions. Long-lasting and excessive activation of glia contributes to neural tissue damages in neuroinflammatory and neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease and Parkinson's disease (Ransohoff and Perry, 2009; Hanisch and Kettenmann, 2007; Garden and Moller, 2006). In microglia, expression as well as secretion of NGAL is increased under inflammatory conditions in the CNS. The expression of NGAL and 24p3R was strongly enhanced by LPS, serum withdrawal, Phorbol 12-myristate 13-acetate PMA, IFN-γ and calcium ionophore A23187 (Lee et al., 2007). NGAL appears to sensitize activated microglia to apoptosis and it also induces deramification of microglia (Lee et al., 2007). It is speculated that activated microglia may secrete NGAL, which acts in an autocrine manner to induce morphological transformation of microglia. At the same time, secreted NGAL proteins may sensitize activated microglia to apoptotic signals, so that activated microglia can be easily eliminated by apoptosis as a self-regulatory mechanism (Lee et al., 2007). NGAL also seems to have an indirect effect on the migration of microglia, NGAL-treated astrocyte-conditioned medium (ACM) significantly enhanced the migration of microglia compared with control-ACM (Kim et al., 2011). Like macrophages, microglia can be subdivided into M1 and M2 populations; M1 microglia being associated with inflammation and tissue-damaging properties, whereas M2 microglia are thought to have anti-inflammatory functions. Recently it has been suggested that NGAL specifically is involved in the polarization of M1 microglia (Jang et al., 2013). The NO induced apoptosis resistant microglia cell line BV-LS13 was found to have significantly lower NGAL expression than its parental BV-2 line which is sensitive to NO induced apoptosis. NGAL overexpression in these cells resulted in an increased sensitivity to apoptosis caused by NO donors sodium nitroprusside SNP and S-nitroso-N-acetylpenicillamine SNAP (Lee et al., 2007). NGAL also was described to stimulate migration of microglia and neurons, both in an *in vitro* assay as well as *in vivo* in zebrafish (Kim et al., 2011).

NGAL has also been implicated in the process of astrocytosis, through the 24p3R (Lee et al., 2009). With astrocytosis, a morphological change takes place in astrocytes, resulting in long and branched processes and an increased cytoplasmic mass. This is accompanied by an increase in intermediate filaments including glial fibrillary acidic protein (GFAP). In case of damage, astrocytes can also proliferate to fill gaps left by death of neurons (Lee et al., 2009). Moreover, NGAL sensitizes astrocytes to apoptotic as well as necrotic cell death (Lee et al., 2009). Later research indicated that chemotaxis could be a mediator in this process, as NGAL

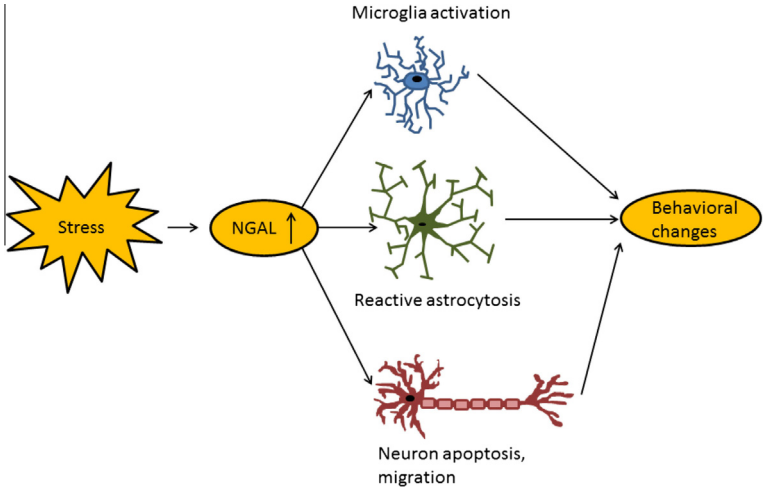

Fig. 2. Proposed mechanism by which NGAL is a mediator between peripheral disease and depression. Different stressors including myocardial ischemia and infection raise systemic levels of NGAL. This systemic increase in NGAL might lead to a local increase of NGAL in the brain. NGAL is known to influence the function of different cell types in the central nervous system. In microglia it was found that high NGAL levels promote deramification of microglia. NGAL was also found to control migration of microglia and to sensitize microglia to apoptosis. Astrocytes are sensitized to apoptosis as well as necrotic cell-death by high NGAL levels. NGAL is also implicated in the process of astrocytosis. For neurons NGAL was found to be a factor in migration. Neurons were also more sensitive to apoptosis in the presence of high levels of NGAL. These changes in the CNS are thought to contribute to behavioral changes including anxiety and depression.

Table 1
Different actions of NGAL in the cardiovascular system and central nervous system.

Functions of NGAL	Reference
Cardiovascular system	
Induces cardiomyocyte apoptosis	Xu et al. (2012)
Induces neutrophil infiltration	Yang et al. (2012)
Induces endothelial dysfunction	Song et al. (2014)
Induces vascular inflammation	Song et al. (2014)
Increases blood pressure	Song et al. (2014)
CNS	
Induces microglia activation	Lee et al. (2007)
Stimulates microglia migration	Kim et al. (2011)
Decreases neural spine formation	Mucha et al. (2011)
Promotes reactive astrocytosis	Lee et al. (2009)
Sensitizes microglia, astrocytes and neurons to apoptosis	Lee et al. (2012), Naude et al. (2012), Lee et al. (2009), Lee et al. (2007)

induced changes in the expression of chemokines CXCL2 and CXCL10. Further evidence that NGAL is important for chemokine-associated migration was demonstrated in a cell culture experiment in which NGAL induced migration of astrocytes, that was abrogated by CXCL10 neutralizing antibodies (Lee et al., 2011). Additionally, in NGAL knock-out mice expression of the chemokine receptor CXCR2 was significantly reduced (Schroll et al., 2012).

In neurons, TNF-α is known to induce NGAL expression (Naude et al., 2012). One of the effects of NGAL on neurons is sensitization to apoptosis caused by various mediators including NO and TNF-α (Lee et al., 2012). In a study where primary neurons were stimulated with conditioned medium from cultured brain slices with reactive astrocytes, a neurotoxic effect of the conditioned medium was shown. This effect was inhibited when NGAL was partially depleted from the medium with immunoprecipitation (Bi et al., 2013).

A role for NGAL has been postulated for diseases of the CNS including multiple sclerosis, Alzheimer's disease and depression. In a murine model of experimental autoimmune encephalitis, disease was more severe in NGAL-/- mice, indicating a protective role of NGAL (Berard et al., 2012).

With respect to dementia, NGAL levels are increased in the CSF of patients with Alzheimer's disease and mild cognitive impairment. Mechanistic studies revealed that NGAL sensitizes nerve cells to amyloid beta toxicity. In post-mortem brain tissue, NGAL expression is increased in brain areas associated with Alzheimer's pathology (Naude et al., 2012). The authors of this paper also showed that NGAL silences a TNFR-2 mediated protective signaling cascade important for TNF-α mediated neuroprotection (Naude et al., 2012). This last finding is in line with the observation that NGAL inhibits microglial M2 polarization (Jang et al., 2013). A summary of functions of NGAL in the CNS is given in Table 1.

Taken together, NGAL was associated with both pro-inflammatory and anti-inflammatory pathways in the CNS. With respect to the pro-inflammatory effect, NGAL was seen to stimulate reactive astrocytosis. NGAL was also found to stimulate microglial M1 polarization while inhibiting microglial M2 polarization, and so is causing a more pro-inflammatory state of the microglia population. Regarding the anti-inflammatory effect, NGAL has a protective role in an experimental model of autoimmune encephalitis. It thus seems regulation of neuroinflammation by NGAL is complex and in need of more research.

2.4. Function of NGAL in depression

Several publications have reported the association of NGAL with behavior and depression. NGAL showed a seven fold upregulation in the hippocampus of mice that underwent a 6 h restraint as a model for stress (Mucha et al., 2011). In addition, treatment of cultured neurons with holo-NGAL revealed a ± 30% decrease in spine density, suggesting a role for NGAL in neuronal spine destabilization and elimination (Mucha et al., 2011). This inhibitory effect of NGAL on neuronal growth may connect NGAL with depression, as depression is often associated with changes in the hippocampus including a loss in synaptic plasticity and a decrease in brain derived neurotrophic factor (Sen et al., 2008; Duman and Monteggia, 2006). Another indicator that NGAL is linked to stress and behavior is the finding that NGAL is highly upregulated in the amygdala after restraint-stress. This increase was shown primarily in neurons and associated with an increase in immature neuroplastic spines, suggesting the formation of fear-memory (Skrzypiec et al., 2013). As the amygdala is involved in fear memory (Roozendaal et al., 2009), it can be hypothesized that the NGAL upregulation found in the amygdala after restraint stress is linked to fear induced behavioral changes, such as depression.

However, it was recently shown that $NGAL^{-/-}$ mice show more anxious and depressive-like behavior when compared with their non-transgenic littermates. The change in behavior was associated with an activation of the hypothalamic–pituitary-adrenal (HPA) axis (Ferreira et al., 2013). In contrast, locomotion activity of $NGAL^{-/-}$ mice did not change in an open field test; only when stimulated with LPS the absence of NGAL was uncovered (Jang et al., 2013). This possibly means that NGAL signaling follow a U-shaped curve, where both absence and overexpression give rise to pathologic behavior of the animals. This phenomenon has been described for other inflammatory mediators as well (Pollmacher et al., 2002). With regards to NGAL and depression in patients, we previously showed that increased plasma NGAL was significantly associated with depression in an elderly population (Naude et al., 2013). This association persisted after correcting for identified determinants of higher plasma NGAL in humans, including increased age, male sex, use of anti-inflammatory drugs and life-style factors. It was also shown that increased plasma NGAL levels closely resemble the current state of depression. We later also reported a correlation between NGAL levels and depression in a population of heart failure patients. NGAL levels showed a positive correlation with the somatic/affective symptoms of depression, but not the cognitive/affective symptoms. This correlation was still significant after correcting for age, sex, cardiac dysfunction (left ventricular ejection fraction (LVEF)) and renal dysfunction (creatinine) (Naude et al., 2014). These studies suggest that NGAL may be a marker for depression. Whether this refers to a causal association still has to be determined.

2.5. Function of NGAL in Cardiovascular disease

The role of NGAL in cardiovascular disease has been examined both in experimental and in clinical studies. In a study combining clinical and experimental data, serum levels of NGAL were measured in patients with HF following AMI and in patients with chronic HF. In both groups, patients with chronic heart failure or AMI had significantly higher levels of NGAL when compared with control subjects. Furthermore, NYHA classes of patients were significantly correlated with NGAL levels (Yndestad et al., 2009). Other studies also mentioned raised NGAL levels in patients with cardiovascular disease (Shrestha et al., 2012; Damman et al., 2008). Recently NGAL was presented as having a high prognostic value in patients with heart failure, as higher plasma NGAL levels were associated with higher mortality (van Deursen et al., 2014). Higher levels of NGAL in these patients could, however, also reflect renal failure, as renal failure is often seen in heart failure patients and leads to increased levels of NGAL (De Berardinis et al., 2014). In an experimental rat model of post-MI HF, NGAL expression was significantly elevated in the non-ischemic area of the left ventricle (LV). In their model the increase in NGAL expression lasts from 2

to at least 64 days after the induction of MI, in conjunction with the development from acute to a chronic stage of HF. Further analysis of the non-ischemic part of the LV 56 days following the induction of MI showed that up-regulation of both NGAL mRNA as well as NGAL protein was mainly restricted to cardiomyocytes (Yndestad et al., 2009). NGAL has also been studied in acute cardiac disease, including AMI. A study comparing NGAL levels in AMI compared to stable coronary artery disease found that NGAL plasma levels were higher in AMI (Sahinarslan et al., 2011). Another study found NGAL present in human atherosclerotic plaques, where NGAL colocalized with macrophages (Hemdahl et al., 2006). The same authors also studied experimental MI in a mouse model. Here they found NGAL was significantly increased in the heart and aorta of MI mice. The colocalization of NGAL with matrix metallo protein 9 (MMP-9) in plaques and infarcted hearts suggests a role for NGAL in the MMP-9 mediated remodeling (Hemdahl et al., 2006). In a 10-year follow up study performed in a healthy population, higher baseline NGAL levels were associated with adverse cardiac events and all-cause mortality (Lindberg et al., 2014). The association of higher NGAL levels with cardiovascular risk was previously reported in a population of community dwelling elderly (Daniels et al., 2012).

Several studies on cardiovascular disease related to NGAL have been performed in NGAL-/- mice. The hearts of NGAL-/- mice show better contractile function and improved functional recovery and reduced infarct size following ischemia/reperfusion (I/R) injury compared to WT mice (Yang et al., 2012). Under baseline conditions, the mitochondrial function of NGAL-/- hearts was significantly enhanced, as demonstrated by biochemical analysis of respiratory chain activity and markers of biogenesis, as well as electron microscopic investigation of the mitochondrial ultrastructure. Acute or chronic systemic administration of NGAL impaired cardiac functional recovery to I/R and dampened the mitochondrial function in hearts of NGAL-/- mice. These effects were associated with an extensive modification of the fatty acyl chain compositions of intracellular phospholipids (Yang et al., 2012). A possible function for NGAL in the recruitment process of infiltrating cells was suggested in a study investigating NGAL in heart transplantation. In NGAL-/- hearts transplanted to NGAL+/+ recipients, a significant reduction of infiltrating granulocytes was observed when compared to the number of infiltrated cells in NGAL+/+ transplanted donor hearts. However, the opposite combination (NGAL+/+ to NGAL-/-) did not fully mirror the NGAL+/+ donor/recipient situation, thus suggesting a graft resident contribution to the infiltration process (Aigner et al., 2007). Polymorphonuclear neutrophils from NGAL-/- mice had a significantly reduced adhesion capacity, which was linked to a reduced expression of adhesion associated surface proteins and to the chemokine receptor CXCR2 on the membranes of these cells (Schroll et al., 2012). A study in a cultured cell-line of cardiomyocytes indicated that NGAL directly induces apoptosis in cardiomyocytes (Xu et al., 2012). Cardiomyocyte apoptosis can influence the remodeling process underlying cardiovascular conditions including heart failure. According to these articles, NGAL is involved in the inflammatory response in the heart, attracting immune cells to the site of damage. Functions of NGAL in the heart are summarized in Table 1.

Thus, in heart failure patients, plasma NGAL is increased and has a prognostic value. The observed prognostic value of higher NGAL levels might be associated with a general higher degree of inflammation in patients with heart failure, as in a healthy population NGAL was associated with all tested markers of inflammation.

3. Discussion: NGAL as possible mediator in cardiovascular disease and depression?

In this review we have discussed NGAL and its role in both cardiovascular disease and depression. Furthermore, we reviewed the potential role of NGAL as common denominator for both conditions. Firstly, NGAL is well recognized to be elevated in heart failure patients (Shrestha et al., 2012; Yndestad et al., 2009; Damman et al., 2008). Higher plasma levels of NGAL in heart failure patients are associated with higher mortality (van Deursen et al., 2014). Secondly, patients with late life depression show elevated plasma levels of NGAL (Naude et al., 2013). Thirdly, recently we showed that in patients with heart failure, depression scores are associated with circulating levels of NGAL, irrespective of measures of cardiac and renal dysfunction (Naude et al., 2014).

As previously discussed, patients suffering from cardiovascular disease are at increased risk of developing depressive like symptoms (Bush et al., 2005; Lesperance and Frasure-Smith, 2000). Likewise the inverse correlation is valid (Lippi et al., 2009). The comorbidity of depression in cardiovascular disease substantially worsens prognosis. The observation that optimal cardiovascular treatment does not reduce depressive symptoms, while antidepressive therapy is not associated with improved prognosis in these patients, may suggest a common underlying mechanism rather than a causal relationship. Many investigators referred to inflammation as a link between these two pathologies (Celano and Huffman, 2011; Poole et al., 2011; Kop et al., 2010; Pasic et al., 2003). In cardiovascular disease, such as AMI and CHF, the patients most often exhibit a higher level of inflammatory markers (Frangogiannis et al., 2002). A higher expression of cytokines in both blood and brain, was observed in patients with depression (Dowlati et al., 2010; Howren et al., 2009; Connor and Leonard, 1998). Research in animal models has indicated that an AMI causes local inflammation in the brain, including microglia activation and higher expression of, amongst others, TNF-α (Rana et al., 2010; Francis et al., 2004).

We proposed a possible role for NGAL in the link between cardiovascular disease and depression. NGAL has multiple functions related to inflammation. Several functions of NGAL are associated with autoimmune reactions and chronic inflammation (Shashidharamurthy et al., 2013). Inflammation of the heart and/or the brain leads to a higher localized expression of NGAL. Additionally, NGAL is upregulated in a mouse model of stress (Skrzypiec et al., 2013; Mucha et al., 2011). In this regard, our group found higher levels of NGAL in the plasma of depressed heart failure patients(Naude et al., 2014). Further information that NGAL is related to depression is provided by a study showing NGAL to inhibit spine maturation of cultured neurons from the hippocampus (Mucha et al., 2011), a brain region often associated with (the neurotrophic hypothesis of) depression.

Two different receptors are known to bind NGAL, 24p3R and megalin, both of which are found in the CNS. Knowing that NGAL plays a role in inflammation in both the heart and the brain, and that inflammation has been mentioned as a mechanism by which cardiovascular disease leads to depression, it could be speculated that NGAL is involved in the link between cardiovascular disease and depression.

In general, the literature shows NGAL to have predominantly pro-inflammatory properties. This is evident from several observations, including NGAL possessing chemotactic properties, specifically for neutrophils, and ability to activate microglial cells (Schroll et al., 2012; Lee et al., 2007). Furthermore, NGAL was shown to silence anti-inflammatory pathways such as TNF-R2 signaling and M2 microglial polarization. Higher NGAL levels might thus indicate an imbalance in pro- and anti-inflammatory pathways giving rise to a state of chronic inflammation. Since neuroinflammation is linked to depressive symptoms, a cardiac induced chronic inflammatory state, when affecting the brain, may correlate cardiovascular disease to depression.

Hypothetically, increased NGAL levels that arise from a stressor like cardiovascular disease might lead to increased cytokine levels

in the brain, either through leakage of cytokines through the blood brain barrier or other mechanisms. Higher NGAL in the brain could lead to microglia activation and changes in neurons including a decrease in spine formation in the hippocampus and an increase in immature neuroplastic spines in the amygdala. Both neuroinflammation represented by microglia activation (Muller, 2014) and neuronal changes in the hippocampus and amygdala have been associated with behavioral changes including depressive and anxious behavior (Roozendaal et al., 2009; Dantzer et al., 2008; Sen et al., 2008; Duman and Monteggia, 2006).

In chronic heart failure patients increased serum NGAL levels associated with the somatic, however not the cognitive symptoms of depression (Naude et al., 2014), the former, but not the latter found associated with inflammation (Kupper et al., 2012). Moreover, in the study of Naude et al., 2014, NGAL was associated with the experienced burden of the disease, reflected by NYHA classification and 6 min walking test, rather than with the depressed cardiac function itself. This observation might link NGAL to specific, still uncovered pathways. Future research is necessary to further elucidate the exact function of NGAL in the link between cardiovascular disease and depression.

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