Early nutritional strategies to modulate the early-life stress- and Alzheimer's disease-induced changes in the brain

Focus on microglia

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1 Preface

CHAPTER ONE

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The early environment as an important factor in determining later-life health

The Developmental Origins of Health and Disease (DOHaD) hypothesis states that environmental influences during critical periods of early development, particularly *in utero* (pre-natal) and the early years of life (peri-natal), can have profound and lasting impacts on an individual's health and risk of disease later in life (1). As there are many systems still in full development, the early-life period represents a vulnerable time window during which the developing fetus and infant are exceptionally sensitive to changes in their environment, and disturbances can affect, but are not limited to, the brain (2), gut (3), central and peripheral immune system (4,5), and the hypothalamic-pituitary-adrenal axis, which regulates the stress response and release of glucocorticoids (6).

The shaping of long-term health outcomes during the pre- and perinatal developmental periods is referred to as 'programming'. In this thesis, we will touch upon aversive (i.e. in the form of stress) and beneficial (i.e. in the form of nutrition) programming and their interactions in shaping the brain in later life.

Aversive programming of the brain during early-life

Early-life adversity (ELA) involves exposure to environmental circumstances during childhood or adolescence that are generally considered challenging or threatening, and to which the brain most likely adapts with promoting mechanisms for survival (7). A wide range of experiences (also called adverse childhood events (ACEs)) meets this definition of ELA for clinical research, ranging from abuse, prolonged and chronic neglect, early-life stress (ES) and factors often associated with e.g. poverty and a low socio-economic status (such as nutrient deprivation and deficiency).

Evidence further supports that ELA affects mood (8,9) and cognitive functioning (10–12) both lastingly into adulthood. Moreover, it has been suggested that ELA (e.g. in the form of maternal stress) increases vulnerability to the onset of disorders, like Alzheimer's Disease (AD), later in life (13,14). Currently, while vulnerable populations that are exposed to ELA can often be identified, ELA can unfortunately most often not be avoided, which calls for preventive/counteracting strategies that can be applied already during early developmental phases.

Beneficial Programming of the brain during early-life - a role for nutrition?

Next to the fact that the brain is programmed by adverse stimuli, there is also evidence that supports a beneficial programming of the brain. Positive childhood experiences (PCEs or counter-ACEs) are experiences thought to benefit the long-term programming of health. PCEs include e.g. positive relationships, household routines, beliefs that provide comfort and exposure to such PCEs from early-life on, generally lead to a better (mental) health at an adult age (15,16) and are thought to protect against cognitive decline (17) and AD (18). These examples follow the resiliency theory, which focuses on promoting factors that independently

lead to better health outcomes (19).

As part of such resilience-promoting factors, nutritional programming via either improving the quality, changing the composition, or the quantity of specific nutrients during early-life might be of interest to potentially counteract negative outcomes in later-life (20,21). Although nutritional programming is thought to have the greatest effect when applied prenatally (22), it is increasingly acknowledged that the window of opportunity for such programming extends into the (early) postnatal period (23–25). It is unclear however, how early nutrition could be a protective factor for e.g. AD.

Similarly, following the resilience theory, promoting factors like nutrition may offset the effects of risk factors on developmental trajectories and later outcomes (19). An increasing number of (pre-)clinical studies has investigated the impact of nutrient intake during and/or after pre-and postnatal stress on the later-life behavior that is often altered by ES. Currently, however, a general overview of such studies, including those on the extent and efficacy of nutritional interventions in specific ES-induced behavioral outcomes, is still missing.

Scope of this thesis

This thesis centers around the negative later-life outcomes of ELA, investigates nutritional interventions early in life and their underlying mechanisms and study whether early interventions can modulate later-life outcomes. We further studied whether early nutrition can also modulate later-life outcomes in APP/swe/PS1E9 mice (APP/PS1, a model for AD) and after ES, to better understand the effects of a genetic and environmental predisposition to cognitive decline, respectively.

Models used in this thesis

To study biological mechanisms, we used a mouse model of chronic ES, based on the provision of limited amounts of bedding and nesting material during the first week of life from postnatal day (P)2-9, which leads to fragmented care by the mother and stress in her pups. In order to not interfere with this delicate model, we used a pelleted diet as opposed to many studies that administer their nutrients via (stressful) oral gavage or injections.

We further studied early nutritional intervention in the APP/PS1 transgenic mouse model for AD. This model is well-established in the field to study amyloid-β (Aβ)-related disease processes in AD. This mouse model displays a progressive Aβ pathology starting at about 4 months of age, with concomitant increases in neuroinflammation and cognitive impairment.

Neurobiological substrates of interest

From animal models of ELA (e.g. ES), we have learned much about the neurobiological substrates that underlie the behavioral changes, and we have even observed that ES and amyloidosis in an AD model share pathogenic pathways (26). Two mechanisms that will be thoroughly investigated in the context of early dietary interventions throughout this thesis are; lipid metabolism (specifically polyunsaturated fatty acids (PUFAs)) and neuroinflammation (specifically microglia). These neurobiological substrates are known to

be affected in both APP/PS1 animals and ES-exposed offspring, as will be discussed next.

Lipid metabolism – PUFAs

The brain has the highest lipid content after adipose tissue (27). Lipids are present in the plasma membranes of neurons and glial cells and mediate structural and functional integrity of the brain cells. Intracellularly, they have regulatory functions, e.g. as second messengers in specific signalling pathways (28–30). Their dysregulation has been implicated in the pathophysiology of brain disorders, like major depressive disorder (31–33) and AD (31,34–38). Interestingly, ES interacts with the susceptibility to develop these type of disorders (8,39).

In this thesis, we will focus on PUFAs, which are main components of membrane phospholipids. PUFAs are necessary for maintaining membrane physiology and must be ingested through the diet (40). In addition, their derivatives serve as messenger molecules, playing a role in various physiological processes, notably (neuro)inflammation (discussed more thoroughly below). There are two main families of PUFAs; the omega (N)-3 and N-6 PUFAs. Linoleic acid (LA) is a N-6 PUFA that is a precursor of longer-chain (LC) PUFA arachidonic acid, whereas α -Linolenic acid (ALA) is the precursor of eicosapentaenoic acid and docosahexaenoic acid (40). LA and ALA compete for metabolization into LC-PUFAs via the same enzymatic pathways and have downstream derivatives with opposing functions, called oxylipins. N-6 PUFA-derived oxylipins have pro-inflammatory, while N-3 PUFA derivatives have mostly anti-inflammatory actions (41,42). These inflammatory mediators can directly modulate microglia, immune cells in the brain, which are continuously adapting to their micro-environment (42,43).

Animal studies show that there is a critical period for PUFA build-up in the brain, particularly during late gestation and early post-natal life, where there is a great demand for complex lipids for normal development (44). This period could therefore be most interesting for the timing of our stress and nutritional paradigms.

So far, very few studies are available on the homeostatic function of PUFA derivatives, and whether the PUFA/oxylipin profile e.g. differs between the sexes or between brain regions, is unknown. A baseline difference (whether in sex or in brain regions) could e.g. determine differences in the response to dietary interventions with N-3 PUFAs and might be crucial for developing N-3 PUFA nutritional interventions.

Based on our previous work, programming of the lipid metabolism occurs, specifically in PUFA metabolism and in relation to ES (45,46), with lasting alterations both in the central and peripheral PUFA- and oxylipin profile in adulthood. It is therefore of interest to explore what happens between the end of intervention and the later behavior and to investigate the dynamics of these lipid species on the short-term in order to be able to better understand the temporal dynamics of ES-programming.

Neuroinflammation – Microglia

Microglia are key players in neuroinflammation and represent the primary immune effector cells residing in the brain. Their morphology allows them to survey brain regions for the presence of pathogens and cellular debris (47). They express a vast number of receptors

to sense, integrate and respond to (changes in) the extracellular environment accordingly (48). Major functions relevant for their response to the environment are phagocytosis and the production of cytokines. Microglia further play a key role in synaptic pruning of developing neuronal circuits (49,50), which coincides with the timing of our stress and nutritional paradigms. Interestingly, microglia are sensitive to programming, or 'priming' by previous experiences (51,52). In previous work, microglia were shown to be primed by ES on the short- and long-term, affecting their basal response and their response to inflammatory stimuli and pathology (39,50,53). Overall, ES-exposed microglia present with a more immune-activated phenotype (54,55). One of the main interests in this thesis centres around anti-inflammatory diets in the context of ES and AD. Interesting targets and key players in this respect are polyphenols as well as N-3 PUFAs, both of which have been described to have anti-inflammatory actions (42,43,56–59). Microglial motility, phagocytosis and the ability of microglia to produce an inflammatory response are directly modulated by changing the ratio of available N-6 and N-3 in the brain (e.g. through diet (42,43)). For example, maternal dietary N-3 PUFA deficiency increases phagocytosis of synaptic elements in the offspring, partly through an activation of 12/15-lipoxygenase signaling (59). We have reported that an early supplementation with N-3 PUFAs reduced neuroinflammation later in life in adult ES-exposed animals (45). However, it remains to be studied what happens with microglia between the end of the dietary intervention and the start of behavioral testing, on the short-term.

Early N-3 PUFA enrichment has lasting effects later in life (i.e. after the dietary intervention has ended), possibly via modulating neuroinflammatory processes. This makes it particularly interesting to study the potential impact of such dietary interventions in a model for AD, in which neuroinflammation also plays a key role. As early N-3 PUFA supplementation can modulate ES-induced microglial alterations later in life in wildtype mice, we will here explore whether it is also possible to modulate microglia-related processes in a disease model for AD, by programming via N-3 PUFAs.

Thesis aims and outline

This thesis builds further on earlier work aimed to increase our understanding of how ES and nutrition can 'program' offspring for life. In previous work, and in this thesis, we underline the detrimental consequences of ES and emphasize the potential of (early) nutritional interventions for counteracting long-term consequences of ES, such as cognitive decline and an increased vulnerability to AD. Here, we aim to further increase knowledge on how early-life nutrition might affect the later-life ES-induced decline in behavior, specifically cognition, and specifically addressed microglia as potential targets. We studied whether they can be targeted by early supplementation or enrichment with coffee polyphenols and N-3 PUFAs, respectively. We additionally aim at linking the PUFA/oxylipin profile to microglial properties, and address if this link is brain region- and/or sex-specific. A large body of evidence describes how ES affects behavior and how nutritional interventions could be effective in mitigating these effects. We employed a search strategy that allowed for an effective literature search to bring together and review these studies in **chapter 2**. In this chapter, we have gathered

all existing clinical and pre-clinical evidence on nutritional interventions aimed at targeting the effects of pre- and postnatal stress on neurobehavioral outcomes and discuss the possible mechanisms involved. We highlight critical gaps in our current knowledge and propose future directions to move the field forward. Key outstanding questions pertain to the optimal timing and duration of such interventions. Specifically, it is important to determine the most effective time window for applying nutritional interventions and the most optimal duration of these interventions. Furthermore, it is yet to be explored whether the answer to these questions varies depending on the nutrient used. For example, we know that certain nutritional interventions (45,60), with the same timing, are effective in reducing ES-induced behavioral deficits in our limited bedding and nesting model of ES, but to what extent this translates to other nutrients or models, is unknown. In addition, we do not know if there are other nutrients that could be effective and whether they work through similar mechanisms. Yet, it is highly plausible that some nutrients exhibit greater potency than others, or that a combination of nutrients is necessary to have a beneficial or synergistic effect.

The identification of coffee-related metabolites as part of a protective molecular signature against cognitive decline in humans (61,62) was the rationale for **chapter 3**. Here, we investigate the potential protective effects of the bioactive coffee-polyphenols chlorogenic and caffeic acid against the ES-induced cognitive decline. The impact on two possible mechanisms that are known to be affected by ES in our previous studies (survival of newborn cells and neuroinflammation)(45,53,63) are investigated here.

PUFAs are other nutrients that have gained specific interest in the context of neurodegenerative and neuropsychiatric disorders. Very little is however known about PUFAs (and their derivatives called oxylipins) in the healthy, homeostatic brain. In **chapter 4**, we choose two brain regions (hippocampus and hypothalamus) from wildtype male and female mice to characterize the profiles of PUFA- and oxylipin species and its relation to microglial morphology. Thereby, we provide valuable insights into lipid-mediated signaling pathways in these brain regions that could be crucial to a sex-dependent and brain region-dependent vulnerability to disease.

In the next chapter, we extend to the programming by diet and ES, and evaluate later changes in PUFA- and oxylipin species and microglial properties. In **chapter 5**, we investigated the effect of the same dietary intervention and ES on hippocampal PUFA- and oxylipin species and how this might affect residing microglia in male mice. By performing detailed volumetric and morphometric analyses on these microglia, we look at microglial changes at a subcellular level, which has not been studied before.

From previous literature, we know that an early dietary decrease in the LA/ALA ratio can have effects on later-life microglial outcomes and behavior. In **chapter 6**, we investigated whether early supplementation with N-3 PUFAs could have similar effects on later-life microglial and pathological outcomes in a transgenic AD mouse model at 6 months of age.

Finally, in **chapter 7**, the main findings of this thesis and their implications are summarized and future directions to move the field forward are proposed.

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