MICROGLIAL PRIMING AND ACTIVATION AS THE LINK BETWEEN OVERFEEDING-INDUCED OBESITY AND NEURODEGENERATIVE DISEASES

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ABSTRACT

More than a couple studies have found a correlation between mid-life obesity and neurodegenerative diseases like Alzheimer's disease and Parkinson's disease. Overfeeding is known to cause peripheral inflammation leading to the development of the metabolic syndrome. Signals of peripheral inflammation are capable of transferring into the central nervous system, where they interact with microglia by acting on receptors like TLRs, RAGE, NLRP3 and cytokine receptors. Stimulation of microglia leads to either activation or priming of these cells. Primed microglia show an exaggerated response to secondary stimulation. Neuroinflammation is one of the key processes in neurodegeneration. Amyloid β (in Alzheimer's diseases) or α-synuclein (in Parkinson's disease) can also interact with microglia through the same receptors as signs of peripheral inflammation do, leading to microglial priming or activation. Microglial activation due to obesity-induced peripheral inflammation has adverse effects on the progression of Alzheimer's disease and Parkinson's disease, especially due to the release of reactive oxygen and nitrogen species.

1: OVERFEEDING, METABOLIC SYNDROME AND NEURODEGENERATIVE DISEASE

1.1: Obesity and metabolic syndrome

Currently, the Western world faces an epidemic of obesity. Worldwide, at least 1.5 billion adults are overweight (BMI≥25) and of these 500 million are obese (BMI≥30). This corresponds with respectively 35% and 11% of the world's adult population. Worldwide the occurrence of obesity has nearly doubled since 1980 and is still rapidly spreading across the world (Obesity and overweight—Fact Sheet N°311 Updated March 2013).

Overnutrition, or caloric excess, is known to be a triggering factor in the development and propagation of inflammation related diseases (Schwartz and Porte, 2005). Overnutrition leads to a disruption of the metabolic homeostasis, which contributes to metabolic syndrome (Reaven, 2005). The innate immune system, evolutionary much older than adaptive immunity, includes physical barriers, NK cells, the complement system and phagocytic cells like macrophages. Pattern recognition receptors (PRRs) are used by the innate immune system to identify threats of damaged cells (DAMPs) or microbes (PAMPs) (Kettenman et al, 2011). Diverse DAMPs and PAMPs are derived from dietary factors and gut microbes. Many PRRs are involved in regulation of gut microbes and disruption of these receptors may lead to an altered gut microbial composition. An altered gut microbial composition, either due to effects of the immune system or by effects of diet, is known to be associated with the development of obesity (Turnbaugh et al, 2006; Jin et al, 2013). PRRs are mostly expressed on macrophages and dendritic cells. A major role for sensing overnutrition is played by Toll-like receptors 2 and 4 (on the cell surface) and NOD-like receptor P3 (cytosolic); these receptors are also expressed on adipocytes, hepatocytes and in the hypothalamus and play an important role in the communication with intestinal microbiota (Kanczkowski et al, 2008; Jin et al, 2013). Activation of PRRs leads to an inflammatory response: excessive production of pro-inflammatory cytokines, reactive oxygen and nitrogen species and reduced anti-inflammatory cytokine production. Expanding adipose tissue also exhibits an enhanced inflammatory status and increased macrophage infiltration, leading to increased secretion of pro-inflammatory cytokines (by adipocytes themselves but especially by the infiltrating macrophages) (Fain et al, 2006). Also endoplasmic reticulum (ER) stress leads to an inflammatory response; overfeeding is known to disrupt ER homeostasis, leading to protein folding dysfunction in the ER. Cells in this condition respond with the induction of a pathway that leads to the secretion of pro-inflammatory cytokines (Ozcan et al, 2004). See also figure 1.

Together, these responses cause a state of chronic low-grade inflammation that leads to endothelial dysfunction, decreased insulin sensitivity and eventually to metabolic syndrome (Giugliano et al, 2006). More than a few epidemiological studies have been published on the association between diet (for example Western diet) and markers of inflammation (Lopez-Garcia et al, 2004; Nettleton et al, 2007; Nettleton et al, 2010). Western diet has also been directly associated with metabolic disease in an epidemiological study (Denova-Gutierrez et al, 2010).

Metabolic syndrome, also known as syndrome X, encompasses disorders like abdominal obesity, insulin resistance, dyslipidemia and hypertension (Schenk et al, 2008). Metabolic syndrome is associated with diabetes, atherosclerosis and cardiovascular disease (Wilson et al, 2005).

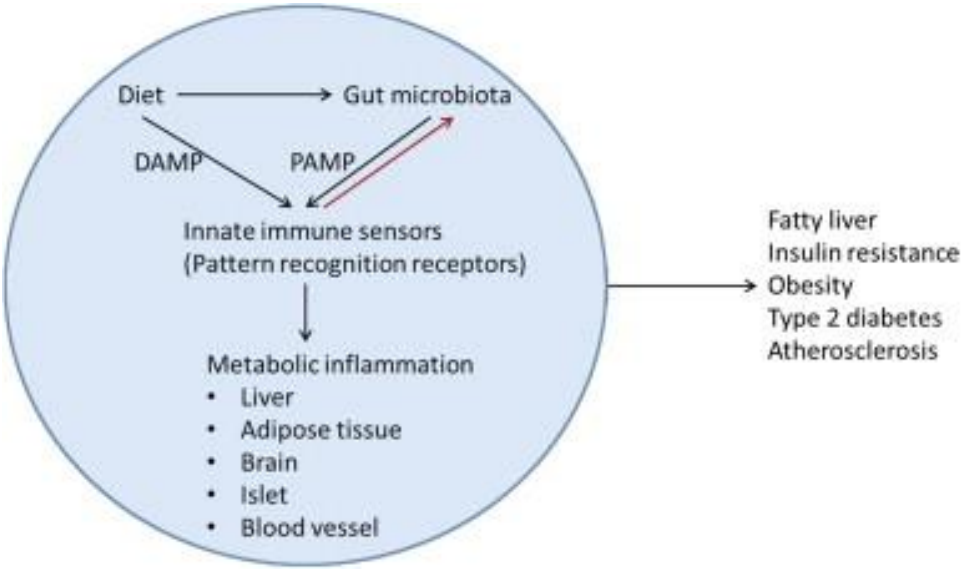

Fig. 1: Excessive nutrition leads to activation of innate immune sensors, either directly via DAMPs or indirect by influencing the composition of gut microbiota. The activated sensors (pattern recognition receptors) induce an inflammatory process which leads to metabolic inflammation and ultimately to the development of metabolic syndrome. PPRs are also involved in the communication between the innate immune system and gut microbiota (Jin et al, 2013).

1.2: Brain aging and neurodegenerative disease

Aging implicates a progressive decline in the efficiency of several physiological mechanisms on molecular and cellular level. This decline is associated with a reduced ability to recover from physical and mutagenic damage that eventually leads to multi-organic cell failure (Chedraui and Pérez-López, 2013). The human brain is not resistant to aging. The post mitotic neuronal population lives as long as we do, as neurogenesis in the mature brain can be considered negligible compared to the total neural population (Sawada and Sawamoto, 2013). Clinically healthy middle-aged individuals show already early indications of age changes in brain function. Neuronal loss has historically been the major point of focus in studying the aging brain (Finch, 2002). Glial cells, astrocytes and microglia, are affected by early stages of aging. Glial fibrillary acidic protein (GFAP) expression in astrocytes increases progressively during aging in humans and inbred lab rodents (Goss et al, 1991; Nichols et al, 1993). The majority of studies on aging-related immunophenotypic changes in microglia have shown increased expression of markers that are usually only found on activated microglia (Conde and Streit, 2006).

Not only the prevalence of obesity, but also that of age-related neurodegenerative diseases (NDDs) like Alzheimer's disease (AD) and Parkinson's disease (PD) are strongly increasing (Karolinska and Prince, 2010; Dorsey et al, 2007). An increase in years lived in disability between 2005 and 2030 is estimated to be 25% for PD and 66% for AD (Global burden of neurological disorders: estimates and projections, 2006). The increased prevalence of these NDDs has a heavy impact on worldwide mortality and healthcare costs (Dorsey et al., 2013).

There are more 35 million patients with AD worldwide (Karolinska and Prince, 2010). This NDD has a large genetic component, an estimated heredity of 58-79%, as a twin study shows (Gatz et al. 2006). AD is characterized by accumulation of extracellular amyloid β in the CNS, hyperphosphorylated Tau within neural cell bodies (neurofibrillary tangles) and inflammation of the brain (Boutajangout and Wisniewski, 2013). Two forms of AD can be distinguished: early-onset familial AD and late-onset sporadic AD. Circa 0.5% of AD patients have the early-onset variant that occurs under 65 years and have inherited APP, PSEN1 or PSEN2 mutations. Late-onset AD is also characterized by several inherited mutations including the APOE4 allele that carries a significant risk of disease development (Schellenburg and Montine, 2012). Epigenetic

and multifaceted environmental factors are other causing factors of late-onset AD (Bakulski et al. 2012).
PD is the second most common NDD with globally more than 4 million patients (Dorsey et al, 2007). The symptoms are resting tremor, bradykinesia, muscle rigidity, postural instability and dementia which typically occur in or after the 5th decade. It is characterized by loss of dopaminergic neurons in the substantia nigra (SN) and the presence of Lewy bodies (which are accumulations of α-synuclein) in the surviving neurons in this region. PD is classically considered a non-genetic disorder, although mutations in several genes (coding for SNCA, PRKN or LRRK2) have been conclusively shown to cause PD (Lessage and Brice, 2009). AD and PD are distinct NDDs, but do share common mechanistic disease pathways particulary concerning neuroinflammatory signaling (Perl et al. 1998; Mattson et al. 1999). Effects of the metabolic disruption caused by obesity share many characteristics that are involved in disease pathways of PD and AD, like oxidative stress, lipid pathway alterations and increased inflammation associated with abnormal protein deposition (Ashrafian et al, 2013).

1.3: Adiposity and CNS function
The recent obesity epidemic is also accompanied by a strong increase in prevalence of NDDs like PD and AD. It has been suggested that this increased prevalence may be partly caused by obesity and the accompanying metabolic syndrome (Hu et al, 2013). The brain corresponds with circa 2% of the total body mass, but consumes 20% of the total energy expenditure (Shulman et al, 2004). Because of the highly metabolic nature of the brain and the widespread effects of obesity on peripheral tissues, it could be expected that disruption of the metabolic homeostasis, due to overnutrition, will affect the brain.

Two CNS regions are key actors in regulating food intake: the hypothalamus receives and regulates signals to affect appetite and the dorsal medulla receives and regulates satiety signals. Any structural damage in these regions, like neoplasms, is known to be able to cause obesity (Lee and Mattson, 2013). The hypothalamus senses fluctuations in energy metabolism through the autonomic nervous system, nutrients and hormones. Leptin is the main hormone produced by adipocytes and is crucial for hypothalamus capability of sensing peripheral energy state (Elmquist et al, 1999). Lack of leptin or its receptors leads to morbid obesity; this is the cause of rare cases of monogenic obesity (Hummel et al, 1966).
Nutrient excess leads to peripheral chronic low-grade inflammation, but can also lead to chronic low-grade inflammation in the hypothalamus. This eventually leads to central leptin and insulin resistance, which consequently has its effect on peripheral metabolism (Thaler et al, 2010). Leptin resistance in the hypothalamus is hypothesized to either be caused by impaired leptin transport to the brain or by impaired leptin signaling in hypothalamic neurons (Jung and Kim, 2013). IKKβ/NF-κB signaling in the hypothalamus is increased by high fat diet; this leads it to increase food intake and nutrient storage (Zhang et al, 2008). Lack of TLR2 and TLR4, normally expressed in the hypothalamus, prevents impaired central insulin action during diet-induced obesity (Sartorius et al, 2012). This implicates a major role of the innate immune system in the brain considering the central effects of obesity.

Obesity is like many NDDs a disease with a large genetic component that is estimated to be 65% (Speakman, 2006). Large genome wide association studies have identified many genes that are associated with obesity and any more genes are expected to be found, as only 1.45% of BMI differences could be explained by the found genes (Hedebrand et al, 2010). These genes have a very small effect size, with the FTO gene having the largest effect size. Several of these genes act as hypothalamic regulators of energy homeostasis: MC4R, POMC, SH2B1 and BDNF (Hedebrand et al, 2010; Fall and Ingelsson, 2012).

Metabolic syndrome is associated with abnormalities in the brain including reduced volumes of the hippocampus, prefrontal cortex and precuneus (Bruehl et al, 2009; Willette et al, 2013). Interestingly, functions affected by high fat diet (memory, attention, working memory and

inhibitory control (Francis and Stevenson, 2013)) are predominantly controlled by two of these affected brain regions. Obesity has also found to be correlated with epilepsy, which suggests that obesity primes the brain for seizures (Lee, 2011).

1.4: Obesity and AD

Many studies have investigated whether high-fat diet, mid-life obesity or associated disorders like type 2 diabetes and vascular disease are correlated with NDDs or CNS aging. Midlife BMI is correlated with AD and vascular dementia, independent of stroke, cardiovascular and diabetes co-morbidities (Whitmer et al, 2007; Kivipelto et al, 2005). Midlife high waist-to-hip ratio (Gustafson et al, 2009) and midlife centralized distribution of adiposity (Whitmer et al, 2008) have been found to correlate positively with dementia. In contrast to this, progression of AD is correlated with a lower body weight in the years preceding the diagnosis and a late-life BMI above 30 is found to be protective (Gustafson et al, 2009; Fitzpatrick et al, 2009). The opposite effect of adiposity during midlife and late-life periods, the "obesity paradox", can be explained by underfeeding already at early stages of dementia; this condition is known as mild cognitive impairment, or MCI (Lee, 2011). Chiang et al (2007) found a J shaped relationship between midlife BMI and dementia, which means that a BMI below 20.5 is already at midlife a risk factor, just like late-life underweight. From the aforementioned studies can be concluded that at midlife both under- and overweight are risk factors for developing late-life AD. At late-life, individuals with normal weight and underweight have more chance of developing AD in the coming years, while overweight individuals have a lower chance.

Not every experimental study is able to find significant effects of obesity on dementia or AD. No effect of diet induced obesity on amyloid β, inflammatory signaling or glial reactivity has been found in a study on mice. The use of mice in experimental studies on AD has serious limitations, for example their short lifespan (Zhang et al, 2013).

Cross-section studies on diet patterns of a middle aged population demonstrated the adverse effect of high saturated fat intake on memory, speed and flexibility (Kalmijn et al., 2004). Earlier research of this group has associated this high saturated fat intake of individuals older than 55 with risk of AD (Kalmijn et al., 1997), while another group showed this same association in adults older than 65 (Morris et al, 2003). A study on 4 weeks high saturated fat/high sugar diet ingestion showed increased amyloid β levels in the cerebrospinal fluid, while amyloid β levels decreased after 4 weeks of low saturated fat/low sugar diet ingestion (Bayer-Carter et al, 2011).

1.5: Metabolic syndrome and AD

Several studies also tried to correlate other components of metabolic syndrome with cognitive function and dementia. A case control study found a strong difference in frequency of metabolic syndrome in AD patients compared to healthy individuals, matched for sex, age and years of education (García-Lara et al, 2010). In this study, of all features of metabolic syndrome, diabetes frequency was found to be the most significantly different between the groups. High peripheral serum insulin levels are indeed correlated with impaired cognitive function (Stolk et al. 1997), cerebrospinal fluid amyloid β levels (Watson et al. 2003) and neurodegeneration (Sato et al, 2013). Other studies have found a direct correlation between type 2 diabetes and dementia (Leibson et al. 1997; Ott et al. 1999). Insulin has been suggested to either clear peripheral amyloid β (Krulstad et al, 2006) or to cause the release of intracellular amyloid β, leading to amyloid β aggregation (Sabayan et al, 2008). Both insulin and amyloid β are substrates of insulin-degrading enzyme (IDE). IDE is identified as a principal regulator of amyloid β levels in neurons and microglia. IDE hypofunction may contribute to some forms of AD and type 2 diabetes (Farris et al, 2003). The production of central produced insulin is inhibited by peripheral insulin production, leading to reduced amyloid β clearance (Reger et al, 2006). Type 2 diabetes has a deleterious effect on cognition that eventually may lead to accelerated CNS aging or AD (Arvanitakis et al, 2004). These effects are most profound in the hippocampus and other temporal lobe structures (den Heijer et al, 2003). A 1999 study in Rotterdam showed an almost doubled risk for dementia and AD for type 2 diabetes patients (Ott et al, 1999) and the Religious Order study showed a 65% increased risk of developing clinical manifestations of AD for

diabetic patients compared to non-diabetics (Arvanitakis et al, 2004). In contrary, a follow up of this study has not found a postmortem histopathological correlation with type 2 diabetes (Arvanitakis et al, 2006). Other studies could not find any correlation between type 2 diabetes and neuritic plaques and neurofibrillary tangles, or even found a negative correlation (Heitner and Dickson, 1997; Beeri et al, 2005). An explanation for this discrepancy could be that less diabetic individuals may survive to an older age and are not included in the post-mortem studies (Wrighten et al, 2009).

1.6: Underlying mechanisms by which obesity affects the development of AD

In what way does overfeeding lead to damage in the CNS and more in particular to NDDs? Brain derived neurotrophic factor (BDNF) is one of the genes found in the large GWAS on obesity and is also highly expressed in the CNS, especially in the hippocampus and the cerebral cortex (Leibrock et al., 1989). BDNF may act as a mechanism by which diet has an effect on memory function, as reduced BDNF levels were found in the ventral hippocampus and medial PFC after high fat diet consumption (Kanoski et al., 2007).

Oxidative stress may be another link between diet and CNS function and aging, as oxidative stress increased after high fat diet feeding which could subsequently be associated with cognitive impairment (White et al, 2009; Wu et al, 2004). AD studies showed oxidative damage before the appearance of plaque pathology (Nunomura et al., 2001), while oxidative stress is also found to be increased in the substantia nigra of PD patients (Jenner, 2003). These findings indicate that the increased oxidative stress caused by high fat diet may eventually contribute to the development of NDDs, besides with the increased oxidative stress due to aging (Dias et al, 2013).

The blood brain barrier (BBB) seems to be vulnerable to metabolic and dietary disruptions. A longitudinal study of 81 women investigated the association between body adiposity (measured by BMI, sex hormone binding globulin and leptin levels) and BBB function 24 years later. Overweight and lower levels of sex hormone binding globulin, inversely correlated with BMI, were related to worse BBB integrity 24 years later in life (Gustafson et al., 2007). In rats did 6 month high fat diet caused increased hippocampal BBB permeability (Freeman & Granholm, 2012).

The most important protein in predicting late-onset AD is ApoE. The three variants of the ApoE gene, ε2, ε3, and ε4, act as important predictors of late-onset AD risk: the ε2 allele is associated with reduced risk, the ε4 allele with increased risk and the ε3 allele is neutral (Schellenburg and Montine, 2012). ApoE acts as the primary cholesterol carrying protein in the brain from astrocytes towards neurons (Ashrafian et al, 2013). Cholesterol levels are raised due to obesity and play a key role in the development of atherosclerosis (Landsberg et al, 2013). Midlife high cholesterol levels have been found to be an additive risk factor for dementia (Kivipelto et al, 2005). ApoE is preventive against atherosclerosis, which is best exemplified by spontaneous hypercholesterolemia, hyperlipidemia and atherosclerosis in ApoE knock-out mice (Maeda et al, 2011). Apo ε4 is associated with plasma cholesterol levels and is a risk factor for atherosclerosis. This variant accelerates through domain interaction diet-induced atherosclerosis (Eberlé et al, 2012). Atherosclerosis in the circle of Willis (as a marker of chronic dyslipidemia) has been correlated with neurodegenerative disease pathology. Atherosclerosis ratings in these autopsies correlated with amyloid plaque and tau pathology (Yarchoan et al, 2012). These findings suggest that ApoE is a possible link between a component of the metabolic syndrome, atherosclerosis, and AD; in addition, hyperlipidemia leads to increased plasma ApoE levels (Rosenfeld et al, 1993).

ApoE is, together with ApoJ and α1-antichymotrypsin, found within diffuse and fibrillary amyloid β plaques, already before the appearance of tau pathology. Some suggested that ApoE acts as a chaperone to amyloid β, with the ε4 allele promoting amyloid β fibrillogenesis (Kim et al, 2009). Another idea is that ApoE4, but not ApoE2 and ApoE3, competes with amyloid β for binding on LRP1, which is a surface receptor on epithelial cells responsible for amyloid β clearance out of the brain (Sagare et al, 2013).

1.7: PD

Lean subjects (measured by BMI, central (abdominal) adiposity or peripheral adiposity) had lower incidence of PD in later life compared to obese subjects. The strongest effect was found for triceps skinfold thickness, a measure for peripheral obesity (Ashrafian et al, 2013). Five years preceding the diagnosis of PD, patients have a higher (saturated) fat intake compared to control individuals (Johnson et al, 1999), higher intake of animal fat 1 year preceding PD diagnosis (Liu et al, 2004) and also cholesterol intake was positively associated with risk of developing PD (Miyake et al, 2010). Three years after diagnosis, PD patients had increased their body mass and fat mass (Vikdahl et al, 2014) Contrastingly, patients with advanced PD have a decreased body mass and BMI; this may be due to motor or non-motor symptoms of the disease, an effect of dopaminergic medication (van der Marck et al, 2012) or because of the increased prevalence of malnutrition (Sheard et al, 2011). PD mice tend to be largely resistant to high-calorie-induced obesity (Rothman et al, 2014). Parkin, a major genetic factor in PD, plays a multifunctional role in modulating cellular fatty acid uptake (Kim et al, 2011), indicating at a possible genetic link between PD and obesity.

1.8: Inflammation as link between obesity and NDD

As peripheral inflammation plays a pivotal role in the process from overfeeding to metabolic syndrome, it could be hypothesized that overfeeding or metabolic syndrome also have its effect on the central immune system. Alterations to the central immune system could consequently lead to CNS damage and NDDs, or at least aid in the development of the diseases. Use of non-steroidal anti-inflammatory drugs (NSAIDs) is found to decrease the chance of developing AD and PD in humans (Szekely et al, 2004; Deleidi and Gasser, 2013) and NSAID treatment of AD mice can decrease the amyloid β burden (Lim et al, 2000). Among the six genetic polymorphisms most tightly linked to late-onset AD found in large GWAS, four play an important role in immunological processes (Moraes et al, 2012); inflammatory genes are also found to be an indicator of PD risk (Deleidi and Gasser, 2013). The main immune cells in the brain, as part of the innate immune system, are the microglia. In the next pages the morphology, origin and functioning of these cells are discussed.

2: MICROGLIA

Microglia are a subtype of glial cells and comprise 10% of all the cells in the CNS (Alliot et al, 1999). They are the professional phagocytes of the CNS and their function is essential for brain development, normal brain function, and in pathology (Dilger and Johnson, 2008). Other tissue-resident macrophages include among others Lagerhans cells in the skin, Kupffer cells in the liver and red pulp macrophages in the spleen (Davies et al., 2013). Like these other tissue-resident macrophages, microglia act in the immune surveillance and in the clearance of cell debris. Also production of growth factors aids in the preservation of neuronal integrity (London et al, 2013).

Pio del Rio-Hortega described microglia already in 1932 in a book chapter for "Cytology and Cellular Pathology of the Nervous System". He postulated the following: *1) microglia enter the brain during early development. 2) These invading cells have amoeboid morphology and are of mesodermal origin. 3) They use vessels and white matter tracts as guiding structures for migration and enter all brain regions. 4) They transform into a branched, ramified morphological phenotype in the more mature brain. 5) In the mature brain, they are found almost evenly dispersed throughout the central nervous system and display little variation. 6) Each cell seems to occupy a defined territory. 7) After a pathological event, these cells undergo a transformation. 8) Transformed cells acquire amoeboid morphology similar to the one observed early in development. 9) These cells have the capacity to migrate, proliferate and phagocytose* (Del Rio-Hortega 1932). As of today, all these postulates can still be used to correctly and validly describe microglia (Kettenman et al, 2011).

Microglia were originally described as a whole new type of immune cell residing in the otherwise immunecompromised CNS, while more recently they were placed in the family of the tissue-resident macrophages. The primary job of the microglia is considered to maintain homeostasis and health in the CNS, instead of fighting of infiltrating microbes (Cronk and Kipnis, 2013). In their non-inflammatory state, microglia are still very active participants in the homeostasis of the CNS (Nimmerjahn et al, 2005).
Microglia have been blamed for pathology due to inflammation. In response to injury, microglia become rapidly activated and undergo morphological and molecular changes that are normally associated with pathology and neurotoxicity (Aguzzi et al., 2013). These changes are found in postmortem human samples, animal disease model samples and also in positron emission tomography images of human patients (Schweitzer et al., 2010).

2.1: Microglial origins

Neurons and most types of glial cells in the brain, like astrocytes and oligodendrocytes, are derived from neuroectoderm. Microglial progenitors however, arise from peripheral mesodermal (myeloid) tissue (Chan et al, 2007). These microglial progenitors colonize the CNS early during fetal and embryonic periods of development. The mature, differentiated microglia are derived from progenitors that are originated from the yolk sac. These progenitors move towards the neural tube and proliferate in situ during development (Alliot et al, 1999; Ginhoux et al, 2010). Microglial progenitors invade the developing brain at several sites called the "microglial fountains". These sites include the plexus choroideus (Kershman, 1939).
In a healthy brain, the residing microglia are not replenished by bone marrow derived monocytes entering the brain, but are sustained by local progenitors. This was suggested by Ajami et al. in 2007 by using irradiated animals to remove bone marrow derived macrophages, followed by bone marrow transplantation with labeled monocytes. In another study, little replacement of microglia occurred after removal of the residing microglia from the brain (Varvel et al, 2012). This shows that bone marrow derived macrophages and microglia are representatives from two genetically distinct populations of cells (see figure 2). The CNS contains sites where bone marrow derived macrophages reside in physiological conditions, like

the meninges, choroid plexus and perivascular space. Bone marrow derived macrophages are dependent on the transcription factor Myb for their development, while yolk sac derived microglia develop independent of Myb (Schulz et al, 2012). Although bone marrow derived macrophage recruitment is in a healthy brain only a marginal phenomenon (Lampron et al, 2012), under pathological conditions this recruitment plays a significant role, either beneficial or harmful (Schilling et al, 2009). Microglia differ from bone marrow derived macrophages in the aftermath of an inflammation. Macrophages do not persist in the tissue but go into apoptosis or emigrate towards nearby lymph nodes. Microglia remain at the site of inflammation and are key actors in the repair and normalization of the affected area, by phagocytosis of debris and apoptotic cells and by releasing growth hormones (Gordon and Taylor, 2005)

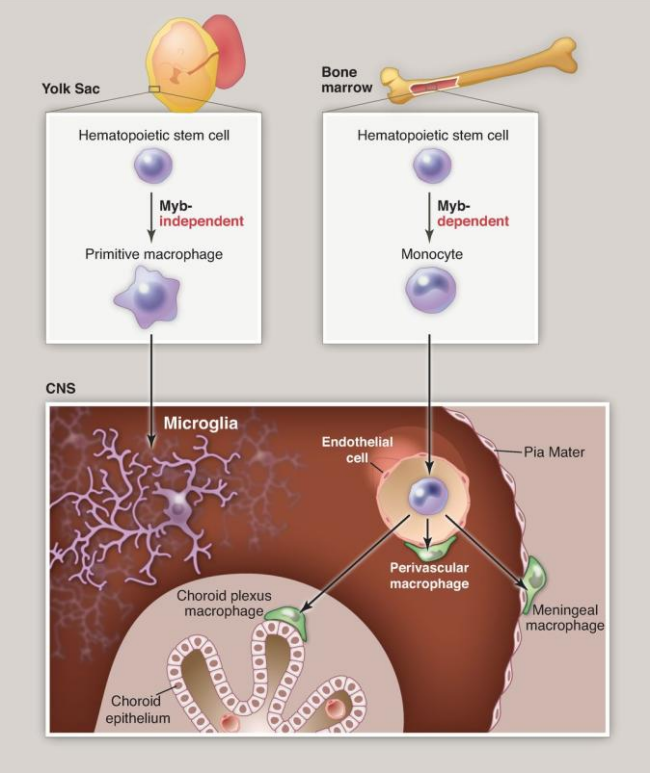

Fig. 2: The development of microglia from the yolk sac is Myb independent. CNS macrophages in the the meninges, choroid plexus, and perivascular space originate from the bone marrow and are Myb dependent (Aguzzi et al, 2013)

2.2: Resting state

Microglia are found in the spinal cord, the brain, the optic nerve and the eye. Scanning electron microscopy shows that the microglial membrane is covered with spines (spiky protrusions), which seems to be a unique characteristic to distinguish microglia from other macrophages (Giulian et al, 1995). Microglia are not only the first line of defense against invading pathogens in the CNS, they also perform supportive tasks by interacting with neurons and other glial cells to maintain homeostasis in the brain. Microglia are key regulators in axonal growth and function and terminal differentiation of distinct neuronal subsets (Polazzi and Contestabile, 2002), an example of this is the provoked death of developing Purkinje cells by microglia found in mouse brains (Marin-Teva, 2004). Also in the post-natal brain microglia are primarily important for CNS homeostasis and functioning, although little is known about the daily function of microglia (Kettenman et al, 2011).

The typical morphology of a microglial cell in a non-inflamed brain is ramified, with a small static soma and highly motile fine cellular processes. This morphology is called the “resting”

state and differs significantly from the morphology of other macrophages (Kettenman et al, 2011). The term "resting" should not be used in the sense of inactivity, as these microglia actively survey the local microenvironment by extending and retracting their processes to sample their environment. They respond rapidly to nearby injury or infection by breaking their regular pattern and fast migration to the location of the insult. (Nimmerjahn et al, 2005). Microglia are scattered through the CNS in a way that every cell covers a constant sized, non-overlapping area, as is shown in figure 3 (Cronk and Kipnis, 2013). Activation of the phagocyte effector functions is actively downregulated by neuron-microglia communication. For example, microglial receptor CD200R interaction with the neuronal membrane protein CD200 is known to dampen microglial activation. This is shown by microglial activation in the uninsulted CNS of CD200 deficient mice and an excessive microglial response to experimental brain injury of these mice (Hoek et al, 2000). Also fractalkine (CX3CL1)-CX3CR1 and SIRPα (CD172a)-CD47 interactions prevent the activation of microglia (Brooke et al, 2004; Cardona et al, 2006).

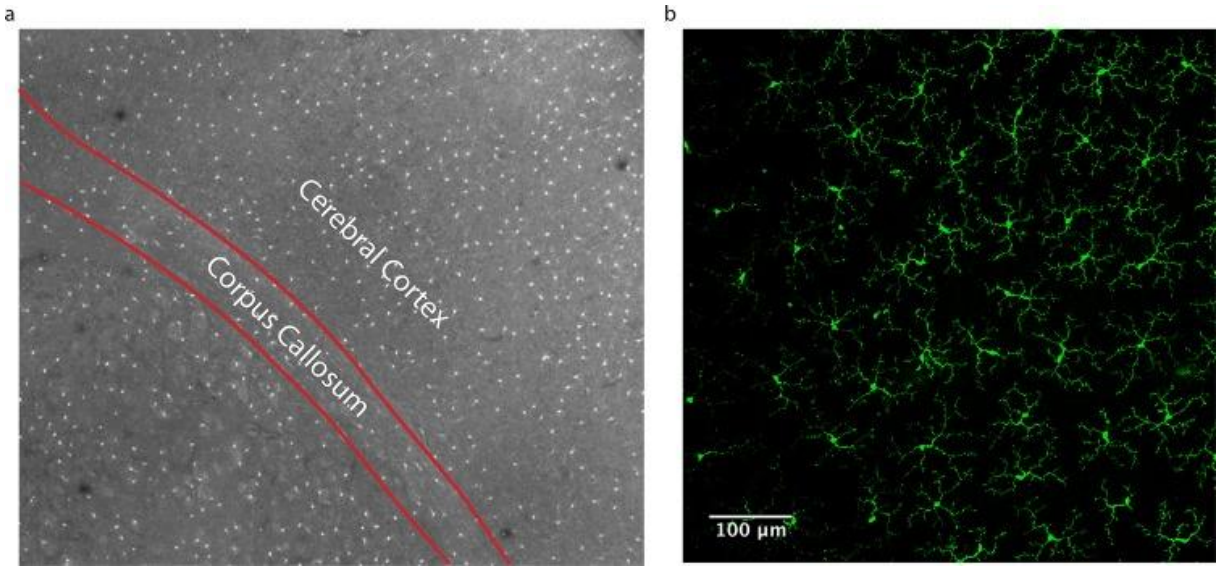

Fig. 3: Microglia in a $CX_3CR_1^{GFP/+}$ mouse, with all microglia carrying the GFP protein. The dispersion of microglia shown in the mouse cerebral cortex (a) and in the optic nerve (b), showing microglia in constant sized, non-overlapping areas (Cronk and Kipnis, 2013).

2.3: Activation

The resting state of microglia is abandoned when they are confronted with endogenous (cell death or protein aggregation) or exogenous threats (pathogens) to the brain homeostasis. Endogenous threats can for example be caused by NDDs, stroke or trauma. As resting microglia are actually actively surveying their environment, the term "activation" can be somewhat misleading. The microglia show changes in morphology, gene expression and behavior which are defined as microglial activation. The cellular complexes are contracted and reabsorbed in the cell body; the cell adopts an amoeboid form like normal macrophages. Microglia become motile, also the soma, and follow chemotactic gradients towards the side of disturbance. This response is pre-programmed to remove or kill the threat and to set the stage for tissue repair (Colton and Wilcock, 2010; Kettenman et al, 2011). To improve the strength of the immunological response and the ability to restore tissue homeostasis, microglia often increase their local densities by proliferation. Bone marrow macrophages may also be recruited from the bloodstream to aid in fighting the disturbance (Shechter et al, 2013).

Both activating factors and the loss of inhibiting factors (like CD200) stimulate microglia to become activated. Because microglia need to respond on very diverse types of threats to the brain homeostasis, they express many surface molecules capable of detecting changes in the nearby environment. Microglia are alerted to invasion of microbes by pathogen associated molecular patterns (PAMPs) and to endogenous threats by damage/danger-associated

molecular patterns (DAMPs) (Kettenman et al, 2011). Pattern recognition receptors recognize microbes: mRNA for Toll-like receptors 1-9 have been found in human brains (Bsibsi et al, 2002). TLR2 and TLR4, located on the microglial cell membrane, are considered key activators of microglia and are also implied to play a major role in NDDs, as they can also be activated by endogenous signals like amyloid β (Choo et al, 2013). Stimulation with TLR4 ligand LPS is a well known method for simulating pathogens to activate microglia (Block et al, 2007). Intracellular PPRs include Nodd-like receptors like NLRP3. After activation, NLRP3 (or some other cytosolic sensor) forms together with adaptor protein ASC and caspases (mainly caspase-1) the so-called 'inflammasome'. The inflammosome can be activated by PAMPs and DAMPs and lead to secretion of IL-1β, IL-18 and caspase-1 activation. The process of inflammosome activation consists of two steps: first, a priming signal often precedes NF-κB to transcribe pro-IL-1β, pro- Il-18 and components of the inflammasome. The second stimulation signal leads to formation of the activated inflammasome, activated caspase-1 and cleavage of pro-IL-1β, pro- Il-18 (Salminen et al, 2009; Walsh et al, 2014); this process is also shown in figure 4. Microglia can also be activated by other microglia via prostaglandins, TNF-α, IL-1β, and chemokines (Aloisi, 2001).

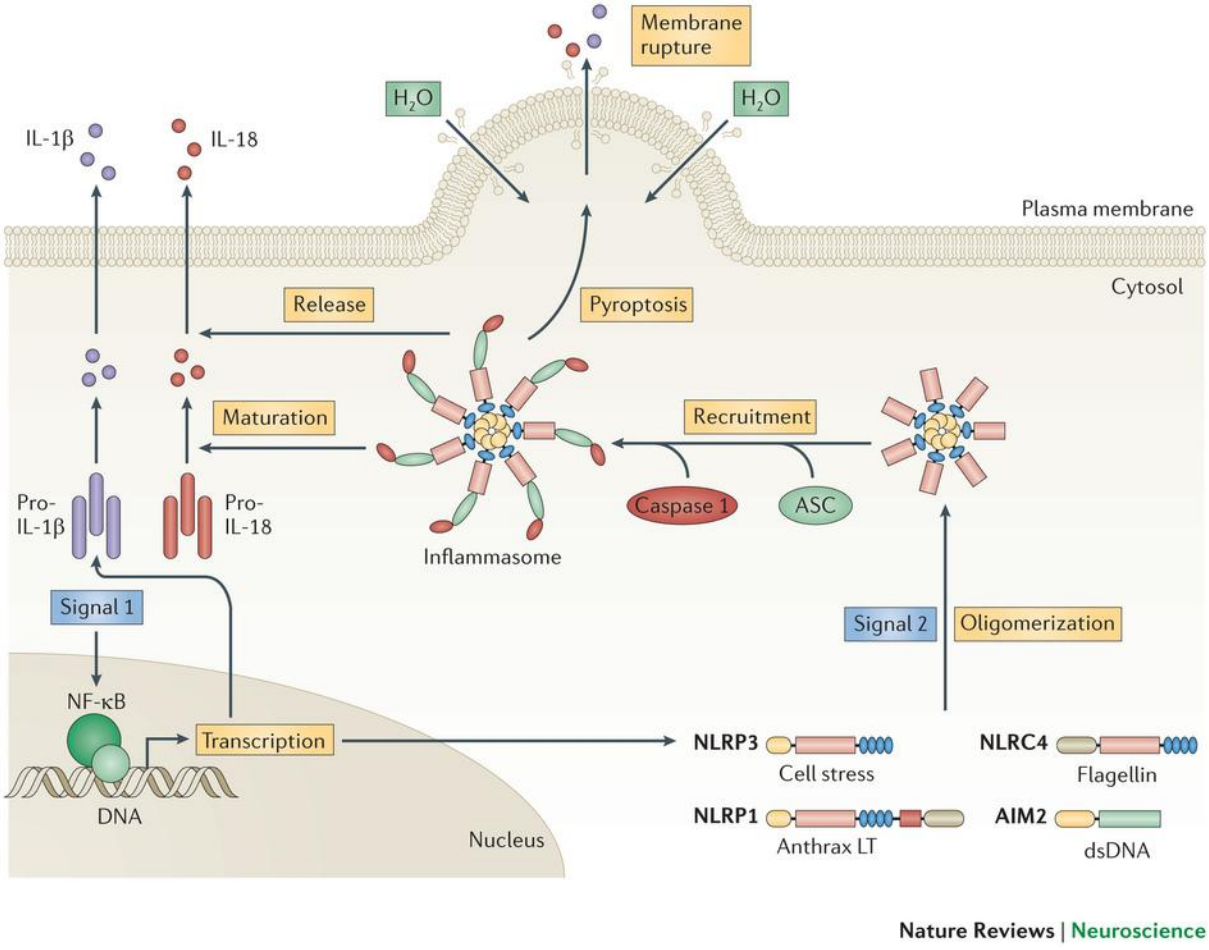

Fig. 4: The inflammasome activation needs 2 signals. A priming signal leads to NF-κB-initiated transcription of inflammasome components, pro-IL-1β and pro-IL-18. After the PPR component of the inflammasome (like NLRP3) recognizes a secondary signal, the inflammasome is constructed and activated. The activated inflammasome initiates a pro-inflammatory response, including the release of IL-1β and IL-18 (Walsh et al, 2014).

Activated microglia show upregulation of innate immune cell surface receptors (pattern recognition, complement, and Fc receptors), antigen-presenting cell capabilities (which they are barely capable of in the resting state) and other cell surface receptors. Activated microglia are the major source of pro-inflammatory (IL-1, TNF-α, IL-6) and immune regulatory (IL-12, IL-18)

cytokines and also produce chemokines and prostanoids (Aloisi, 2001). By producing chemokines and presenting antigens to T cells (especially T helper type 1 cells, due to IL-12 secretion (Ito et al, 2002)), the microglia can also stimulate the adaptive immunity in defeating bacterial or viral infections (Kettenman et al, 2011). This aid of the adaptive immunity is limited by the 'immune privilege' of the CNS, to prevent the brain from an escalated inflammation (Galea et al, 2007). Upon arrival at the lesion site or near the invading microbes the microglia use phagocytosis and the generation of proteases, NO and reactive oxygen species to eliminate the threat to CNS homeostasis (Tan et al, 1999; Aloisi, 2001).

Macrophages show different types of activation. Classical, or M1, activation follows microbial challenge, is initiated by IFNγ and leads to high pro-inflammatory cytokine release and phagocytosis (Mosser and Edwards, 2008). Alternative, or M2a, activation follows Th2 cytokines IL-4 and IL-13. These macrophages use the mannose receptor to phagocytose microbes. They produce anti-inflammatory cytokines like IL-10 and TGFβ as well as pro-inflammatory cytokines and coordinate tissue repair (Gordon and Martinez, 2010). M2-like activation (M2b and M2c) lead to other distinct macrophage phenotypes. Less research is done on different activation strategies of microglia (Mosser and Edwards, 2008). It seems that microglia can adopt M1 or M2 like activation states, but they are more plastic than macrophages and may more easily switch between different activation states, depending on the local environment. Later in the process on inflammation, the microglia may shift their phenotype more towards a supportive tissue-repairing (M2-like) cell. (Town et al, 2005; Perry and Teeling, 2013). While M1-like microglial phenotypes are considered to induce neurodegeneration, the M2-like phenotype is associated with neuroprotection (Colton, 2009).

2.4: Markers

Microglia in the CNS can be visualized using antibodies against proteins on their membrane, nucleus or in their cytosol. Different types of markers can be used to distinguish microglia from other CNS cells. These markers include CD68, CD163, ILB4, CD11b and CD45 (Kettenman et al, 2011; Butovsky et al, 2013). Many markers show increased expression after activation due to CNS injury. Iba1 is a calcium-binding protein that is specifically expressed in microglia in the brain, whose expression is associated with microglial activation in the ischemic brain (dependent on severity of the ischemic brain injury) (Ito et al, 2001).

It is not as easy to distinguish microglia from bone marrow derived macrophages, as virtually all common the aforementioned markers are found on both cell types (Carson et al, 2007). Limited numbers of bone marrow macrophages may possibly cross the BBB and enter the CNS (Cuadros and Navascues, 1998; Varvel et al, 2012). In a healthy brain it is possible to separate these cell types by morphological analysis, but after invasion of bone marrow macrophages this has become impossible.

Infiltrating macrophages can be differentiated from parenchymal microglia by their higher CD45 level, for example in FACS analysis, although this distinction will fade over time (Zhang et al, 2002). Other possible markers to make distinctions are superoxide dismutase and GLUT5 (Enose et al, 2005; Vannuci et al, 1997.) Butovsky et al (2013) identified a genetic and microRNA signature of microglia which can be used to distinguish them from other myeloid cells and other CNS cell types. They discovered 239 genes that were specifically expressed by microglia. Many studies use radiation bone marrow chimerism or mice expressing an inducible myeloid-specific suicide transgene as methodes to distinguish microglia from bone marrow macrophages, especially studies on Aβ clearance (Prinz et al, 2011). This approach has been noted to introduce confounds, as changes were found in BBB function, hematopoietic stem cells and in the brain after radiation bone marrow chimerism (Ajami et al, 2007).

3: MICROGLIAL PRIMING

Recent studies on the aging brain and NDDs have suggested an essential role of priming of the innate immune system. The priming state of immune cells is defined as a sensitized, reactive state which is presented as an altered morphology, enhanced expression of certain cell-surface molecules and a moderately increased secretion of inflammatory cytokines. Aging, NDDs or peripheral inflammation have all been suggested to provide priming signals. Primed immune cells show an exaggerated response to an inflammatory challenge compared to immune cells which are not exposed to priming signals (Cunningham et al, 2005; Norden and Godbout, 2013).
For optimal activation, bone marrow macrophages require both a priming stimulus, a well-known is IFN-γ, followed by a secondary triggering stimulus, LPS for example (Dalton et al, 1993). This concept has already been shown in vitro with macrophages, which are primed to IFN-γ prior to a TLR agonist challenge. These macrophages show a stronger inflammatory response compared to macrophages challenged with TLR agonist without prior IFN-γ exposure (Schroder et al, 2006). After priming, the macrophages are in a more sensitized state and have an increased expression of certain cell-surface receptors, including MHC class II (Schroder et al, 2006). More recently, also aged microglia are found to be primed (see figure 5A). In the brain of healthy aging mice, microglia are found to increase their MHC II expression without being activated, while MHC II expression is normally a marker for microglial activation. Central or peripheral administration of LPS in these mice leads to an exaggerated inflammatory response, including the secretion of pro-inflammatory cytokines (Godbout et al, 2005; Perry et al, 2009). IFN-γ concentrations are increased in the brain of aging humans; IFN-γ is normally used to experimentally induce macrophage priming (Maher et al, 2006). Also peripheral signals are found to be functioning as priming or secondary stimuli (Perry et al, 2007; Lee et al, 2002). Primed microglia respond longer and stronger to a secondary stimulus than non-primed microglia (Perry et al, 2007).

3.1: Primed microglia

Cell-surface markers are the most potent indicators microglial priming. Aging microglia show besides MHC II also an increasing expression of ED1, LCA, CD4, CD68, F4/80 and CD11c, TLRs and complement receptors. (Kullberg et al, 2001; Hart et al, 2012; Godbout et al, 2005). Many of the molecules that show increasing expression over age are also strongly expressed in activated, non-ramified microglia (Perry et al, 2007). Another characteristic of primed (aged) microglia is their altered morphology compared to non-primed (younger) microglia. A partial reduction in protrusions and a larger cell body was shown in microglia of aging mice which could indicate decreased tissue monitoring of these resting microglia (Sierra et al, 2007). The morphologically priming (larger with thicker protrusions) of aged microglia can be correlated with a higher MHC II protein expression (Vanguilder et al, 2011). Microglia in the aged brain show also hypertrophy of their cytoplasm, cytosolic inclusions and a dislocated nucleus (Conde and Streit, 2006). Primed microglia in healthy aged brains not only express several receptors more intensely, but have also been found to moderately increase their baseline secretion of several pro-inflammatory markers, including TNFα, IL-1β, IL-6, and IL-12b/p40 mRNAs. Contrastingly, IL-10 and TGFβ expression, which are anti-inflammatory, were even stronger increased by these microglia (Sierra et al, 2007; Henry et al, 2009). These anti-inflammatory cytokines may prevent the primed microglia from further activation in absence of a secondary triggering signal, leaving these microglia in a long-term steady state.
The increasing expression of complement receptors and TLRs (Godbout et al, 2005) during aging, may explain the sensitized state of primed microglia, as the threshold for activation is lowered by this increase in number of receptors. TLR2 and TLR4 levels are increased in aging

brains and stimulation with their agonists leads to a stronger pro-inflammatory response in aged mice compared to younger mice (Njie et al, 2012).

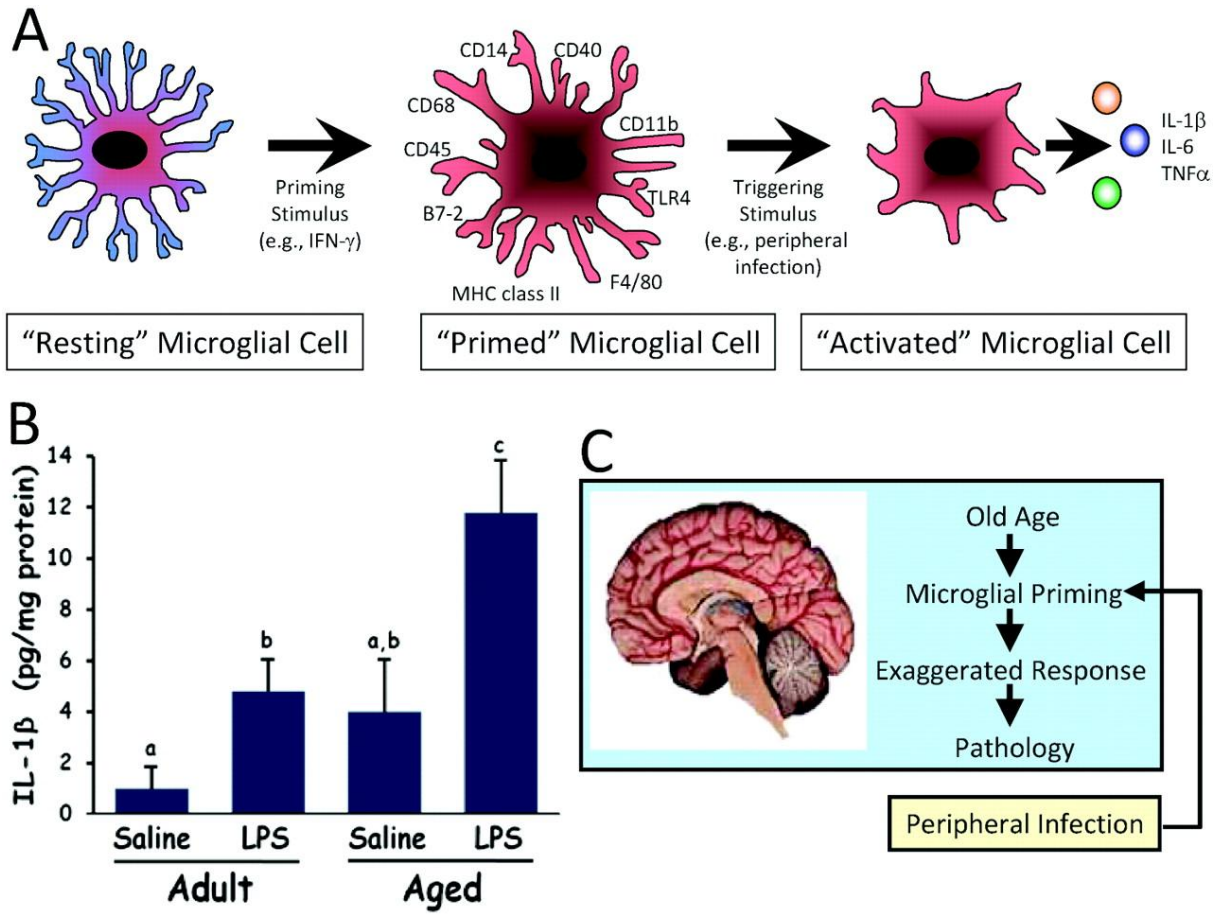

Fig 5: The process of microglial priming. ***A*** *shows that a priming stimulus like IFN-γ, lead to a microglial cell with a different morphology (larger cell body and thicker contracted processes) and enhanced expression of cell-surface markers (like MHC II). Triggering of these primed microglia by a secondary signal leads to activated pro-inflammatory microglia.* ***B*** *shows that the primed microglia (due to aging) express moderately higher baseline levels of IL-1β than non-primed (adult) microglia, but secondary LPS stimulation leads to considerably larger response. Together (****C****), a priming signal (aging) and a triggering signal (peripeheral infection) lead to an exaggerated response which eventually results in pathology (Dilger and Johnson, 2008)*

3.2: Impaired microglial regulation leads to priming

A member of the complement system, C3, is also suggested as one of the inducers of microglial priming. Deletion of C3 convertase, Crry, leads to higher levels of C3 and its cleavage products C3b and iC3b. Binding of C3b and iC3b has proven to prime microglia and lead to dramatically enhanced responses to secondary LPS stimulation (Ramaglia et al, 2012). Godbout et al (2008) found that depressive behavior was more pronounced in aged mice after LPS injection. The microglia of these aged mice showed a stronger upregulation of the IDO pathway, indicating the involvement of IDO in the primed microglial response.

Healthy microglia are normally prevented from going into activation by several neuron-produced proteins. Decreased levels of CD200 (and IL-10) were found in aged mice compared to younger rats (Frank et al, 2006). Microglia of CD200−/− mice show heightened responses to LPS in vitro, indicating a primed state of these cells (Costello et al, 2011). Neuron-derived fractalkine (CX(3)CL1) ligand levels, normally maintaining microglia in a quiescent state, are reduced in the

brains of aged rats. Treatment with fractalkine attenuates age-related increase in microglial activation (Lyons et al, 2009).
IL-4 levels reduce with age and microglial response to the anti-inflammatory effects IL-4 decreases as well (Fenn et al, 2012). Deficits in pathways of other anti-inflammatory cytokines, IL-10 and TGFβ, are also suggested to lead to a reduced capability to shut off microglia (Norden and Godbout, 2013). Glucocorticoids and certain neurotransmitters may also play a role in microglial priming (Cunningham, 2013).

3.3: Secondary stimulation

The Me7 model of prion disease in mice is a commonly used model, because these mice suffer from a neurodegenerative disease that starts in the hippocampus and has many characteristics of AD, especially neuroinflammation (Cunningham et al, 2005). In this model, microglia expressed higher levels of cull-surface proteins like F4/80, CD11b, and CD68, but do not secrete proinflammatory cytokines, but instead secrete TGFβ and prostaglandin E2. Only a secondary triggering signal 'switches' these microglia from its primed state towards an aggressive proinflammatory phenotype, including expression of IL-1β, IL-6, TNFα and iNOS, resulting in a significantly faster progression of the disease (Cunningham et al, 2005).
The difference between unprimed activation and primed activation of microglia was shown in the same 2005 study of Cunningham et al. While direct application of LPS to the brain of healthy mice only resulted in a moderate IL-1β secretion, no iNOS secretion and subsequently very limited neutrophil infiltration took place. Primed microglia, by using the ME7 model of prion disease, did not only show higher IL-1β secretion, but also abundant iNOS expression and massive infiltration of neutrophils after (secondary) application of LPS. This principle has been proven in many different settings and with different central stimuli and cytokines (Xie et al, 2003; Huang et al, 2007; Abraham et al, 2008). The responsibility of microglia for the exaggerated reaction to secondary stimuli was proven by using minocycline, known to be an anti-inflammatory microglia inhibitor (Nikodemova et al, 2007). Minocycline administration reduces age-related MHC II upregulation and normalizes inflammatory reactions on LPS in aged mouse brains (Griffin et al, 2006; Henry et al, 2008). Not only magnitude, but also the duration of the response is higher after triggering primed microglia. IL-1β, TNFα and IDO expression was found to be prolonged in aged mouse brains after LPS stimulation (Godbout et al, 2008). Not only central stimuli, but also peripheral signals can prime or trigger microglia. Aged microglia show an exaggerated response to systemic inflammation (Godbout et al, 2005), pointing to existence of mechanisms transferring markers of systemic inflammation across the BBB (see figure 5A, 5B and 6). A minor abdominal surgery leads to neuroinflammation 24 hours later in aged mice but not in younger mice (Rosczyk et al, 2008). Aged brains show a stronger and prolonged response to a challenging life event such as a severe bacterial infection, surgery, or an intense psychological stressor, leading to profound memory impairments. The primed state of the aged microglia appeared to be the source of this amplified response (Barrientos et al, 2012). Peripheral LPS stimulation of microglia also increased both pro- and anti-inflammatory cytokine production, like respectively IL1β and IL-10. Clear evidence for primed microglia as the cause of the neuroinflammation is the finding that MHC II+ microglia are responsible for this increased cytokine production (Henry et al, 2009). Integration of the peripheral immune system to the immune system in the brain is normal in healthy brains. Activated by the peripheral immune system, normal microglia produce cytokines to coordinate a behavioral response (sickness) that is normally adaptive. The released cytokines (including IL-1β, IL-6 and TNFα) also stimulate the production of secondary inflammatory mediators like NO and prostaglandins (Goehler et al, 1999) and this results in sickness behavior that assists the immune reaction to the peripheral infection. Humans with a peripheral infection, for example in the upper respiratory tract, experience changes in mood and cognitive function (Bucks et al, 2008). In case of aging, infectious agents (like S. typhimurium (Püntener et al, 2012)) or NDDs this integration gets distorted, leading to acceleration of disease symptoms. Prolonged release of the pro-inflammatory mediators also leads to the prolonged presence of sickness symptoms, as well as cognitive impairments (Bucks et al, 2008; Corona et al, 2012; Burton and Johnson, 2012).

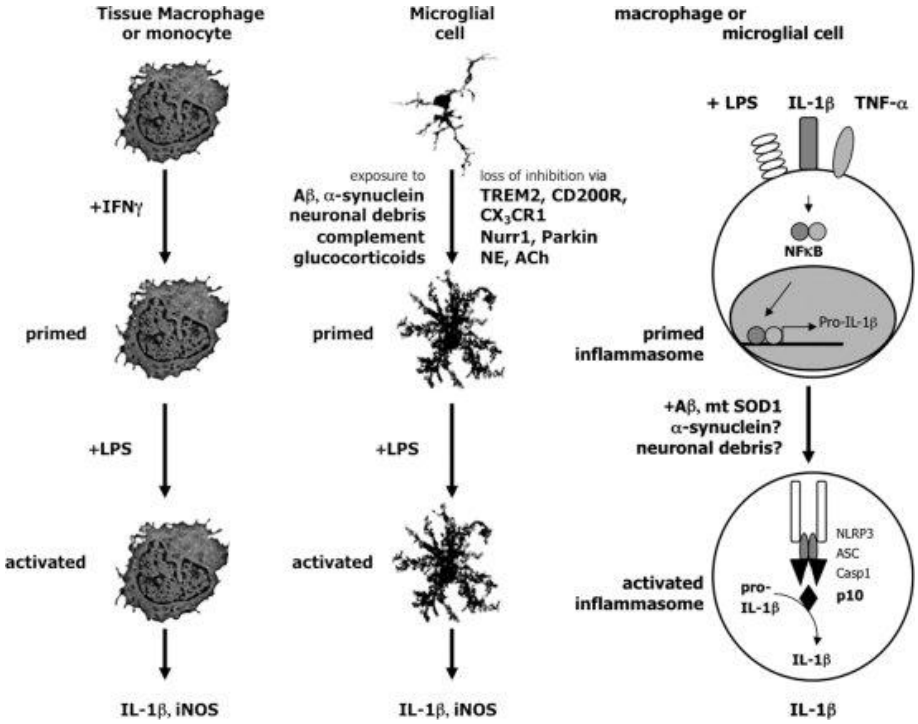

Fig 6: Three processes in which a priming stimulus leads to a (exaggerated) response after a secondary triggering stimulus. Bone marrow macrophages are well known to be primed by IFNγ, but this is also the case for microglia. Microglia can be primed by a lot of other stimuli, including proteins involved in NDD, and by loss of inhibition. After secondary stimulation, macrophages and microglia are fully activated and produce, among others, IL-1β. Macrophage and microglial inflammasomes can also be primed, leading to the induction of pro-IL-1β transcription and translation. Only after secondary stimulation, for example by proteins involved in NDD, the inflammasome becomes fully activated and is capable of inducing the secretion of IL-1β (Cunningham, 2013).

3.4: Peripheral signals entering CNS

What is the mechanism by which signals of peripheral inflammation reach the brain?

The brain and the peripheral immune system are separated by the BBB. During peripheral inflammation several mechanisms could be responsible for communication across the BBB. The first and fastest mechanism of communicating is via the afferent neural pathways like the vagal nerve, "the inflammatory reflex" (Tracy, 2002). Other, slightly slower mechanisms are also possible. Circumventricular organs may be the "gate" across the BBB; these organs are located close to the hypothalamus and lack a contiguous BBB. Cytokines are able to passively diffuse into the CNS from the bloodvessel in the circumventricular organs (Komaki et al, 1998). The BBB itself can also be crossed by cytokines in an energy-dependent way. Several interleukins and TNFα are known to be transported into the CNS this way, although this process is saturable (Banks et al, 1995). The cytokines may also affect the endothelial cells in the brain which in turn release new cytokines on their CNS side (Fabry et al, 1993). Prostaglandin E_2 is one the most important of these new cytokines in this process, as it can more easily cross the endothelial membrane due to its small size and lipophilic properties (Ek et al, 2001). The cytokines entering the CNS by one of the aforementioned mechanisms are bound to TLR2, TLR4, beta-adrenergic receptor or other receptors on the membrane of nearby microglia, resulting in microglial priming or an inflammatory response in the brain (Johnson et al, 2013; Weber et al, 2013).

4: NEUROINFLAMMATION IN ALZHEIMER'S DISEASE

Mice expressing mutant APP or tau do not show massive neuronal loss like human AD patients. This suggests that addition of a different component of AD, besides plaques and tangles, is necessary for neurodegeneration: neuroinflammation. Brains of NDD patients, including AD and PD, are considered to be in a state of chronic neuroinflammation, shown as activation and proliferation of microglia (Bamberger et al, 2003). Mouse AD models have shown microglia activation even before the formation of amyloid plaques (Heneka et al, 2005). Targeting the immune system may dampen the pathologic response of the immune system against the pathogenesis of amyloid β.

The net deposition of amyloid β in the brain is equal to the production of amyloid β minus its clearance. Increase of amyloid β production or a decreased clearance capability will lead to the AD pathology. It can be stated that familial early-onset AD is related to amyloid β overproduction, while late-onset AD is preceded by a decreased amyloid β clearance from the brain (Eikelenboom et al, 2011; Mawuenyega et al, 2010). Amyloid β is known to be an activating factor for microglia and it is a possibility that low levels of amyloid β will prime microglia in earlier stages of AD (Dilger and Johnson 2008).

The presence of amyloid β plaques are, together with tau pathology, one of the major hallmarks of AD. Post-mortem studies have found an accumulation of myeloid cells around these plaques, either resident microglia or bone-marrow derived macrophages (Mackenzie et al, 1995). In early stages of AD, microglia are found near diffuse amyloid β plaques (Akiyama et al, 1999), but they are more predominantly found near the more dense fibrillary amyloid β plaques (Mackenzie et al, 1995); these microglia express MHC II molecules, indicating either a primed or an activated state. Ly-6C^{hi} monocytes or bone marrow–derived progenitors, like granulocyte-macrophage progenitors, are able to infiltrate the CNS during NDD, even without obvious BBB breakdown (Malm et al, 2005).

4.1: Systemic inflammation effects on AD

Peripheral infections, acute or chronic, are associated with an increase in cognitive decline in AD patients; this was concluded after measuring serum TNFα levels in AD patients (Holmes et al, 2009).

An acute example of this is delirium, which is a severe neuropsychiatric syndrome that is characterized by changes in arousal and cognitive deficits, like severe confusion and disorientation. Delirium is related to aging and is highly prevalent in AD patients (Murray et al, 2012). Delerium is caused by systemic inflammation, which serves as a secondary triggering factor for primed mircoglia and leads to acute cognitive impairments (which can be reversible) and accelerated cognitive decline in AD patients (see fig 7) (Murray et al, 2012; Fong et al, 2009). Systemic administration of LPS for 12 weeks in APPswe transgenic mice found to increase APP expression and neuronal processing of APP, leading to increased intraneural amyloid β generation (Sheng et al, 2003). This indicates that peripheral inflammation has direct effects on amyloid β levels, although and later was proven that systemic LPS indeed leads to extracellular plaques as seen in AD, probably by altering β- and γ-secretase activities (Lee et al, 2008). Systemic inflammation also exaggerates neurodegeneration in AD by increasing microglial activation, which leads to detrimental secretion of pro-inflammatory cytokines like IL-1β, IL-6 and TNFα as well as induction of iNOS and NADPH oxidase (Cunningham, 2012).

Tau pathology is another hallmark of AD progression. In AD, cleavage of tau protein induces its hyperphosphorylation and the formation of neurfibrillary tangles (Rissman et al, 2004). LPS treatment for six weeks in AD mice increased the severity of tau pathology, by increasing tau hyperphosphorylation (Kitazawa et al, 2005). Pro-inflammatory cytokines can disrupt intracellular patterns of tau in human derived glial cells (Bick et al, 2008). Tau pathology mouse models show neuroinflammation, with co-localization of aggregated tau, IL-1β, COX-2 and

microglial activation. This neuroinflammation actually precedes the formation of tangles in these mice (Belluci et al, 2004; Yoshiyama et al, 200&), implicating a role of neuroinflammation in linking amyloid β deposition and the formation of neurofibrillary tangles.

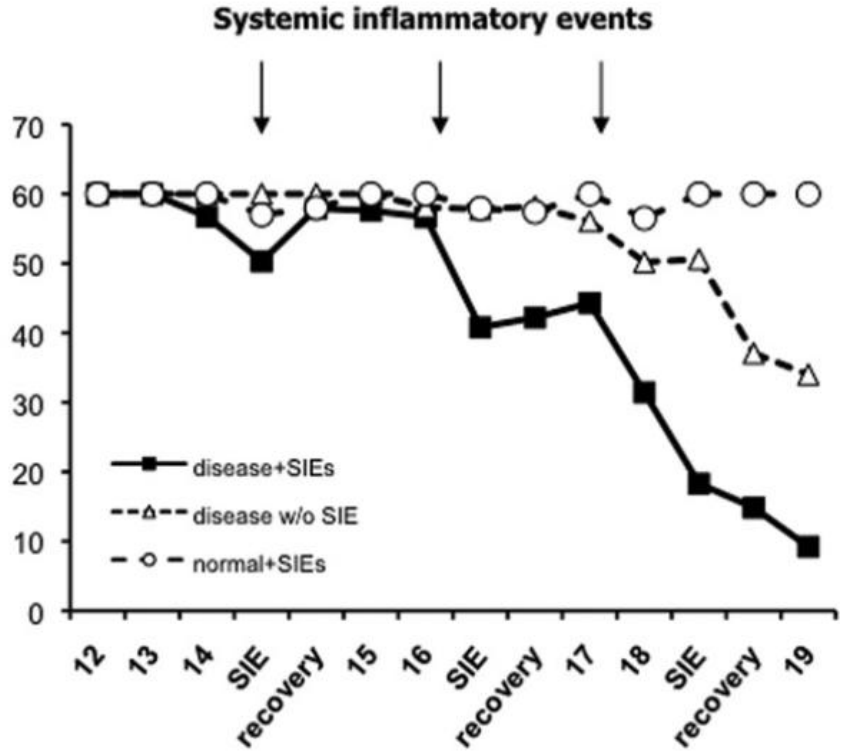

Fig. 7: effects of systemic inflammation on co-ordination of motor function of Me7 mice. This was measured by the horizontal bar test, in which 60 seconds is the optimal score. Mice without the Me7 prion disease showed no observable effect of systemic inflammatory events (administration of a TLR ligand) on their test score. Mice with this disease showed an acute effect of the systemic events on their test performance, followed by recovery to baseline levels or stabilization early in the disease. With progression of the disease, a systemic inflammatory event induces a strong and progressive decline in motor function co-ordination. Me7 animals without confrontation with systemic inflammatory events show a gradual decrease of motor co-ordination, but this decrease is moderate compared to Me7 animals confronted with 3 systemic inflammatory challenges. This model mimics the effects of inflammation in AD patients, where it can cause a reversible state of delirium but also induce accelerated cognitive decline (Cunningham, 2012; Field et al, 2010; Murray et al; 2012).

4.2: Microglial amyloid β phagocytosis

Microglia are able of phagocytosing amyloid β by a cell surface receptor comprising of CD36, α6β1 integrin and CD47 (Koenigsknecht-Talboo and Landreth, 2004). Nevertheless, they do not seem to influence amyloid β deposition, as a mouse model using selective depletion of microglia did not find changes in plaque formation and amyloid β levels (Bamberger et al, 2003; Grathwohl et al, 2009). Microglia are attracted toward amyloid plaques but do not appear to be able clear them. Continuous amyloid β stimulation seems to impair microglial functions like directed process motility and phagocytic activity, especially to microglia close to plaques. Vaccination with amyloid β surprisingly restored microglial function in these acute brain slice preparations (Krabbe et al, 2013). On the other hand, amyloid β phagocytosis is necessary for some types of further pro-inflammatory signaling (Halle et al, 2008). The pro-inflammatory cytokines subsequently suppressed phagocytic activity of microglia, at least in vitro (Koenigsknecht-Talboo and Landreth, 2005). Besides the increased pro-inflammatory cytokines,

also CD40 ligand co-stimulation of microglia in presence of amyloid β shifts the activated microglial phenotype from phagocytic towards antigen presenting (see fig. 8) (Town et al, 2005).

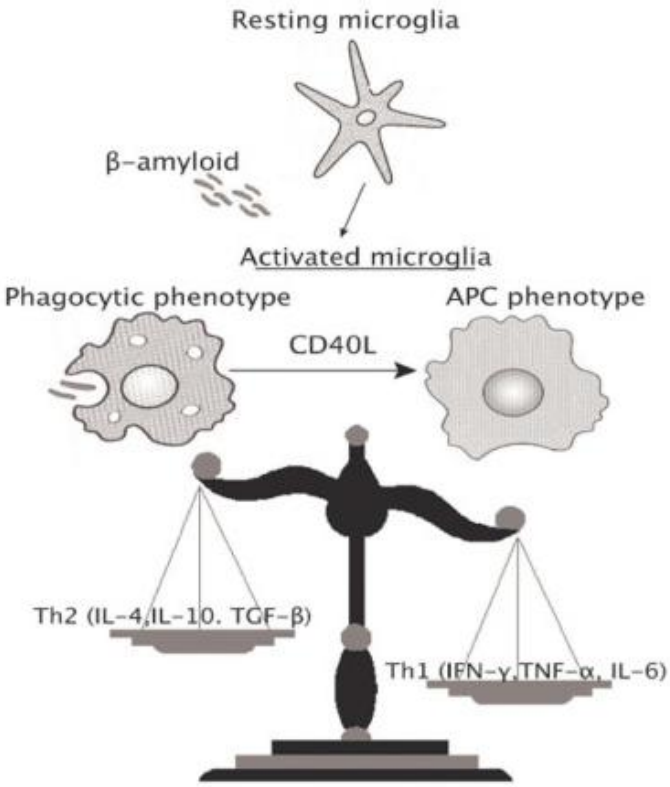

Fig 8: Resting microglia are activated by amyloid β. In the presence of CD40 ligand, activated microglia shift from a phagocytic phenotype towards an antigen presenting phenotype. T helper type 1 cell associated (pro-inflammatory) cytokines aid to this shift, but are partly counteracted by T helper type 2 cell associated cytokines (Town et al, 2005).

4.3: Priming and the inflammasome

Microglial priming (resulting in upregulation of MHC II among others) is detected in AD mice models. Microglia of AD mice show exaggerated inflammatory response (cytokines and NO) to systemic LPS administration (Lee et al, 2002), in accordance with the reaction of aged or IFNγ-primed microglia. Microglial priming and their pro-inflammatory hyperactivity after secondary stimulation may aggravate neurodegeneration in AD. Indeed studies have suggested that microglia which secrete high levels of pro-inflammatory cytokines have reduced phagocytic capacities (Koenigsknecht-Talboo and Landreth, 2005). Older microglia have reduced phagocytosis compared to younger mice in an AD mouse model (Hickman et al, 2008). Amyloid β is thought to be the priming signal for microglia, which is followed by a triggering secondary signal due to central or peripheral inflammation, caused by LPS among others. Specifically in areas of prior pathology, microglial activity is induced (Cunningham, 2012).

An important cytosolic amyloid β sensing pathway involves the construction of the inflammasome, caspase 1 activation and IL1β/IL-18 secretion after activation of intracellular PPRs like NLRP3. The NLRP3 inflammasome is activated by signs of damage and inflammation like ROS, mitochondrial dysfunction and K^+ efflux (Walsh et al, 2014) but also by NDD-associated proteins like fibrillary amyloid β and aggregated α-synuclein (Halle et al, 2008; Codolo et al, 2013). Amyloid β stimulation of inflammasomes stimulated leads to a pro-inflammatory response if these inflammasomes are already stimulated with a priming signal like LPS (leading

to pro-IL-1β and pro-IL-18 transcription); this activation also requires microglial phagocytosis of the amyloid β (Halle et al, 2008). In addition, the same study found involvement of cathepsin B release and endosomal rupture in the inflammasome pathway (Halle et al, 2008). Cathepsin B is found in larger amounts in microglia surrounding plaques (Mueller-Steiner et al, 2006). Cleaved caspase-1 levels are elevated in AD patients, proving inflammasome activation; NLRP3 inflammasome activation was restricted to plaque-associated microglia (Heneka et al, 2013). Knockout of NLRP3 or caspase 1 in an AD mouse model resulted in enhanced amyloid β clearance, absence of neurobehavioral defects and a phenotypical shift of microglia towards the more anti-inflammatory M2-type (Heneka et al, 2013). Capase-1 activation by the inflammasome is even more of interest as it can lead to cleavage of the tau protein by the induction of caspase-6 (Guo et al, 2006). This implicates a role for the NLRP3 inflammasome in linking amyloid β accumulation with tau pathology

It should be noted that in many of the inflammasome studies, LPS is responsible for the priming of the inflammasome, followed by a secondary signal from amyloid β. Studies on classical priming of microglia use LPS as secondary signal after microglial priming due to aging or by exposure to NF-κB, α-synuclein or amyloid β. It may be possible that microglial activation can be achieved by amyloid β exposure after priming with markers of (systemic) inflammation like LPS. Vice versa could be suggested that inflammasomes could be primed (e.g. assembly of its compartments and transcription of pro-IL-1β and pro-IL-18) by amyloid β and subsequently be activated by systemic infection, eventually leading to secretion of high levels of caspase 1, IL-1β and IL-18.

4.4: Microglia become primed/activated by amyloid β interaction with TLR2/4

Both Toll-like receptor 2 and 4 are considered as key receptors involved in microglial activation in AD leading towards a M1-like phenotype. TLRs, like all PPRs, respond to contact with either PAMPs or DAMPs; Amyloid β fibrils acts as a DAMP signal (see paragraph 2.3) for many PPRs, including TLR2 and TLR4. Activation of these TLRs leads downstream signaling resulting in transcription of many inflammatory regulators (Udan et al, 2008). TLR2 and TLR4 are essential for amyloid β phagocytosis; both TLR2 and TLR4 knockouts lead to increased levels of amyloid β in the brain (Tahara et al, 2006). But activation of TLR2 and TLR4 also leads to a more pro-inflammatory M1-like phenotype, including the induction of iNOS and TLR4 expression is found to be increased in AD (Walter et al, 2007; Palencia et al, 2008). Co-receptors like CD14, CD36 and MD-2 regulate TLR activation (Akashi-Takamura and Miyake, 2006); especially CD14 is a key player in activation of TLRs by fibrillary amyloid β (Fassbender et al, 2004). Amyloid β stimulation of TLR2 and TLR4 is followed by an exaggerated response (including high iNOS induction) to their respective agonists Pam3Cys and LPS (Lotz et al, 2005), which indicates that these TLRs are involved in microglial priming by amyloid β. So TLR2 and TLR4 may be protective in the case of its initiation of amyloid β phagocytosis, but during the development of AD they turn the microglia more towards a neurotoxic, pro-inflammatory phenotype. This may be due to development immunotolerance for amyloid β. It may also be wise to consider the aggregation state of amyloid β, as fibrillary amyloid β can act on different receptors than soluble amyloid β (Lee and Landreth, 2010; Lucin and Wyss-Coray, 2009).Recently, Weber et al (2013) described a novel TLR2 and TLR4 antagonist which was successfully used to prevent microglial priming by stress sensitization and thus prevented the exaggerated response to a secondary immunologic challenge.

4.5: Other actors in microglial activation

The key actors in AD-associated neuroinflammation are cytokines, but several studies have also provided evidence of the involvement of chemokines. CCL2 (or MCP-1) and its receptor plays a major role in attraction of bone-marrow macrophages. CCL2 is produced by astrocytes, microglia and infiltrating macrophages in a response to amyloid β (Ishizuka et al, 1997); CCR2 expression is found on many different types of immune cells including microglia (Boddeke et al,

1999; Yamasaki et al 2012). CCL2 interaction with CCR2 leads to microgliosis and facilitation of amyloid β oligomerization (Kiyota et al, 2009), possibly by enhancing ApoE expression (Yamamoto et al, 2005). Microglia are less prone to activate in response to pro-inflammatory stimulation in CCL2 null mice (Rankine et al, 2006).
The complement system cooperates with anti-amyloid β IgG antibodies and Fc receptors to initiate increased amyloid β phagocytosis (Lee and Landreth, 2010). FcγRIII and FcγRIV, but not inhibitory FcγRII are markedly upregulated after systemic LPS challenge of primed microglia, together with IgG leakage into the brain (Lunnon et al, 2011). IgG leakage into the brain is common in AD, mainly due to the ageing-related increased BBB permeability (Cunningham et al, 2012). Increased BBB permeability will also lead to stronger signal entrance of peripheral inflammation into the CNS. The process of IgG crossing of the BBB has been used in studies on amyloid β immunization. Humans immunised against amyloid β have shown a dramatic increase in amyloid β clearance, although this was not accompanied with clinical benefit (Holmes et al, 2008).
The complement system is a key participant in the innate immune system and the complement cascade is revealed to be strongly induced in NDD; amyloid β is able to initiate both neuroinflammatory antibody-dependent (C1q) and –independent pathways (C3b) (Lee and Landreth, 2010). The increased IgG levels may also be a trigger for complement activation. Complement products, including the membrane attack complex, are colocalized with fibrillary amyloid β plaques (Webster et al, 1999). C3 cleavage products have been proven to prime microglia (see paragraph 3.2), but C3 inhibition leads to amyloid β accumulation and neurodegeneration (Wyss-Coray et al, 2002), showing the opsonizating effects of C3. The membrane attack complex, a possible cause of bystander cell lysis, is found in post-mortem AD brains and it was suggested that secondary inflammatory stimulation is necessary for complete construction of this complex (Cunningham, 2012). See also figure 9.

Fractalkine (CX3CL1) is produced by neurons and binding with microglial CX3CR1 inhibits microglial activation (Ransohof, 2009). Neurodegeneration will initially lead to increased release of fractalkine (increased inhibition), but massive neuronal loss eventually leads to decreased fractalkine levels (decreased inhibition), associated with increased IL-1β levels. Decrease of fractalkine inhibition of microglia leads to increased amyloid β phagocytosis, but this comes at the cost of increased tau pathology (Prinz et al, 2011). CX3CR1 levels in aged microglia are protractedly downregulated in mice after peripheral LPS injection and this was accompanied by increased IL-1β levels (Wynne et al, 2010). As fractalkine levels are also decreased in aging and fractalkine treatment inhibits microglial activation (Lee et al, 2010; Lyons et al, 2009), fractalkine and its receptor may play an important role in preventing microglial priming or activation in AD.

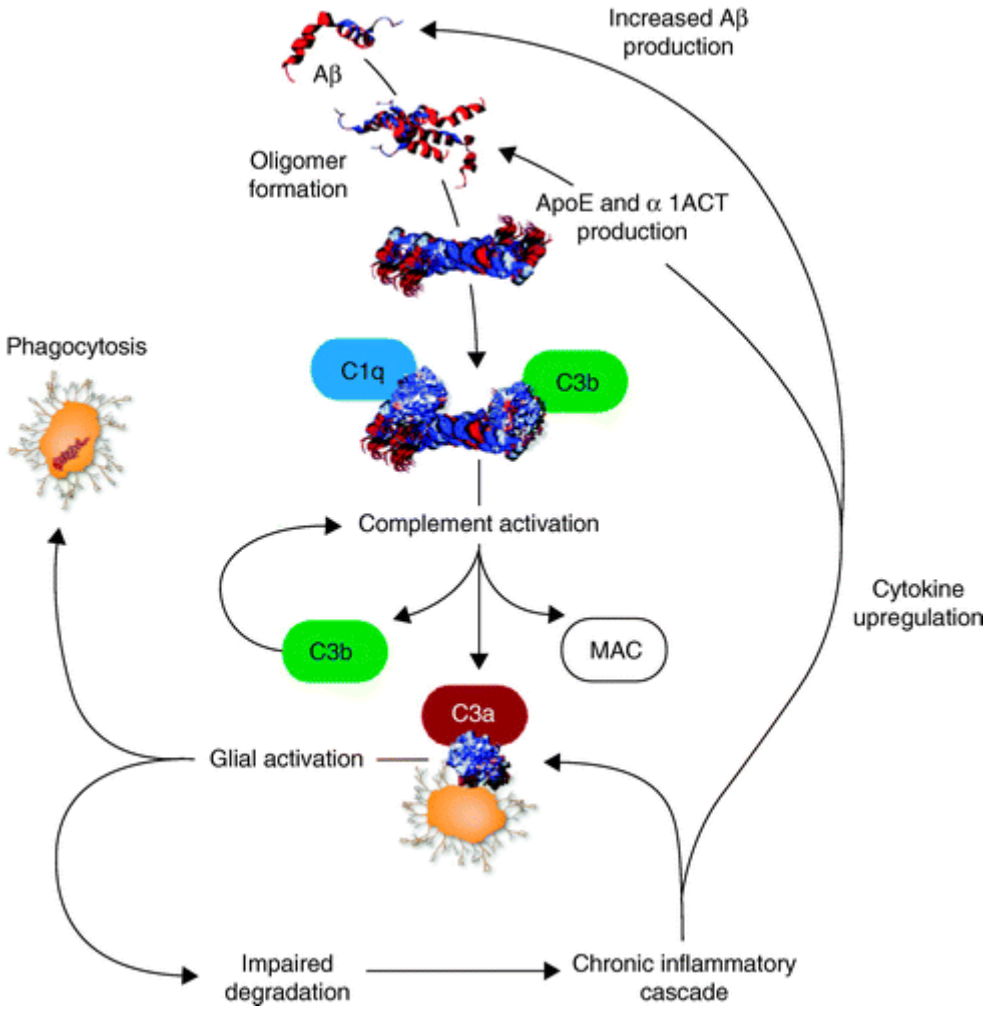

Fig. 9: The involvement of the complement system in AD. Amyloid β oligomerization initiates the complement cascade, resulting in increased phagocytosis but eventually also in chronic inflammation due to impaired amyloid β degradation. Positive feedback loops lead to increased complement activation, microglial activation and amyloid β production/ oligomerization (Weggen et al, 2007)

RAGE is a cell surface protein on microglia and endothelial cells (among others) that acts as a PPR for inflammatory proteins as well as amyloid β oligomers and promotes amyloid β transport from the plasma into the CNS. RAGE activity is balanced by LRP-1, which exerts the reverse function and transports amyloid β out of the CNS (Choo et al, 2013). RAGE activation initiates a pro-inflammatory pathway in microglia leading to NF-κB activation which also increases RAGE expression itself (Bierhaus et al, 2005). NF-κB activation is considered to be the priming signal of microglial inflammasomes, after which secondary triggering leads to IL-1β, IL-18 and caspase-1 secretion (Walsh et al, 2014). RAGE levels are increased in aged mice (Hickman et al, 2008) which implies an explanation of the increasing incidence of AD with age.
P2X7 receptor (P2X7R) expression is increased in AD and senses ATP released by necrotic neurons. P2X7R signaling leads to microglial activation and release of pro-inflammatory cytokines (thereby starting a positive feedback loop by damaging neurons) (Monif et al, 2010). PPARγ is a nuclear hormone receptor and PPARγ signaling enhances microglial amyloid β uptake; CD36 mediates this process. PPARγ stimulation in AD mice increased microglial recruitment to plaques and CD36 expression, decreased amyloid β burden; these mice had an improved cognitive performance in the Morris water maze (Yamanaka et al, 2012).

4.6: Effector mechanisms of activated microglia

Microglia priming leads to disease exacerbation of NDDs, including AD and PD (Perry, 2010; Couch et al, 2011). Prion diseased animals show increased neuronal apoptosis and accelerated onset of behavioral deficits after a secondary LPS challenge (Perry, 2010); similar results have also been found in an AD mouse model (Lee et al, 2008). This microglial activation involves the production and secretion of regulatory and pro-inflammatory cytokines, due to cleavage of pro-IL-β by caspase 1. IL-1β is a pro-inflammatory cytokine which acts on the IL-1R1 receptor which leads to the induction of pathways resulting in NF-κB activation (Parker et al, 2002). IL-1β expression is dramatically increased after activation by systemic inflammation of primed microglia in the ME7 model of prion disease (Cunningham et al, 2005). IL-1β activation may eventually lead to induction of effector mechanisms like iNOS, COX, NADPH oxidase and proteases (Cunningham, 2011). IL-1β and TNFα also create a positive feedback loop in which they stimulate the expression of pro-inflammatory cytokines, like IL-1β and TNFα themselves (Griffin et al, 1998). TNFα secretion is increased by many of the same stimuli as IL-1β and also leads to NF-κB activation after binding to TNFR1, resulting in expression of effector enzymes like iNOS and proteases (Pugazhenthi et al, 2013). More than IL-1β is TNFα directly involved in apoptosis; direct engagement of p55 with its receptor is already sufficient to induce apoptosis by initiating a pathway involving TRADD, FADD and caspase 8 (Micheau and Tschopp, 2003). The fate of the cell depends on the balance between the NF-κB pathway and the apoptosis pathway (Beg and Baltimore, 1996). In combination with IFN-γ, TNFα or IL-1β triggered increased amyloid β production by astrocytes, thus creating a positive feedback loop (Blasko et al, 2000) IL-6 is in many cases upregulated together with IL-1β and TNFα and has like these cytokines neurotoxic effects (Allan and Rothwell, 2002). It is though a more multifunctional cytokine and also has more regulatory immunosuppressive effects (Raivich et al, 1999). IL-18 is a main product of inflammasomes: caspase 1 cleaves pro-IL-18 which induces IFNγ secretion (Gu et al, 1997). Microglia also produce anti-inflammatory cytokines like IL-4 (a Th2 cytokine), IL-10 (a M2 cytokine) and TGFβ which can prevent a full pro-inflammatory response of microglia, or change their phenotype from M1-like towards M2-like after activation (Gordon and Martinez, 2010; Letterio and Roberts, 1999).

Microglial activation leads to pathways resulting in induction of iNOS, NADPH oxidase and myeloperoxidase; the microglia probably need a prior priming signal for this induction. IL-1β, IL-6 and TNFα are key mediators in production of these enzymes/proteins. NADPH oxidase is responsible for superoxide (O^{2-}) production (which also leads to even more microglial activation), NF-κB regulated iNOS produces nitric oxide (NO) and myeloperoxidase produces hypochlorous acid. These reactive species are responsible for many of the adverse effects of microglial activation (Cunningham et al, 2005). Activation of both NDAPH oxidase and iNOS will lead to formation of peroxynitrite ($ONOO^-$) and results in neuronal death through apoptosis and phagocytosis (Brown and Neher, 2010). The reactive oxygen and nitrogen species induce the upregulation of "eat me" signals by neurons which are subsequently phagocytized by microglia (Kang et al, 2003). Amyloid β can also directly increase levels of reactive species trough TRPV1 cation channels and Kv1.3 K^+ channels (Schilling and Eder, 2011).

4.7: NSAIDs and prostaglandins

Long term use of NSAIDs, targeting inflammation, has been found to be preventive against the development of (McGeer and McGeer, 2007). The anti-inflammatory mechanism of NSAIDs is based on its inhibition of the production of prostaglandins, which are lipid compounds derived from fatty acids (Vane and Botting, 1998). COX-1 and COX-2 are involved in the production of prostaglandins and their activity is actually targeted by NSAIDs (Vane et al, 1998). Systemic LPS leads COX-1 to increase prostaglandin secretion resulting in behavioral changes, without affecting IL-1β, IL-6 and TNFα expression (Teeling et al, 2010). Prostaglandin E2, a major immunological effector in the CNS, is known for its disease exacerbation in AD and its secretion by microglia is increased after stimulation with (systemic) LPS or amyloid β, but not by other pro-inflammatory cytokines (Hoozemans et al, 2002). Targeting downstream prostaglandin production may have comparable results on the suggested delay of AD development as NSAIDs,

but with minimized side effects. Stimulation of prostaglandin receptors EP1, EP2, EP3 and EP4 all leads to distinct pathways and distinct effects on AD, but knock-out and antagonist studies showed that stimulation of all these receptors except EP4 correlates with increased amyloid β toxicity (Cudaback et al, 2014). EP2 antagonists decrease APP holoprotein in experimental AD (Pooler et al, 2004). EP4 stimulation is found to exert anti-inflammatory effects in the CNS, but contrastingly EP4 antagonism also leads to increased cognitive function and decreased amyloid β levels in the AD mouse model (Shi et al, 2010; Hoshino et al, 2012). Prostaglandin E2 is also very important in signaling peripheral inflammation signals into the brain (Ek et al, 2001). A possible other reason to pharmaceutically target prostaglandin E2 is to prevent markers of systematic inflammation (either priming signals or secondary triggering signals) from reaching microglia. In vitro and animal studies found that NSAIDs did decrease amyloid β burden in mice (Gasparini et al, 2004; Lim et al, 2000) and its aggregation (Hirohata et al, 2005). Clinical trials using NSAIDs against the progression of established AD have not provided the results which were hoped for (Callaway, 2012). The largest clinical study in mildly affected AD patients on high doses of tarenflurbil (the most promising type of NSAIDs) for 18 months came with completely negative results: no significant differences were found with the placebo group (Green et al, 2008). In a 2009 review on this topic, Imbimbo concluded that NSAIDs and selective COX-2 inhibitors are not beneficial after clinical AD symptoms become evident and that NSAID use in early and later stages may have adverse effects by inhibiting microglial amyloid β phagocytosis and also by interfering with compensatory neurogenesis processes. A long term preventive study did show a robust reduction in AD risk in subjects on a NSAID (Breitner, 2009), but it could also be that individuals using NSAIDs already had an overly active immune system, which prevented them from developing AD.

4.8: Bone marrow macrophage infiltration

In AD brains, the number of microglia is dramatically increased. This may arise from proliferation of resident microglia, by recruitment of bone-marrow derived macrophages from the blood or a combination of these two (Perry et al, 2009). Bone-marrow macrophages, while adopting a microglial phenotype, are found to be more effective in delaying of stopping the progression of AD compared to yolk-sac derived microclia (Naert and Rivest, 2011). Simard et al (2006) demonstrated this by killing almost all nearby myeloid cells by intracerebroventricular installation of gancyclovir for 28 days in chimeric mice, leading to an increased plaque size and number 6 months later. They also showed massive infiltration of labeled bone-marrow macrophages towards amyloid plaques, by chemoattraction of amyloid β. Furthermore, these infiltrating macrophages also influence the microglia to maintain their resting state: bone-marrow macrophages conditioned medium leads to inhibition of microglial proliferation and their secretion of pro-inflammatory cytokines. This medium also inhibited microglial phagocytosis and even induced their apoptosis. An important effector of bone-marrow macrophages in these processes was found to be NO (Yan et al, 2013).

5: OVERFEEDING, NEUROINFLAMMATION AND AD

So, acute systemic inflammation is able to affect microglia resulting in effects on behavior and cognition, either physiologically (sickness behavior, paragraph 3.4) or pathologically (delirium, paragraph 4.1). It could be suggested that also chronic albeit low-grade inflammation has the ability to affect microglia and aggravate NDD pathologies. Chronic inflammation is associated with accelerated cognitive decline in AD patients, determined after examining baseline TNFα levels over a 6 month period in AD patients (Holmes et al, 2009).
Overfeeding leads to metabolic disruptions which can eventually result in systemic/peripheral inflammation, either by directly interacting with PPRs of the innate immune system or by affecting the gut microbiota (Jin et al, 2013). This state of chronic inflammation causes the metabolic syndrome, which encompasses abdominal obesity, insulin resistance, dyslipidemia and hypertension (Schenk et al, 2008).
Drake et al showed in 2011 that many components of the metabolic syndrome (although in the context of risk factors for stroke) are associated with brain inflammation. Systemic inflammation due to for example obesity leads to a primed inflammatory environment in the brain prior to stroke presentation; the occurrence of stroke in these brains was predicted to cause an exaggerated inflammatory response in the brain and aggravated post-ischemic damage. Drake et al determined that this primed state was due to the effects of systemic inflammation on microglia. At least this study establishes that advanced age and obesity have synergistic effects on neuroinflammation.

5.1: Apolipoprotein E

ApoE is involved in development of both AD and atherosclerosis (see paragraph 1.6). ApoE also has anti-inflammatory properties; macrophages of ApoE knock-out mice stimulated with TLR agonists (like LPS) tend to be more M1 activated due to increased IL-12 production (Ali et al, 2005). Conversely, macrophage ApoE expression is mediated by inflammatory cytokines like TNFα (Duan et al, 1995). So ApoE levels are of importance for macrophage secretion profile, which implicates a role of ApoE levels in preventing overfeeding-induced systemic inflammation, contributing to both AD and atherosclerosis. Human hyperlipidemia indeed results often in ApoE accumulation in plasma (Rosenfeld et al, 1993).
ApoE variant ε4 increases the risk of developing AD or atherosclerosis. Interestingly, it was found that ApoE4 interacts with macrophages through domain interaction resulting in increased MHC II expression in macrophages (Eberlé et al, 2012). It could be suggested that microglia respond in a similar way to ApoE4 and indeed displayed ApoE4 mice increased microglial activation after central LPS administration than mice with other ApoE variants (Zhu et al, 2012). High levels of ApoE in fibrillary plaques negatively affect the microglial clearance of amyloid β, whereby the E4 variant has the most adverse effects (Mulder et al, 2014). These studies indicate that interaction between overfeeding-induced systemic inflammation and ApoE is of great importance for the scale of microglial activation in AD; ApoE variants should therewithal be taken into account, especially since ApoE4 is the largest genetic risk factor for late-onset AD.

5.2: PPARγ

PPARγ agonist stimulation (mediated by CD36) leads to increased amyloid β uptake by microglia and increased cognitive performance (Yamanaka et al, 2012). Endogenous fatty acids and fatty acid derivatives are PPARγ ligands and this interaction has also favorable effect on lipid synthesis and oxidation as well as glucose uptake (Nicholls and Uno. 2012). PPARγ seems to be one of the crucial proteins in integrating fat metabolism with inflammation and its signaling is required for the maturation of the anti-inflammatory M2 phenotype (Odegaard et al, 2008). This

indicates that PPARγ signaling may be involved in linking obesity with AD and suggests possibilities in targeting this protein.

5.3: BBB, IgG and Fc receptors

Breakdown of the BBB is thought to precede and trigger both neuroinflammation and neurodegeneration (Zlokovic, 2011). Pro-inflammatory stimulation of microvessels of AD patients also leads them to produce harmful factors, like thrombin. Thrombin is directly harmful for neurons, but also activates microglia. These AD microvessels secrete pro-inflammatory mediators similar to that of reinforced activated microglia, like IL-1β, TNFα, NO, CCL2 and prostaglandins (Zlokovic, 2011). BBB barrier permeability is increased due to overfeeding (Freeman & Granholm, 2012), making the brain even more susceptible to neuroinflammation or microglial priming by peripheral signals. HFD-induced obesity in aged mice is associated with exacerbation of BBB disruption (Tucsek et al, 2013). On top of that is the BBB also strongly involved in amyloid β influx (RAGE activity) and outflux (LRP-1 activity) (Choo et al, 2013), suggesting that overfeeding may also shift the balance between RAGE and LRP-1 activity; not only amyloid β but also other inflammatory mediators can bind RAGE. RAGE has already been suggested to be involved in adipocyte hypertrophy and insulin resistance (Yamamoto and Yamamoto, 2013). ApoE4 competes with amyloid β for LRP-1, while ApoE2 and ApoE3 do not (Sagare et al, 2013).

The HFD-induced increase in BBB permeability in aging mice also leads to increased IgG leakage in the brain; IgG receptors FcγRIII and FcγRIV are upregulated in the hippocampus of these mice (Tucsek et al, 2013). These receptors, expressed on microglia, are also upregulated by peripheral LPS challenge of primed microglia (the ME7 prion model, resembling AD and PD) and the same study also showed IgG leakage into the brain (Lunnon et al, 2011).The production of IgG is increased by B-cells in white adipose tissue of obese animals and accumulation of IgG was also found in the hypothalamus of obese rats, exclusively concentrated in microglia (Yi et al, 2012). IgG is a priming or stimulating factor for microglia, so accumulation of IgG in the microglia will probably lead to a more sensitive state or even activation. This was indeed shown by Tucsek et al, where upregulated Fc receptors and increased IgG entrance was associated with an increased number of microglia and upregulation of pro-inflammatory mediators. Effects of obesity on aging microglia could be expanded to AD, as amyloid β is found to have quite similar priming effects as aging.

5.4: Microglial pattern recognition receptors sense overfeeding-induced peripheral inflammation

Activation or priming of the innate immune system due to overfeeding or by amyloid β acts through many similar PPRs, including the cell surface receptors TLR2 and TLR4 and the inflammasome PPR component NLRP3. More directly, HFD has been found to lead to increased hypothalamic expression of TNFα, IL-1β, and IL-6 in rats. This was due to direct interaction of fatty acids with TLR2 and TLR4 and by the induction of ER stress (Milanski et al, 2009). The hypothalamus is of course more susceptible to direct effects of fatty acids as it is located close to the circumventricular organs which allow passive diffusion of metabolic signals across the BBB. This diffusion is necessary for normal hypothalamus functioning (Komaki et al, 1998). Nevertheless shows this study that HFD is able to increase pro-inflammatory cytokine secretion in the CNS by priming or activating microglia. It is plausible that other regions in the brain, like the hippocampus, also receive TLR ligands from the blood. There are several ways peripheral signals can cross the BBB (see paragraph 3.4) and obesity also disrupts the BBB integrity.
The NLRP3 inflammasome is triggered by compounds like free fatty acids in metabolic disorders and by amyloid β in AD, in both cases this leads to secretion of Il-1β and Il-18 and thus to inflammation (Masters, 2013). The findings of Halle et al in 2008 and Heneka et al in 2013 underline the importance of the NLRP3 inflammasome in AD (paragraph 4.3). Nevertheless, inflammasome compartments as well as pro-IL-1β and pro-IL-18 transcription is often only

initiated after a priming signal, like TLR ligand stimulation (Walsh et al, 2014). Signals of peripheral inflammation, caused by overfeeding, can enter the brain (aided by disruptions in the BBB) and may be a plausible priming signal inflammasomes. Amyloid β can subsequently be the secondary triggering factor for the inflammasome, leading to an overfeeding-induced exaggeration of IL-1β and IL-18. Milanski et al did not investigate the NLRP3 inflammasome in their study on the effect of HFD on hypothalamic inflammatory markers. It is very plausible that metabolic signals of HFD, like high levels of fatty acids, will be a direct priming signal for inflammasomes in hypothalamic microglia through NF-κB initiated transcription.

5.5 Directly linking overfeeding with AD through inflammation

Microglial priming manifests itself by altered microglial morphology and increased expression of cell surface proteins like MHC II. Primed microglia are more responsive to inflammatory stimuli and show an exaggerated response to these stimuli compared to non-primed microglia. In a way, the process of microglial priming and inflammasome priming are alike, see figure 6. Microglial priming is a well known phenomenon in aging and loss of inhibitory proteins and cytokines are thought to be responsible for this priming. Amyloid β is also a well known cause of microglial priming and the exorbitant response of these microglia to acute peripheral inflammation manifests itself as delirium, a common syndrome in AD patients. Overfeeding-induced peripheral inflammation is chronic, but low grade, and it is the question whether this type of inflammation is capable of triggering the priming microglia to a detrimentally exaggerated response. Studies using prolonged LPS dosages in mice found not only effects on microglial activation (Holmes et al, 2009; Cunningham et al, 2012), but also on amyloid β generation (Sheng et al, 2003; Lee et al, 2008).

Oxidative stress was also considered to be the link overfeeding and obesity with NDDs and cognitive impairment (White et al, 2009; Wu et al, 2004; Nunomura et al., 2001; Jenner, 2003). Indeed, hippocampal oxidative and nitrosative stress (measured by 3-nitrotyrosine) was found to be increased with aging in mice, but was even more increased in aging mice on HFD, see figure 10. The same aged mice on HFD showed increased microglial activation (Tucsek et al, 2013). Activation of primed microglia leads to the induction of enzymes like iNOS and NADPH oxidase, which are responsible for the production of high levels of reactive oxygen and nitrogen species (Cunningham et al, 2005). Peripheral inflammation, caused by overfeeding, is able to cause reinforced microglial activation and is therefore responsible for this increased oxidative stress.

Diabetes mellitus is a hallmark of the metabolic syndrome. AD transgenic mice crossbred with diabetic mice showed that the onset of diabetes exaggerated cognitive dysfunction through inflammation. Conversely do the crossbred mice also show an accelerated diabetic phenotype compared to diabetic mice (Takeda et al, 2010) , indicating at a self-enhancing process. Induction of diabetes in rats leads to cognitive deficits, increased hippocampal amyloid β levels, oxidative stress and inflammation. Inhibition of the NF-κB pathway by minocycline decreased amyloid β levels and increased cognitive function (Cai et al, 2011). A follow-up study showed that minocycline decreases amyloid β production and tau hyperphosphorylation through inhibiting neuroinflammation in an animal model of diabetes. This model was established by HFD and streptozocin injection (Cai et al, 2013). Dietary factors do have the potential to affect the priming state of microglia; dietary flavenoids can mitigate microglial cells in aged mouse brains (Jang and Johnson, 2010).

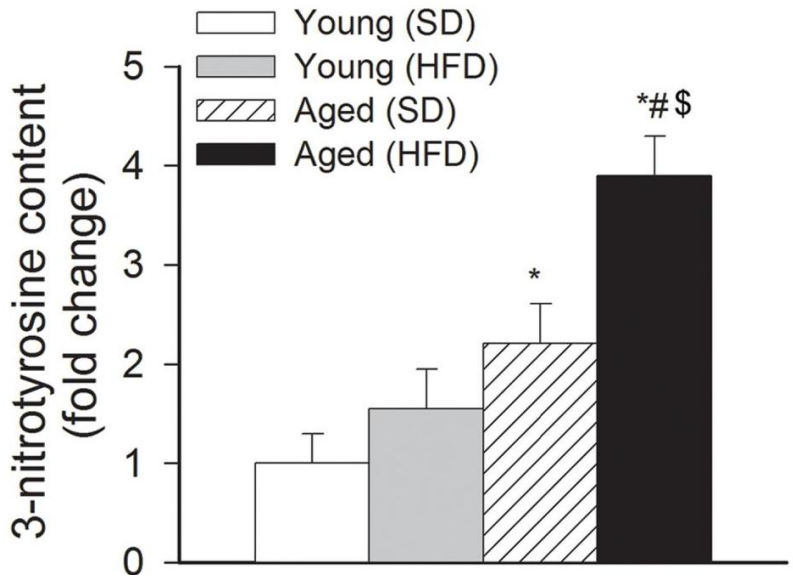

Fig. 10: Relative change in hippocampal 3-nitrotyrosine, which is a marker of peroxynitrite action. Hippocampi of aged mice on standard diet (SD) have a significant (~2-fold) increase of 3-nitrotyrosine compared to young mice. Aged mice on HFD have a significant increase compared to young mice on the same diet, but also an approximate 2-fold 3-nitrotyrosine increase compared to aged mice on standard diet (Tucsek et al, 2013)

6: PARKINSON'S DISEASE, INFLAMMATION AND OVERFEEDING

Parkinson's disease, the second most common NDD, is characterized by α-synuclein accumulations (Lewy bodies) and loss of dopaminergic neurons in the substantia nigra (SN). Neuroninflammation is another characteristic of PD (Marinova-Mutafchieva et al, 2009), and transgenic animal models of PD imply that neuroinflammation even precedes neurodegeneration (Chung et al, 2009); this proves that microglia are not only activated by necrotic neurons. Genetic studies have found correlations with pro-inflammatory cytokines and risk of developing PD (Deleidi and Gasser, 2013). Positron emission tomography studies revealed activated microglia in pons, basal ganglia, and frontal and temporal cortical regions of PD patients (Gerhard et al, 2006) and post-mortem studies on PD brains indentified T-cell infiltration of the SN (Hunot et al, 1999). In PD-associated brain regions, microglia increasingly express many activation related proteins, including MHC II, CD68, COX and iNOS (McGeer et al, 1988; Sanchez-Guajardo et al, 2013), pro-inflammatory cytokines, including IL-1β, TNFα and IL-6 (Mogi et al, 1994a; Mogi et al, 1994b), and other proteins like iNOS, COX-1, COX-2 and prostaglandin E2 (Knott et al, 2000). In addition, also microglial proliferation was apparent in PD-related brain regions (Imamura et al, 2003). Due to the changed microenviroment in PD brains, microglia shift their activated phenotype from M2 to M1, similar to AD microglia (Sanchez-Guajardo et al, 2013).
Early blockade of neuroinflammation of PD animal models with anti-inflammatory drugs like minocycline, NSAIDs, COX-2 inhibitors or cytokine inhibitors prevents the degeneration of dopaminergic neurons in the SN (Deleidi and Gasser, 2013). H5N1 influenza infection can spread to the brain and induce neuroinflammation resulting in exacerbation of PD pathology by α-synuclein aggregation and neuronal loss (Jang et al, 2009). These studies implicate a key role of microglial activation in PD pathogenesis.
Lewy bodies consist of α-synuclein, which is normally found in neuronal presynaptic terminals; in PD it is found in high levels as extracellular protein and in this state it is capable of activating microglia (Su et al, 2008). Microglia expressing microglia are associated with α-synuclein depositions (Croisier et al, 2005). Conversely, initiation of neuroinflammation leads to neuronal death through TNFα, iNOS, NADPH oxidase (among others), resulting in higher levels of α-synuclein (Lema Tome et al, 2012). Cytokine exposure regulates intracellular α-synuclein levels in human microglia (Bick et al, 2008) and in-vitro exposure of cultured microglia to cerebrospinular fluid of PD patients increases intacellular α-synuclein levels (Schiess et al, 2010). It seems that microglial activation and α-synuclein reinforce each other, resulting in progression of PD.

6.1 Microglial activation and priming pathways

Microglia in PD and AD share many inflammatory pathways and mechanisms, as both α-synuclein and amyloid β are recognized by several PPRs as a DAMP signal. In both diseases is microglial phagocytosis as common phenomenon, both of the misfolded proteins and cellular debris from degenerating neurons (Park et al, 2008; Zhang et al, 2011). Monomeric, but non-aggregated α-synuclein is capable of stimulating microglial phagocytosis (Park et al, 2008). TLR4 is one of the major PPRs that initiate α-synuclein phagocytosis, deferring disease progression (Stefanova et al, 2011), while oligomeric forms of α-synuclein are more associated with microglial activation (Roodveldt et al, 2011). Nevertheless, internalization of α-synuclein will also lead to increased microglial activation and induction of iNOS and NADPH oxidase (Zhang et al, 2005). So it is still debated what role TLR4 mediated phagocytosis has on progression of PD. Interestingly, α-synuclein exposure also increases expression of microglial TLR and co-receptor CD36 (Beraud et al, 2011). Monomeric forms of α-synuclein seem to be responsible for microglial priming; secondary stimulation with TLR1, TLR2 or TLR7 agonists lead to increased levels of CCL2, IL-6 and TNFα and decreased levels of anti-inflammatory IL-13 (Roodveldt et al, 2013).

As well as in AD and aging is microglial priming observed in PD (Couch et al, 2011). As mentioned in paragraph 3.2 and 4.5, disturbance of neuron-microglia communication is thought to be one of the responsible factors for the altered phenotype of the microglia. CD200L and CD200R (involved in inhibition of microglial activation) deficiency has been associated with microglial priming and loss of dopaminergic neurons in the midbrain (Wang et al, 2011). Fraclakine-CX3CR1 interactions have a similar inhibitory effect as CD200 interactions and CX3CR1-deficient mice show increased neuronal loss in PD mouse models (Cardona et al, 2006). Also anti-inflammatory cytokines line IL-13 and IL-10 have been found to be protective against neuronal loss in PD (Roodveldt et al, 2013; Arimoto et al, 2007). Immuneregulatory mediators are also thought to control inflammatory response to neurodegeneration in PD (Perry et al, 2007).

BBB dysfunction is already observed in early PD (Kortekaas et al, 2005), indicating increased entrance of inflammatory signals from the serum, including IgG. Serum of PD patients is found to contain disease specific auto-antibodies (Han et al, 2012). In a recent study of Zhang et al (2013), it was found that neuron-derived IgG was actually protective in PD models, by blocking microglial activation through TLR4 and FcγR1 pathways. The complement system is as well implicated as an actor in PD, by mediating α-synuclein activation of microglia through NADPH oxidase (Zhang et al, 2007). As well as in AD, RAGE is also involved in PD; RAGE ablation protects SN dopaminergic neurons in a PD model and NF-κB translocation in the microglial nucleus was inhibited. Levels of S100, a RAGE ligand, were increased in this animal model and this increase was associated with apoptotic neurons (Teismann et al, 2012).

The NLRP3 inflammasome can be triggered by amyloid β and plays an essential role in AD-associated neuroinflammation by caspase 1 activation and IL-1β and IL-18 secretion. Recently, this inflammasome is found to be triggered by aggregated α-synuclein. Stimulating TLR2 with monomeric or aggregated α-synuclein is found to prime the inflammasome, leading to production of pro-interleukins. The NLRP3 inflammasome is involved in maturing and secreting these interleukins through caspase 1 activation; this process relies on α-synuclein phagocytosis followed by increased reactive species production and cathepsin B release (Codolo et al, 2013). IL-1β overexpression is also in PD associated with excitotoxic injury and neuronal damage (Shie and Woltjer, 2007). PD affected regions show increased caspase levels (Chakraborty et al, 2010), which indeed suggests inflammasome activation.

6.2 Systemic inflammation effects on PD

Peripheral inflammation is linked with the development or progression of PD (Tsui et al, 1999). Microglia tend to be primed by α-synuclein and show exaggerated responses to both central and peripheral LPS stimulation (Couch et al, 2011). Chronic low-dose LPS injections in the SN are also able to induce neuroinflammation and resulted in delayed and progressive loss of dopaminergic neurons (Gao et al, 2002). PD model mice are more susceptible to long-term peripheral inflammation (due to LPS injections) than wild-type mice, expressed as increased SN neuron loss compared to wild-type mice (which also showed neuron loss) (Frank-Cannon et al, 2008).

Levels of pro-inflammatory cytokines are increased in PD brain regions, but these levels are dwarfed after subsequent microbial infection (Depino et al, 2003). Central inflammation in the SN induces degeneration of dopaminergic neurons, but this degeneration is accelerated by systemic inflammation (Pott Godoy et al, 2010). Microglial priming by α-synuclein did not lead to increased phagocytic capacity after secondary TLR stimulation compared to TLR stimulation of unprimed microglia, despite the difference in pro-inflammatory response of these microglia (Roodveldt et al, 2013).

Parkin, a PD-related protein, can be downregulated by inflammation, leading to exaggerated microglial response to secondary peripheral inflammation (Frank-Cannon et al, 2008); this implies interaction of genetic factors and inflammation in PD. PD patients show early autonomic

dysfunction and involvement of the vagus nerve (Deleidi and Gasser, 2013), which is also one of the gateways into the CNS for peripheral inflammatory signals (the inflammatory reflex, see paragraph 3.4). Interestingly, LPS-induced inflammation resulted in dopaminergic neuron degeneration, but this process is independent of TLR4 (which is a LPS receptor) (Castano et al, 1998), implicating the involvement of a different pathway like RAGE and the NLRP3 inflammasome.
Gut inflammation is also linked to the development of PD. PD patients show increased levels of cytokines in the entric nervous system, as well as glial markers (Devos et al, 2013). Animal models confirm this link (Villaran et al, 2010). Overfeeding leads to alterations of gut microbes and this subsequently initiates activation of the innate immune system by recognition of PAMPs by PPRs (Jin et al, 2013). Morris et al (2010) studied the effects of HFD on PD animals. Two weeks after induction of the PD-like syndrome, mice on HFD exhibited greater dopamine depletion and increased oxidative stress in the SN and striatum compared to mice on chow diet. So this study provides evidence that HFD indeed exacerbates PD. A strict diet which includes limiting animal fat intake (maximally 25 grams per day) is effective in reducing symptoms of PD (Renoudet et al, 2012).

CONCLUSIONS

Neurodegenerative diseases, AD and PD as the most prominent, have a major inflammatory component. Microglia are the major immunecells in the CNS and are therefore an important point of focus in the development of NDDs. Regulation of microglia depends on many factors: they are activated by stimulation of their PPRs with DAMPs or PAMPs, or by pro-inflammatory mediators like IL-1β, TNFα and prostaglandin E2. Neuron-microglia communication is also important in regulating the activation state of microglia, as well as mediation of anti-inflammatory cytokines.

Microglial priming is a well described phenomenon in aging brains. Primed microglia are recognized by their changed morphology and upregulation of a number of cell surface proteins including PPRs. These microglia show a stronger response to a secondary triggering stimuli, like signals from peripheral inflammation.
Priming of microglia also occurs in AD and PD due to signaling of respectively amyloid β and α-synuclein. Peripheral signals can act either as priming or as secondary triggering stimulus for these microglia, leading to exaggerated microglial activation characterized by high levels of oxidative and nitrative stress, which consecutively leads to accelerated neurodegeneration. Delerium is an example of acute response on peripheral inflammation.
Levels of obesity have risen and are rising rapidly and also the prevalence of AD and PD are and will be significantly rising. Besides aging of the human population, the rise in obesity could be suggested to be a cause of the increasing prevalence of NDDs. Mid-life overfeeding and obesity are indeed associated with increased risk of developing AD or PD. As overfeeding is known to lead to chronic low-grade inflammation, which results in the metabolic syndrome, it is probable that overfeeding-induced inflammation underlies the association between obesity and NDDs.

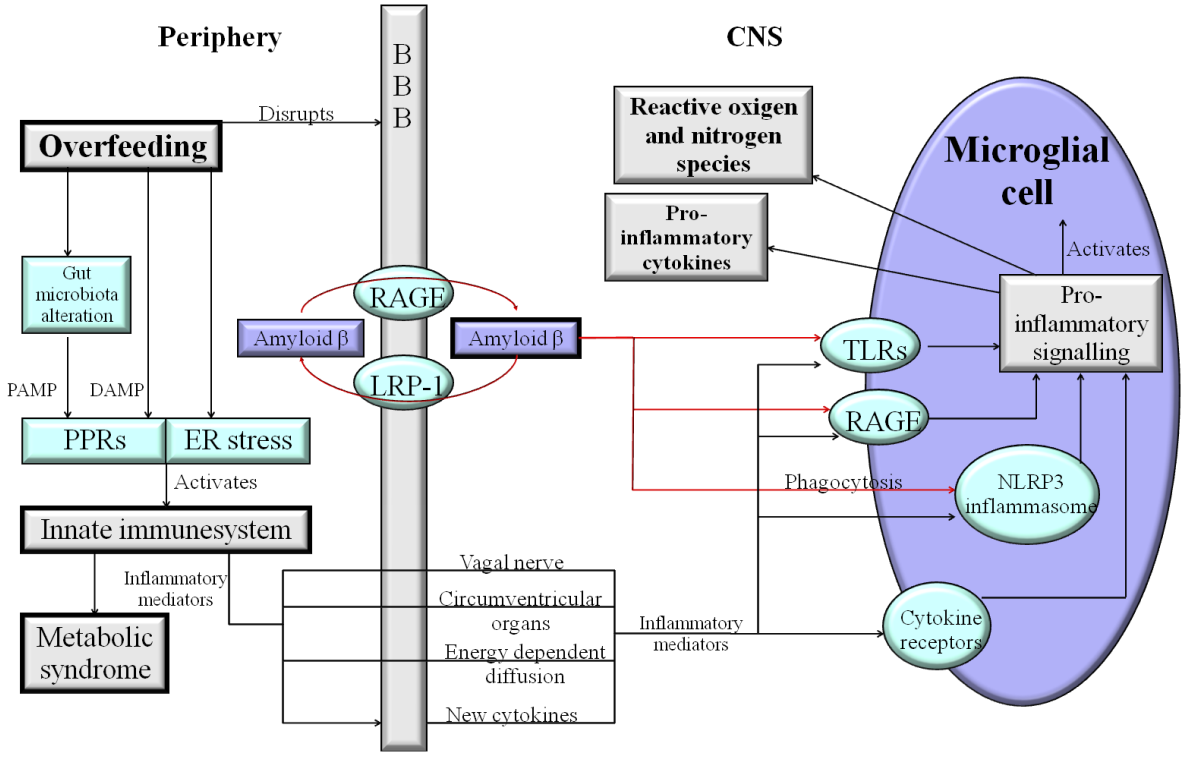

Fig 11: a simplified diagram which connects overfeeding to exaggeration of AD

Figure 11 shows in a simplified way the pathway by which overfeeding in the presence of amyloid pathology leads to pathologically activated microglia characterized by secretion of pro-inflammatory cytokines and reactive species. This process in AD shows large similarities with the pathways in which overfeeding interacts with α-synuclein pathology in PD. Overfeeding stimulates PPRs of the innate immunesystem directly (via DAMPs or by inducing ER stress) or indirectly (by altering gut microbiota populations). This results in low-grade peripheral inflammation which is at the base of the metabolic syndrome and is also heavily involved in NDDs. Signals of peripheral inflammation travel into the CNS in several ways: either direct or by stimulating endothelial cells of the BBB which consecutively release new cytokines. These signals interact with microglial receptors, leading to microglial priming or activation, probably depending on the amplitude and duration of this signal. RAGE, TLR2 and TLR4 are some of the most important PPRs, which can be stimulated by both inflammatory proteins and amyloid β and α-synuclein. Activation of these receptors leads to microglial activation, including phenotype switching and induction of phagocytosis. Amyloid β/α-synuclein or pro-inflammatory mediator interaction with these receptors can be both the priming signal and the secondary triggering signal which leads to exaggerated neuroinflammation.
The NLRP3 inflammasome is a cytosolic complex that, when activated, leads to pro-inflammatory cytokine secretion, including most of the IL-1β in the CNS. The inflammasome is different from other PPRs, as it often needs a priming signal before being able to be activated. It could be suggested that the aforementioned PPRs play an important role in stimulating the inflammasome, by initiating the NF-κB controlled priming of the inflammasome or by initiating phagocytosis, which is essential for inflammasome activation.
Overfeeding also disrupts the BBB, making it more permeable, resulting in even more signaling of peripheral inflammation into the brain. This decrease in BBB integrity may also disturb the balance between endothelial RAGE and LRP-1 action.
Not included in this figure are the negative and positive feedback loops. Neuroinflammation can enhance itself in many ways in AD and PD: by directly increasing production of amyloid β or α-synuclein, by increasing PPR expression leading to a more sensitized state, by increasing the pro-inflammatory cytokine secretion and reactive species production and by degenerating

neurons leading to cell debris and in PD to release of intraneuronal α-synuclein. Negative feedback loops like anti-inflammatory cytokine signaling and neuron-microglia interaction may prevent the pro-inflammatory cascade in NDDs, but they are downregulated or disrupted in aging and possibly also due to overfeeding-induced peripheral inflammation. The chronic inflammated state of the brain in NDDs, whether or not due to overfeeding-induced peripheral inflammation, is probably due to the inability of negative feedback mechanisms to counteract the positive feedback mechanisms, after which the neuroinflammation eventually leads to neurodegeneration. The importance of microglial activation by peripheral inflammation in AD is even more pronounced considering its ability to increase or even precede tau pathology.

Taken together, it has become clear that overfeeding-induced chronic low-grade inflammation can accelerate and exacerbate the development of AD and PD. There is also evidence, epidemiological and experimental, that this inflammation may even cause these NDDs, for example by increasing production of amyloid β and α-synuclein or by inducing tau pathology. Microglia are the principle actors of the CNS immune system, but also resident astrocytes and infiltrating bone marrow macrophages and adaptive immune cells play an important role in neuroinflammation; overfeeding may also affect these immune cells.
NSAIDs have been found to be preventive against development of AD and PD. Nevertheless, NSAID or COX-2 inhibitor treatment of patients with early or late AD has not been successful. Other mechanisms are more promising in treating NDDs: preventing inflammasome activation, targeting PPARγ, administrating minocycline as a microglial inhibitor and in AD anti-amyloid β antibodies (which can more easily enter the CNS due to decrease in BBB integrity). Diet alterations in AD and PD patients can also be useful to delay and dampen neurodegeneration.

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