**Abstract:** Inflammation is a central element of many neurodegenerative diseases. Formyl peptide receptors (FPRs) can trigger several receptor-dependent signal transduction pathways that play a key role in neuroinflammation and neurodegeneration. They are chemotactic receptors that help to regulate pro- and anti-inflammatory responses in most mammals. FPRs are primarily expressed in the immune and nervous systems where they interact with a complex pattern of pathogen-derived and host-endogenous molecules. Mounting evidence points towards a contribution of FPRs – via neuropathological ligands such as Amyloid beta, and neuroprotective ligands such as Humanin, Lipoxin A4, and Annexin A1 – to multiple pathological aspects of neurodegenerative diseases. In this review, we aim to summarize the interplay of FPRs with neuropathological and neuroprotective ligands. Next, we depict their capability to trigger a number of ligand-dependent cell signaling pathways and their potential to interact with additional intracellular cofactors. Moreover, we highlight first studies, demonstrating that a pharmacological inhibition of FPRs helps to ameliorate neuroinflammation, which may pave the way towards novel therapeutic strategies.

**Keywords:** Alzheimer’s disease; biased agonism; FPR; neuroinflammation.
Within these anatomical structures, FPR1 and FPR2 are predominantly found in glial cells, such as microglia and astroglia, that play a key role in many neurodegenerative diseases (Brandenburg et al. 2010; Lacy et al. 1995; Le et al. 2001a). In addition, FPRs can also be found in a few highly specialized sets of motor and sensory neurons (Becker et al. 1998; Bufe et al. 2012; Chiu et al. 2013; Liberles et al. 2009).

FPRs are known for their capability to interact with a large variety of ligands (Migeotte et al. 2006; Ye et al. 2009). These ligands include many exogenous pro-inflammatory molecules such as formyl peptides released by bacteria and several host-endogenous compounds such as Serum amyloid protein A (He et al. 2003), the Amyloid β isoform Aβ1–42 (Le et al. 2001a) and the antimicrobial Cathelicidine LL-37.

Figure 1: The role of FPRs in health and disease.
(A) A schematic overview of pathological conditions in which an involvement of FPRs was observed (Migeotte et al. 2006; Weiß and Kretschmer 2018; Yu and Ye 2015). (B) Phylogenetic relationships of human and murine FPRs. All three human FPRs and the murine mFpr1, mFpr2 and mFpr3 are involved in inflammatory responses. The remaining murine members of this receptor family and mFpr3 are associated with olfactory functions (Bufe et al. 2015, 2019; Gao et al. 1998). (C) Exemplary measurements of calcium flux induced by Aβ1–42 through human and mouse FPRs. FPR-transfected HEK293T cells were loaded with a calcium-sensitive fluorescent dye and subsequently treated with 10 µM of Aβ1–42. The bars display the Aβ1–42-induced change in fluorescence, which indicates calcium mobilization after activation of the respective receptors.

Figure 2: Expression of FPRs in different cell types.
FPRs are expressed in different cells of the central nervous system such as glial (Brandenburg et al. 2010; Lacy et al. 1995; Le et al. 2001a) and neuronal cells (Becker et al. 1998; Bufe et al. 2012; Chiu et al. 2013; Liberles et al. 2009) and in various cells of the peripheral immune system (Chen et al. 2002; Dahlgren et al. 2016; Devosse et al. 2009; Lee et al. 2018). Their expression was also observed in other peripheral cell types such as hepatocytes, fibroblasts, and platelets (Czapiga et al. 2005; Rossi et al. 2015; Øie et al. 2016).
(De Yang et al. 2000). Surprisingly, ligands that elicit pro- and anti-inflammatory responses can interact with the same receptor (Figure 3). hFPR2 for example, is on one hand activated by peptides that are well-known to elicit pro-inflammatory responses such as chemotaxis, release of inflammatory cytokines, and superoxide generation (Migeotte et al. 2006; Ye et al. 2009). On the other hand, other hFPR2 ligands, such as the glucocorticoid induced calcium and phospholipid-binding protein Annexin A1 (also known as Lipocortin 1) and its N-terminal fragment (Ac2–26), or the polyunsaturated fatty acid derivatives Lipoxin A4 and Resolvin D1 trigger anti-inflammatory effects (Levy and Serhan 2002; Parkinson 2006; Perretti and D’Acquisto 2009).

These observations raise the question how different ligands that interact with the same receptor can trigger opposing effects. While this is yet not fully understood, a number of recent findings give first insight into the underlying molecular mechanisms. One answer is based on the concept of biased agonism (Figure 3(A)) i.e. that different ligands can trigger ligand-specific mutual exclusive signal transduction events, which is well-established for G-Protein coupled receptors (Wootten et al. 2018). In two recent studies by Zhang et al. and Gröper et al. the possibility of biased agonism was investigated for several formyl peptide receptor ligands (Gröper et al. 2020; Zhang et al. 2020). Gröper et al. found clear evidence for ligand-dependent biases in hFPR1 signal transduction for a number of classical FPR-ligands. To this end, they examined the cAMP concentration, ligand-dependent internalization and Extracellular Signal-regulated Kinase (ERK1/2) activation for a number of classical FPR-ligands. All tested compounds led to a dose-dependent decrease of cAMP levels and an increased ERK1/2 phosphorylation. However, only the synthetic FPR-specific agonist W-peptide and formyl peptides of mitochondrial or bacterial origin were capable to trigger receptor internalization. This effect was not observed with other ligands such as the anti-inflammatory Ac2–26, an N-terminal fragment of Annexin A1, or the viral peptide fragment gG2p20, derived from a secreted glycoprotein sgG-2 of herpes simplex virus type 2 (Gröper et al. 2020). Similar agonist-biased differences in hFPR2 signal transduction were observed by Zhang et al. (2020). Using single-molecule FRET to measure conformational changes of hFPR2, they observed that the pro-inflammatory ligand Aβ1–42 as well as the anti-inflammatory ligand Ac2–26 and W-peptide caused structural changes of the receptor. Of note, Aβ1–42 elicited these changes at concentrations as low as 10 pM. However, these three ligands differed in Ca2+ mobilization and cAMP inhibition as well as in β-arrestin signaling (Figure 3(A)). Next, some signaling events that were triggered by W-peptide could be modulated in an opposite manner depending on whether cells were pre-incubated with Aβ1–42 or Ac2–26. Binding assays showed that neither Ac2–26 nor Aβ1–42 could compete with W-peptide binding on hFPR2, suggesting that the receptor possesses allosteric binding sites for both, Ac2–26 and Aβ1–42. Taken

Figure 3: Schematic overview of FPR-induced signal transduction.
(A) Schematic representation of a biased agonism of different FPR2 ligands as proposed by Zhang et al. (2020). While full agonists like the W-peptide induce the activation of all signaling pathways through the human FPR2, other agonists only activate selected pathways. Aβ1–42 may induce pro-inflammatory effects through a biased activation of FPR2, which omits second messenger signaling (Zhang et al. 2020). (B) After ligand binding, FPRs utilize different signaling molecules such as second messengers (cAMP, calcium ions), members of MAP kinase pathways (p38, ERK1/2), and β-arrestins to induce physiological effects. These effects include the induction of chemotaxis, superoxide generation, the release of interleukins and matrix metalloproteinases (MMPs), and the degranulation of immune cells (Migeotte et al. 2006; Ye et al. 2009).
together, these experiments indicate that binding of ligands to hFPR1 and hFPR2 can induce different ligand-biased signal transduction events.

In addition to biased agonism, ligand-dependent binding preferences to divergent FPR oligomers may exist. Different FPR subtypes are frequently co-expressed within the same cell. It is therefore conceivable that they form varying homo- and heterodimers, with divergent ligand and signal transduction preferences. In line with this idea, a first study investigated whether FPR oligomerization might be responsible for different signaling events. Using co-immunoprecipitation and bioluminescence resonance energy transfer assays, a constitutive FPR dimerization was demonstrated in transfected HEK293 cells (Cooray et al. 2013). For hFPR1, homodimerization as well as heterodimerization with hFRP2 and hFPR3 were reported. Additionally, the pro-resolving ligands Annexin A1 and AC26 could stimulate hFRP2 homodimers, whereas the pro-inflammatory ligand Serum amyloid protein A was not able to activate this dimer (Cooray et al. 2013). This indicates that anti-inflammatory and pro-inflammatory signals may preferentially activate different FPR oligomers. Additional cofactors may also contribute to the formation of cell-type-dependent receptor complexes with an altered signal transduction. For example, rat Fpr1 as well as Fpr2 were shown to interact with different surface receptors, such as the Macrophage Receptor with Collagenous Structure (MARCO) and the Receptor for Advanced Glycation End-products (RAGE) (Brandenburg et al. 2010; Slowik et al. 2012).

The diverse biological functions of FPRs are currently best understood in the innate immune system. There, they primarily function as pattern recognition receptors that activate multiple defense mechanisms in innate immune cells during bacterial infections (Figure 3(B)). To this end, they primarily detect formyl-methionine (f-Met)-containing peptides as non-self-structures. Bacteria use a formylated methionine during the initiation of protein biosynthesis, whereas almost all mammalian proteins start with a non-formylated methionine (Bude and Zufall 2016; Bufe et al. 2015). f-Met-peptides likely originate from N-terminal breakdown products of bacterial signal peptides that are required for the transfer of proteins through the plasma membrane. Therefore, f-Met peptides can be seen as a bacterium-specific, pathogen-associated molecular pattern (PAMP) that is released during bacterial infections such as meningitis, sepsis or pneumonia and triggers pro-inflammatory responses through an activation of FPRs (Weiß and Kretschmer 2018).

In addition to a vast amount of f-Met-peptides from bacteria, FPRs can also recognize host-specific f-Met-peptide-fragments released by damaged mitochondria (Dahlgren et al. 2016). From an evolutionary point of view, mitochondria can be traced back to a former bacterial origin. Therefore, it is not surprising that they still contain a small number of f-Met-peptides (Lind et al. 2019). By contrast to the numerous sequence divergent formyl-peptides from bacteria, these few host-endogenous molecules are generally not released in healthy tissue. However, they can be passively liberated upon cellular injuries such as tissue damage or necrotic cell death. This enables FPRs to have a dual surveillance capability: they can either directly detect pathogens through recognition of a bacteria-specific PAMP or indirectly through detection of a mitochondria-derived host-endogenous damage-associated molecular pattern (DAMP) (Bloes et al. 2015; Dahlgren et al. 2016). This dual function is extremely useful for reacting to a multitude of different pathogens that cause cell death or necrosis. Therefore, it is not surprising that the activation of FPRs influence a wide range of key inflammatory processes (Figure 3(B)), such as chemotaxis, calcium flux, production, and release of different cytokines and proteases as well as a superoxide anion generation (Bude et al. 2015; Ye et al. 2009).

Under certain physiological conditions, the capability of FPRs to detect tissue damage can be problematic, since mitochondrial products can also be released under aseptic conditions such as necrosis, tissue trauma or ischemia. Unwanted pro-inflammatory processes, triggered by FPRs, can damage healthy tissue or contribute to systemic inflammation and may therefore play an important role in the progressive deterioration seen during neurodegeneration.

Neurodegenerative diseases in the CNS share the occurrence of neuroinflammation, which is usually the secondary response to a primary cause. Neuroinflammation is caused by a chronic activation of an innate immune response in the CNS by stimulation of microglia and astrocytes (Guzman-Martinez et al. 2019). This has been demonstrated, for example, in Alzheimer’s disease (AD), Parkinson’s disease (PD), and Amyotrophic lateral sclerosis (ALS) (Guzman-Martinez et al. 2019). Brain tissue is per se very sensitive towards inflammation, therefore, the secondary inflammatory response can be even more damaging than the underlying primary cause (Guzman-Martinez et al. 2019; Leng and Edison 2021).

Neuroinflammation and neurodegeneration are associated with a shift in glial function (Leng and Edison 2021; Li and Barres 2018). Glial cells have neuro-supportive and neuro-protective functions in healthy tissue (Richter et al. 2020). However, pathological stimuli can trigger reactive glial phenotypes that contribute to synaptic dysfunction and neuronal death (Li and Barres 2018; Liddelow et al. 2017). In these states, glial cells propagate neurodegeneration
through the induction of oxidative stress and the production and release of pro-inflammatory cytokines and chemokines (Liddelow and Barres 2017; Liddelow et al. 2017). Neuro-supportive microglial cells only express low amounts of FPRs (Brandenburg et al. 2010; Lacy et al. 1995; Tiffany et al. 2001), whereas reactive microglia have a significantly higher amount of FPRs, making a contribution for these receptors in initiation and progression of neuroinflammation highly plausible (Bihler et al. 2017; Y. Cui et al. 2002; Tiffany et al. 2001).

The role(s) of FPRs in neuroinflammation

In a healthy environment, microglia provide trophic support to the CNS and are involved in regulating synaptic processes (Kettenmann et al. 2013; Leng and Edison 2021; Nimmerjahn et al. 2005; Richter et al. 2020). They furthermore form long branches that survey their microenvironment for pathological stimuli (Leng and Edison 2021; Nimmerjahn et al. 2005). Detection of harmful stimuli results in an activation of microglia, which in turn leads to morphological changes. They lose their ramifications and take over an amoeboid shape (Dailey and Waite 1999; Nimmerjahn et al. 2005). Reactive microglia show a drastic shift in gene expression: expression of neurotrophic factors is reduced, while the expression of genes associated with phagocytic functions and pathogen recognition is highly upregulated (Hammond et al. 2019; Olah et al. 2020; Pulido-Salgado et al. 2018). Therefore, reactive phenotypes suspend most of their trophic support and instead assume phagocytic functions, which help to clear pathological molecules from the CNS (Bisht et al. 2016; Kettenmann et al. 2013; Leng and Edison 2021).

Several lines of evidence indicate that FPRs contribute to the transformation of microglia into more reactive phenotypes. First, in vitro studies show that the exposure of microglial cell lines to pro-inflammatory stimuli such as Amyloid β (Aβ1–42), Interferon-γ and bacterial lipopolysaccharides leads to an increased FPR expression and an enhanced reactivity (Chen et al. 2007; Y.-H. Cui et al. 2002; Lorton et al. 2000; Tiffany et al. 2001). Second, there is clear evidence for an in vivo upregulation of FPR expression in AD and Multiple sclerosis (MS) (Bihler et al. 2017; Le et al. 2001a; Schröder et al. 2020). For example, an increased expression of hFPR2 has been shown in invading microglia at the site of senile plaques in clinical samples of AD patients (Le et al. 2001a). Similarly, increased mFpr1 expression was observed in reactive microglia in a Cuprizone-induced MS mouse model (Bihler et al. 2017). Third, inhibition of FPR activity ameliorates the reactivity of microglial cells. For example, application of the FPR inhibitor N-tert-butyloxycarbonyl-Phe-Leu-Phe-Leu-Phe (Boc-2) was shown to decrease microglia activation in vivo in an AD mouse model (Schröder et al. 2020), whereas mFpr1-deficient mice displayed less reactive microglia in an MS model (Bihler et al. 2017). Fourth, FPRs might aid microglia in the clearance of harmful stimuli such as apoptotic cells and pathological peptides, which are known to propagate pro-inflammatory effects (Brandenburg et al. 2007, 2008; Y. Cui et al. 2002; da Rocha et al. 2019; McArthur et al. 2010; Yazawa et al. 2001). Microglia, for example, can internalize neuropathological peptides such as Aβ1–42 and the Prion protein fragment PrP106–126 through FPR2 (Brandenburg et al. 2007, 2008; Le et al. 2001a; Yazawa et al. 2001). In addition, application of the FPR inhibitor N-tert-butyloxycarbonyl N-formyl-Met-Leu-Phe (Boc-1) effectively attenuated microglial phagocytosis of apoptotic neuronal cells in vitro (McArthur et al. 2010). Hereby, FPR2 has been implicated in the mediation of phagocytosis through interactions with endogenous Annexin A1 and subsequent modulation of STAT pathways (da Rocha et al. 2019; McArthur et al. 2010). Finally, stimulated microglia migrate to well-known FPR-ligands such as the bacterial chemoattractant f-MLF and the synthetic W-peptide (Y. Cui et al. 2002; Y.-H. Cui et al. 2002; Tiffany et al. 2001).

While the findings above implicate FPRs in the pro-inflammatory response of microglia, other lines of evidence indicate their potential in resolving neuroinflammation. For example, administration of the FPR ligands Resolvin E1 and Lipoxin A4 were shown to ameliorate the production of pro-inflammatory cytokines in an AD mouse model (Kantarci et al. 2018). Next, Annexin A1 and the mitochondrial peptide Humanin, whose neuroprotective properties have been observed previously, can interact with FPRs (Ernst et al. 2004; Rüger et al. 2020; Ying et al. 2004). The Annexin A1-derived FPR-agonist Ac2–26 was shown to ameliorate neuroinflammation in a murine model for pneumococcal meningitis (Rüger et al. 2020). Moreover, stimulation of mFpr2 by anti-inflammatory agonists reversed microglial reactivity and reactive oxygen species production in vitro and prevented subsequent neuronal death (Wickstead et al. 2020). According to these findings, stimulation of FPRs with specific ligands may be useful to resolve neuroinflammation in the CNS, which provides an interesting but yet not tested novel treatment strategy for neurodegenerative diseases in humans.

Besides microglia, astrocytes are also heavily involved in upholding the healthy environment of cerebral tissues.
As one of the most abundant cell types in the brain, astrocytes fulfill a supporting role in the CNS by mediating blood flow and the homeostasis of synaptic metabolites and neurotransmitters (Attwell et al. 2010; Leng and Edison 2021; Rouach et al. 2008). They furthermore enable the clearance of CNS waste products through the glymphatic system (Iliff et al. 2012; Jessen et al. 2015). Under pathological conditions, however, they enter reactive gliosis leading to changes in their phenotype (Liddelow and Barres 2017; Maragakis and Rothstein 2006). In general, this reactive state can be classified into two types: an A1 phenotype that typically occurs due to inflammatory stimuli and propagates neuroinflammation, and an A2 phenotype that has been linked to ischemic conditions and is associated with neuro-supportive effects (Liddelow and Barres 2017). Accordingly, the A1 phenotype has been implicated in neurodegenerative diseases (Leng and Edison 2021; Maragakis and Rothstein 2006). By adopting this state, astrocytes undergo several changes in gene expression, leading to a decline in supportive functions and an increased production of neurotoxic factors (Liddelow and Barres 2017). While it is known that astrocytes express FPR1 and FPR2, it is not well understood how these cells utilize these receptors (Becker et al. 1998; Brandenburg et al. 2010; Lacy et al. 1995).

Interestingly, FPRs may contribute to the reactive state of astrocytes because mFpr1-deficient mice displayed a reduced astrocyte activation in a MS model (Bihler et al. 2017). Similarly, mFpr2-deficient mice showed a reduced number of activated astrocytes as compared to wild type mice after induction of neuroinflammation through injections of Streptozotocin (Zhang et al. 2019).

**FPRs may contribute to an infiltration of peripheral immune cells into the brain**

Under healthy condition, the blood brain barrier (BBB) separates cerebral tissue from the periphery and thereby protects the CNS from pathogens. Many neurodegenerative diseases such as AD or MS lead to a dysfunction of the BBB and an influx of potentially harmful stimuli (Desai et al. 2007). This elicits infiltration of peripheral immune cells into the brain (Gallizioli et al. 2020; Jay et al. 2015; Michaud et al. 2013). Among those infiltrating cells are dendritic cells (DCs), which have been implicated in neurodegeneration during MS and AD (Ferretti et al. 2016; Gallizioli et al. 2020; Greter et al. 2005). DCs induce the recruitment of T-cells into the CNS and subsequently trigger their activation through chemokine release, which then enables a strong pro-inflammatory response (Greter et al. 2005). Different phenotypes of DCs infiltrate the CNS in rodent MS and AD models (Bailey-Bucktrout et al. 2008; Ferretti et al. 2016; Greter et al. 2005; McMahon et al. 2005).

Several observations argue for a contribution of FPRs to the invasion of DCs. First, FPRs are implicated in preserving BBB integrity through interactions with endogenous Annexin A1 (Cristante et al. 2013; Vital et al. 2016). Moreover, mFpr2/3-deficient mice displayed leakiness of the BBB and increased neutrophil infiltration in the brain in a model for sterile inflammation (Vital et al. 2016). Next, FPR-agonists induce calcium mobilization and chemotaxis of DCs, which argues for an involvement of FPRs in DC trafficking (Chen et al. 2002). Interestingly, mature DCs express high amounts of hFPR3 (Chen et al. 2002), whereas the expression of other FPRs can also be observed in immature DCs but seems to subside after maturation (Chen et al. 2002).

**The role(s) of FPRs in AD and other neurodegenerative diseases**

AD is a complex disorder of the CNS, whose most prominent clinical features include the pathological formation of extracellular senile plaques in cerebral tissues and an intracellular fibrillation of hyperphosphorylated tau proteins in affected neurons. The plaques contain a number of different Aβ fragments (Table 1), which are all generated by the cleavage of the Amyloid precursor protein (Müller et al. 2017). These fragments are named according to their respective length. Hereby, a fragment of 42 amino acids (Aβ1–42) was shown to be one of the most abundant peptides in senile plaques (Portelius et al. 2010a). Interestingly, clinical samples from AD patients show a high expression of hFPR2 in microglia at the sites of senile plaques (Le et al. 2001a). In cultured glial cells, Aβ1–42 furthermore induces an upregulation of mFpr2 on mRNA and protein levels, which could be prevented through treatment with the FPR antagonist Boc-1 (Heurtaux et al. 2010). Two recent studies further substantiated an involvement of FPRs in AD by demonstrating that the inhibition of FPR activity leads to clear protective effects. A study by Zhang et al. used Streptozotocin-treatment as a model for sporadic AD to examine the role of mFpr2 (Zhang et al. 2019). In wild type mice, Streptozotocin induced cognitive impairment as well as neuroinflammation and the hyperphosphorylation of tau proteins. In comparison to treated wild type mice, Streptozotocin-treated mFpr2−/−
mice displayed an improved spatial memory. A subsequent study showed that treatment of APP/PS1 AD model mice with the FPR inhibitor Boc-2 resulted in a significantly improved spatial memory performance (Schröder et al. 2020). Furthermore, Boc-2-treatment increased neuronal density, led to an upregulation of neurotrophic factors and decreased senile plaque load, which indicates that inhibition of FPRs might be a useful treatment strategy for AD.

Tiffany et al. already provided first evidence for a role of FPRs in AD in 2001 (Tiffany et al. 2001). In this study, Aβ1–42 induced FPR-dependent chemotaxis in FPR-transfected HEK293T cells and primary cultures of murine monocytes. The same effect was observed in a murine glial cell line, where it could be inhibited by Pertussis toxin – a well-known inhibitor of GPCR-mediated signal transduction. Sequential stimulation of this cell line with f-Met peptides and Aβ1–42 showed a reciprocal cross-desensitization (Tiffany et al. 2001). Furthermore, application of Aβ1–42 induces oxidative stress and the release of pro-inflammatory markers such as Interleukin 1β (IL-1β) in rat and murine microglia (Lorton et al. 2000; Tiffany et al. 2001; Wickstead 2019). These effects could be cross-desensitized by FPR agonists in rat microglia and did not occur in primary cells from mFpr2-deficient mice (Lorton et al. 2000; Wickstead 2019).

Several further studies support a direct interaction between Aβ1–42 and FPRs and show that Aβ1–42 can elicit multiple signaling effects through these receptors. One example is the Aβ1–42 induced calcium mobilization through human and murine FPRs in transfected rat basophilic leukemia (RBL) cells (Le et al. 2001a). Moreover, Aβ1–42 induced a decrease of cAMP in rat microglia and astrocytes, which was inhibited by the synthetic FPR2-specific antagonist WRW4 (Brandenburg et al. 2008). Taken together, these results clearly argue for a direct involvement of FPRs in the detection of Aβ1–42 and the subsequent recruitment of microglia to damaged brain areas.

Besides a direct activation of second messenger cascades, Aβ1–42 can modulate several additional signaling pathways through FPRs. Zhang et al. demonstrated nuclear translocation of β-arrestin 1 and a recruitment of β-arrestin 2 to the cell membrane upon application of Aβ1–42 to hFPR2-transfected RBL cells. Furthermore, they found Aβ1–42 to differentially modulate the phosphorylation of p38 Mitogen-Activated Protein Kinase (MAPK) and ERK1/2 (Zhang et al. 2020).

The regulation of these pathways via FPRs is associated with activation of pro-inflammatory transcription factors such as the Activator Protein 1 (AP-1) and Nuclear Factor κB (NF-κB), which are typical markers of neuroinflammation.

**Table 1:** Aβ peptides of different lengths detected in brain and cerebrospinal fluid (CSF) samples of AD patients.

| Aβ fragments | Source | References |
|--------------|--------|------------|
| C-truncated  |        |            |
| 1–13 to 1–20 | CSF    | (Brinkmalm et al. 2012; Maddalena et al. 2004) |
| 1–15 to 1–20 | CSF    | Halim et al. (2011) |
| Glycosylated |       |            |
| 1–16 to 1–17 | Brain, | (Brinkmalm et al. 2012; Güntert et al. 2006; Maddalena et al. 2004) |
| 1–20         | Brain  | Wildburger et al. (2017) |
| 1–28         | CSF    | Brinkmalm et al. (2012) |
| 1–30         | CSF    | Brinkmalm et al. (2012; Maddalena et al. 2004) |
| 1–31         | Brain  | Wildburger et al. (2017) |
| 1–33 to 1–34 | CSF    | (Brinkmalm et al. 2012; Maddalena et al. 2004) |
| 1–37 to 1–40 | Brain, | (Brinkmalm et al. 2012; Maddalena et al. 2004; Portelius et al. 2010b) |
| 1–37 to 1–40 | CSF    | Brinkmalm et al. (2012) |
| Oxidized     |        |            |
| 2–42 to 11–42| Brain  | (Näslund et al. 1994; Portelius et al. 2010b) |
| 2–40         | Brain  | (Gkanatsiou et al. 2019; Liu et al. 2006; Näslund et al. 1994) |
| PE3–40/42    | Brain  | (Gkanatsiou et al. 2019; Portelius et al. 2010b) |
| 4–42 to 5–42 | Brain  | Wildburger et al. (2017) |
| Oxidized     |        |            |
| 4–40         | Brain, | (Brinkmalm et al. 2012; Portelius et al. 2010b) |
| 4–43         | Brain  | Portelius et al. (2015) |
| 5–40         | Brain  | (Gkanatsiou et al. 2019; Liu et al. 2006; Näslund et al. 1994) |
| 5 – AMM A42  | Brain  | Wildburger et al. (2017) |
| 8–42 Oxidized| Brain  | Wildburger et al. (2017) |
| 9–40         | Brain  | Portelius et al. (2010b) |
| 11–42        | Brain  | Gkanatsiou et al. (2019) |
| 11–42 Oxidized| Brain | Wildburger et al. (2017) |
| pE11–42      | Brain  | (Näslund et al. 1994; Portelius et al. 2010b) |
| pE11–42 Oxidized| Brain| Wildburger et al. (2017) |
| 17–42        | Brain  | Gowing et al. (1994) |

| N-truncated  |        |            |
|--------------|--------|------------|
| 2–42 to 11–42| Brain  | (Näslund et al. 1994; Portelius et al. 2010b) |
| 2–40         | Brain  | (Gkanatsiou et al. 2019; Liu et al. 2006; Näslund et al. 1994) |
| PE3–40/42    | Brain  | (Gkanatsiou et al. 2019; Portelius et al. 2010b) |
| 4–42 to 5–42 | Brain  | Wildburger et al. (2017) |
| Oxidized     |        |            |
| 4–40         | Brain, | (Brinkmalm et al. 2012; Portelius et al. 2010b) |
| 4–43         | Brain  | Portelius et al. (2015) |
| 5–40         | Brain  | (Gkanatsiou et al. 2019; Liu et al. 2006; Näslund et al. 1994) |
| 5 – AMM A42  | Brain  | Wildburger et al. (2017) |
| 8–42 Oxidized| Brain  | Wildburger et al. (2017) |
| 9–40         | Brain  | Portelius et al. (2010b) |
| 11–42        | Brain  | Gkanatsiou et al. (2019) |
| 11–42 Oxidized| Brain | Wildburger et al. (2017) |
| pE11–42      | Brain  | (Näslund et al. 1994; Portelius et al. 2010b) |
| pE11–42 Oxidized| Brain| Wildburger et al. (2017) |

| C- & N-truncated |        |            |
|------------------|--------|------------|
| 2–14             | CSF    | Maddalena et al. (2004) |
| 2–16             | Brain  | Güntert et al. (2006) |
| 3–15 to 3–17     | Brain  | (Brinkmalm et al. 2012; Güntert et al. 2006) |
| 3–15 to 4–15     | CSF    | Halim et al. (2011) |
| Glycosylated     |        |            |
| pE3–19 to pE3–20 | Brain  | Gkanatsiou et al. (2019) |
| pE3–24           | Brain  | Gkanatsiou et al. (2019) |
| 4–16 to 5–16     | Brain  | Güntert et al. (2006) |
All peptides are sorted according to their length and C- or N-terminal truncations. Post-translational modifications are indicated as follows: pE: pyroglutamylation, racemization: D-configuration of amino acids, oxidation: occurrence of oxidized amino acids in the peptide, glycosylation: glycans linked to peptide, AMM: C-terminal ammonium ion.

(Heurtaux et al. 2010; Li et al. 2018; O’Neill and Kaltschmidt 1997; Sodin-Semrl et al. 2004). FPR-dependent MAPK signal transduction and translocation of β-arrestins may be involved in the inflammatory response in glial cells during AD (Brandenburg et al. 2008; Chen et al. 2019; Huet et al. 2007; Kong et al. 2010). Hereby, Aβ1–42 induced phosphorylation of ERK in primary cultures of rat astrocytes and microglia. This effect was ameliorated through the FPR2-antagonist WRW4 (Brandenburg et al. 2008). Furthermore, pretreatment of primary murine microglia with the FPR-inhibitor Boc-1 reduced Aβ1–42-mediated phosphorylation of NF-κB and a sub-unit of AP-1 (Heurtaux et al. 2010). FPR-dependent glial activation has also been linked to the phagocytic response against Aβ1–42. Different studies observed a dose-dependent internalization of Aβ1–42 through FPR2 and a subsequent intracellular accumulation of the peptide (Yazawa et al. 2001; Zhang et al. 2020). An intracellular co-localization of Fpr2 and Aβ1–42 was shown in rat microglia and astrocytes (Brandenburg et al. 2008). Heurtaux et al. compared the effects of differently sized Aβ oligomers on murine microglial activation: small oligomers induced a significant upregulation of pro-inflammatory factors and increased subsequent phagocytic response that could be inhibited through application of the FPR antagonist Boc-1 (Heurtaux et al. 2010). Larger oligomers, however, did not induce significant effects. In accordance with these findings, aggregation of Aβ1–42 resulted in a decrease in FPR-mediated chemotaxis of human monocytes (Le et al. 2001a).

In addition to AD, FPRs are implicated in the pathogenesis of further neurodegenerative diseases such as Prion disease (Brandenburg et al. 2007, 2008; Le et al. 2001b; Yazawa et al. 2001), ALS (Zhang et al. 2011), MS (Bihler et al. 2017; Kilic et al. 2015; Müller-Ladner et al. 1996), and PD (Cardoso and Empadinhas 2018; Cussell et al. 2020; Zhang et al. 2005). The pathology of Prion disease is in some aspects similar to AD. Both share the occurrence of proteinaceous particles and an infiltration of activated mononuclear phagocytes in brain lesions, which results in fibril formation and neuroinflammation (Prusiner 1998). Interestingly, the detection of the Prion protein fragment PrP106–126 in brains of AD patients suggests a coexistence of both pathologies in some patients (Leuba et al. 2000). Using calcium imaging, Le and colleagues showed that PrP106–126 is an agonist of hFPR2 (Le et al. 2001b). Next, Brandenburg et al. linked the internalization of PrP106–126 in glial cells to mFpr2 (Brandenburg et al. 2007). Furthermore, fragments of the Prion protein elicited an activation and migration of monocytes and the release of pro-inflammatory, neuro-toxic cytokines (Combs et al. 1999; Le et al. 2001b) and an increase in glial Phospholipase D activity through interactions of PrP106–126 with FPR2 was described (Brandenburg et al. 2007; Le et al. 2001b). However, FPR2 is not the only receptor involved in Phospholipase D-mediated endocytosis of the Prion protein because other receptors such as the 37-kDa/67-kDa Laminin receptor are also involved (Leucht et al. 2003; Morel et al. 2005).

The pathology of MS is complex and not known in detail yet. However, the occurrence of demyelinating lesions indicates an involvement of the innate immune response (Hernández-Pedro et al. 2013). During acute and chronic MS progression, FPR expression is highly increased in foam cells (Müller-Ladner et al. 1996). Furthermore, the FPR ligand f-MLF triggered pathology conditions in an well-known experimental autoimmune
encephalomyelitis animal model of MS (Kilic et al. 2015). In the Cuprizone demyelination model, evidence for an involvement of mFpr1 was also found (Bihler et al. 2017; Kipp et al. 2009; Torkildsen et al. 2008). mFpr1 expression not only increased in murine cortex upon treatment but even more convincing, mFpr1-deficient mice showed a smaller amount of demyelination in the corpus callosum as well as less active astrocytes in the cortex and less active microglia in corpus callosum and cortex (Bihler et al. 2017). Furthermore, decreased cortical mRNA expression of the pro-inflammatory cytokine Tumor Necrosis Factor α (TNF-α) as well as of the anti-inflammatory cytokine Interleukin-1 Receptor Antagonist (IL-1RA) were found in mFpr1-deficient mice.

ALS is the most common form of adult motor neuron disease. It is characterized by a progressive degeneration of motor neurons in motor cortex, brainstem, and spinal cord (Maragakis and Rothstein 2006). Interestingly, activated microglia are found in both, the familial and sporadic form of ALS (Beers et al. 2006; Boillée et al. 2006; Kawamata et al. 1992; McGeer and McGeer 2002). In familial ALS, microglial cells are activated due to genetic mutations in the Superoxide Dismutase 1 (SOD1) gene (Corcia et al. 2012; Maragakis and Rothstein 2006; Maruyama et al. 2010). Upregulation of hFPR1 and hFPR2, found by gene expression profiling of peripheral blood mononuclear cells from patients with sporadic ALS, suggested a contribution of these receptors to ALS (Zhang et al. 2011). Interestingly, an activation of Phospholipase D is linked to some ALS-related phenotypes (Kankel et al. 2020). Due to the capability of hFPR2 to activate Phospholipase D and the linkage of Phospholipase D activation inside glial cells to multiple neurodegenerative diseases, it is conceivable that the increase in Phospholipase D activity in ALS might be mediated by hFPRs (Brandenburg et al. 2007, 2008; Koch et al. 2004; McDermott et al. 2004; Shen et al. 2001).

Besides AD, PD is the most common age-related neurodegenerative disease (de Lau and Breteler 2006). PD is associated with the degeneration of dopaminergic neurons of the substantia nigra as well as the occurrence of intraneuronal eosinophilic protein aggregates composed of proteins such as α-Synuclein, Parkin, Ubiquitin, and neurofilaments, which are called Lewy bodies (Dauer and Przedborski 2003; Forno 1988). Activated microglial cells are involved in the neurotoxicity towards dopaminergic neurons (McGeer et al. 1988; Sanchez-Guajardo et al. 2015; Zhang et al. 2005). In PD, microglial cells are activated through misfolded α-Synuclein (Harm et al. 2013; Kim et al. 2013; Vila et al. 2000; Zhang et al. 2005). This results in increased release of reactive oxygen species via NADPH oxidase as well as of pro-inflammatory cytokines (Minghetti and Levi 1998; Wilms et al. 2009). α-Synuclein has been found in glial cells, which gives rise to the idea of a possible involvement of glial cells in its clearance (Lee et al. 2008; Sacino et al. 2014). Lipopolysaccharides increase the expression of mFpr2 in microglia and thereby increase pro-inflammatory cytokines TNF-α as well as IL-1 (Y. Cui et al. 2002; Y.-H. Cui et al. 2002). Moreover, lipopolysaccharides induce activation of microglia, which results in a delayed, progressive, and selective destruction of nigral dopaminergic neurons similar to the consequences of PD (Gao et al. 2002).

In PD, characteristic Lewy bodies are also found in the enteric nervous system as well as in the vagus nerve of early stage PD patients (Cersosimo et al. 2013; Pouclet et al. 2012). Therefore, the gastrointestinal tract could be involved in PD or could be the starting point for the pathogenesis of PD. Mitochondrial dysfunction or mitochondrial damaging toxins released by a dysbiotic gut could result in an increased release of DAMPs. These DAMPs could trigger neuroinflammation and finally PD (Cardoso and Empadinhias 2018; Wilkins et al. 2017). Damaged mitochondria can activate the innate immunity and initiate inflammation pathways via FPRs (Dahlgren et al. 2016). The connection between the gut and the brain could be achieved through the gut-brain axis, including the vagus nerve (Cardoso and Empadinhias 2018). Thus, PD might be the result of DAMPs triggered by gut pathogens, which are interacting with FPRs (Cussell et al. 2020). Interestingly, germ-free mice treated with bacterial metabolites develop neurodegeneration similar to PD (Sampson et al. 2016).

Key areas of future research

As delignated above, many lines of evidence suggest a role of FPRs in neurodegenerative diseases. However, their precise contribution is not yet clear. In our opinion, a number of critical issues urgently need to be addressed in order to solve this problem. First, a careful comparison of the Aβ interaction with human and mouse FPRs for pan-species similarities and differences is lacking. Such a study could be extremely helpful to judge the suitability of mouse models. Next, most studies so far focused on role of FPR2 in neurodegeneration and neglected the other receptors although we (Figure I(C)) and others (Le et al. 2001a) found that FPR1 can also be activated by Aβ42. The biological significance of these in vitro findings needs to be examined. Next, the recent studies on the agonist bias of FPRs suggest that Aβ42 may not strictly act as a classical activator but may rather influence FPR signaling as an allosteric modulator in combination with other agonists through...
multiple pathways. These effects and their biological consequences need to be investigated in more detail. Finally, as indicated in Table 1, many different cleavage and degradation products of Aβ can be found in cerebral plaques and the cerebrospinal fluid of AD patients. Thus, it is possible that they also contribute to FPR activation. In line with this idea, we showed that Aβ16–22, a fragment of Aβ, was capable to induce calcium mobilization through mFpr1 (Bufe et al. 2012). Thus, other physiological fragments of Aβ might therefore be interesting targets for future studies.

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