



UvA-DARE (Digital Academic Repository)

At the crossroads of epilepsy and Alzheimer's disease

Investigating the role of LRP1 in the cerebral vasculature

Rozeboom, A.

Publication date

2025

[Link to publication](#)

Citation for published version (APA):

Rozeboom, A. (2025). *At the crossroads of epilepsy and Alzheimer's disease: Investigating the role of LRP1 in the cerebral vasculature*. [Thesis, fully internal, Universiteit van Amsterdam].

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, P.O. Box 19185, 1000 GD Amsterdam, The Netherlands. You will be contacted as soon as possible.

Chapter 5

General discussion

The bidirectional relationship between epilepsy and Alzheimer's Disease (AD), two prevalent neurological disorders [1], has gained increasing recognition in recent years [2-7]. Individuals with AD have a threefold higher risk of developing epilepsy, while those with a history of epilepsy are twice as likely to develop AD [8]. Although epilepsy may not be the primary concern in AD, managing epileptiform activity is crucial to prevent further cognitive decline, as AD patients with subclinical epileptiform activity tend to deteriorate more rapidly than those without [9-11]. Conversely, although cognitive impairments are frequently observed in individuals with epilepsy, they may exhibit a distinct cognitive profile compared to patients with AD [12]. Therefore, it remains unclear whether these cognitive symptoms and combined neuropathological etiologies can be generalized. Currently, there are no cures for either disease, and available treatment options have notable limitations. Although late-onset epilepsies in elderly patients are frequently managed effectively with initial drug monotherapy, a significant subset faces drug-refractory epilepsy, resulting in reduced quality of life and an increased risk of seizure-related injuries in this vulnerable group [13]. Approximately one-third of epilepsy patients does not respond to anti-seizure medications (ASMs) [13-16]. Furthermore, there is insufficient evidence regarding the efficacy and safety of ASMs in AD patients who experience seizures [17]. Notably, a prospective randomized clinical trial demonstrated that less than one-third of AD patients with seizures achieved seizure freedom following ASM treatment [18]. These findings highlight the urgent need for new therapeutic targets that can benefit both epilepsy and AD.

The primary objective of this thesis is to unravel mechanisms underlying dysregulated processes in the epileptogenic brain, with a focus on the role of low-density lipoprotein receptor-related protein 1 (LRP1) in brain capillaries [19], which is important for amyloid beta ($A\beta$) clearance from the brain [19-26] and has been shown to decrease in expression during aging [23, 27, 28]. This may lead to $A\beta$ accumulation [20] and increased neuronal excitability [29]. The ultimate aim is to apply the obtained knowledge for new treatment strategies in the elderly population when symptoms of epilepsy and AD emerge.

5.1 The role of LRP1 in neuropathological processes at the BBB

LRP1 is a multifunctional transmembrane receptor involved in endocytosis, signaling, and various physiological processes, including brain homeostasis, lipoprotein metabolism, and brain inflammation [30]. Notably, LRP1 expression in brain capillaries diminishes with aging, as shown in mice [23], rats [27, 28], in Tg-2576 mice, an AD mouse model, [24], and in AD patients [23, 24, 27, 31, 32]. In **Chapter 2**, we investigated LRP1 expression changes in the human and rodent epileptogenic brains. Although an age dependent capillary LRP1 decline is not clear in samples of human controls, our findings indicate a persistent downregulation of LRP1 protein expression in blood vessels in the human and

rat epileptogenic brain, to a similar extent as in the AD brain. While the precise mechanism underlying this downregulation remains unclear, it may result from seizure-induced pathophysiology, such as hypoxia [33, 34] or hypoglycemia [35, 36]. As a consequence, brain A β levels may increase [19-26]. To investigate this, we examined in **Chapter 2** soluble A β and amyloid plaque deposition in the brain of patients with temporal lobe epilepsy (TLE). In contrast to what we found in AD brain tissue, A β deposits were scarce or absent in TLE patients, and soluble A β levels did not significantly increase. At the same time, LRP1 expression in blood vessels declined to a similar extent in both diseases. This lack of significant A β accumulation in TLE patients could be due to age-related effect, as these patients were much younger than the AD cohort. Moreover, increased expression of glial LRP1 in TLE brains may compensate dysfunctional brain A β clearance (see next paragraph). Nonetheless, our findings align with previous research suggesting that A β pathology may be less pronounced in adult TLE compared to AD [37-42]. Furthermore, disease-related factors may also play a role. Notably, for transcytosis across the BBB, LRP1 transfers A β off to P-glycoprotein (P-gp), located on the luminal side of the brain endothelium, which further facilitates the efflux of A β [43-45]. Interestingly, P-gp expression is upregulated in TLE [46-48], whereas it is typically downregulated in AD [49]. In AD patients, LRP1 degradation in brain capillaries may be exacerbated by pathological concentrations of A β , which can promote proteasomal degradation of LRP1 [24]. Furthermore, a fragment generated through amyloidogenic processing of APP, known as APP intracellular domain (AICD), binds the LRP1 promoter and represses its transcription [50].

In **Chapter 2**, we observed an increase in LRP1 expression in glial cells in both human and rat TLE brains, suggesting that seizure activity induces opposite regulatory effects on LRP1 in glia compared to endothelial cells. Similar changes in glial LRP1 expression were noted in the hippocampi of AD patients. This finding aligns with a bioinformatics analysis of transcriptomic data from TLE patients, that identified upregulated astrocytic LRP1 as a hub epilepsy-associated gene, with elevated expression confirmed in the hippocampus of epileptic rat models [51]. Furthermore, a proteomics study demonstrated upregulation of hippocampal LRP1 in a rat model of epileptogenesis 10 days after SE [52]. Astrocytic LRP1 plays an important role in A β clearance through cellular uptake and degradation [53] and therefore it is tempting to speculate that this glial upregulation of LRP1 may further enhance A β clearance within the TLE brain. Inhibition of LRP1 in astrocytes has been shown to reduce key A β -degrading enzymes, such as matrix metalloproteases MMP2, MMP9, and the insulin-degrading enzyme, highlighting its importance in extracellular A β degradation [53]. Moreover, mice in which LRP1 was knocked out in radial glial cells and their progeny, including hippocampal astrocytes and neurons, developed early postnatal seizures and exhibited hippocampal neuronal hyperexcitability, suggesting that astrocytic LRP1's role in reducing brain

excitability [54]. Interestingly, these mice also displayed impaired glial uptake of tissue plasminogen activator (tPA), a serine protease activated during neuronal activity [55]. In TLE patients and animal models, tPA is upregulated [56, 57] and is recycled by astrocytes via LRP1 to prevent NMDA-induced neurotoxicity [58]. Collectively, these findings suggest that the upregulation of astrocytic LRP1 in epilepsy patients may serve as a homeostatic response to also potentially counteract the reduced expression of LRP1 in brain blood vessels. This mechanism may help mitigate increased parenchymal A β and tPA levels, supporting neuronal survival and maintaining brain homeostasis under epileptic conditions. These findings highlight the complex interplay between LRP1, A β , and disease-specific mechanisms in epilepsy and AD.

Besides transporting A β , LRP1 has also many other functions. Interestingly, LRP1 is also known as transforming growth factor beta type 5 receptor (TGF β VR) and binds directly to TGF β 1, a key immune system modulator [59]. Moreover, LRP1 can form a heterocomplex with the TGF β R1, preventing the formation of a functional TGF β R and subsequent activation of this pathway [60]. Thus, lower expression of LRP1 in blood vessels may promote inflammation via activation of the TGF β pathway as has been shown in mice in which LRP1 was knocked out in vascular smooth muscle cells [61]. TGF β is a multifunctional cytokine involved in many processes (for review, see [62]), for example gliogenesis [63] and angiogenesis [64]. Cortical exposure to albumin, which occurs when the BBB is dysfunctional, induces epilepsy mediated by activation of the TGF β pathway [65]. BBB dysfunction is observed in both epilepsy and AD models, as well as in patients [66, 67]. Additionally, elevated expression of TGF β has been found in epilepsy patients and after status epilepticus (SE) in rats [68-71] and AD patient brain tissue [72, 73]. Moreover, higher TGF β mRNA expression is found in 5xFAD mice brain tissue [74]. Interestingly, GFAP gene activation is dependent on TGF β [75] and mice that overexpress TGF β 1 from astrocytes showed perivascular amyloid beta depositions [73]. Targeting TGF β 1 signaling could be a potential therapeutic strategy in AD [76] and epilepsy [77, 78]. Thus, downregulation of LRP1 in brain capillaries may contribute to perivascular inflammation, epileptogenesis and cognitive deficits through impaired scavenging of TGF β by LRP1.

In **Chapter 2**, we observed increased LRP1 expression in CA1 neurons of TLE patients, which may protect these surviving neurons through LRP1-mediated endocytosis and lysosomal degradation of A β [79]. However, neuronal LRP1 expression might also contribute to neurodegeneration by promoting the uptake of toxic compounds. For example, LRP1 can internalize APP, enhancing its amyloidogenic processing and leading to net production of A β that exceeds its clearance capacity [80]. In addition, LRP1 mediates the endocytosis and propagation of tau proteins [81], which aggregate into neurofibrillary tangles when

phosphorylated, as observed in AD patient brains. LRP1 facilitates the uptake and spread of α -synuclein, another protein linked to neurodegenerative diseases [82]. These findings suggest that elevated neuronal LRP1 expression may exacerbate the spread of harmful substances, potentially disrupting brain networks. Supporting this, in **chapter 2** we found hyperphosphorylated tau in TLE patients, reinforcing a strong epilepsy-AD link for tau, consistent with previous studies [37, 38, 40, 42]. Hyperphosphorylated tau (p-tau) has also been reported in the intrahippocampal kainic acid model of TLE [83]. Although the 5xFAD model is considered to be a model where tau and p-tau play a minor role (see **Figure 2** in **Chapter 1**), there are a few publications that describe higher p-tau levels in the 5xFAD mouse model beginning at five months of age as compared to wild-type controls [74, 84]. Interestingly, tau reduction in aged mice protects against PTZ induced seizures [85]. However, anti-tau antibodies have not produced clinical benefits in AD patients in clinical trials [86], possibly since merely the loss of functional tau may contribute to disease progression, tau accumulation is a terminal event in neurodegenerative disorders, and tau is phosphorylated at different positions in various tauopathies. These findings suggest that neuronal LRP1 overexpression and associated tau pathology may have broader implications for the interplay between epilepsy and neurodegeneration, warranting further investigation as our exploration of this topic has been limited.

5.1.1 LRP1's role in epileptogenesis and neuroinflammation

In **Chapter 3**, we investigated the impact of an inducible knockout of brain endothelial LRP1 on epileptogenesis using transgenic mice. Our findings revealed that the loss of brain endothelial LRP1 in control mice led to the development of epileptiform spikes, demonstrating that LRP1 plays a critical role in maintaining neuronal excitability. This finding raises an important question: What neurobiological mechanisms underlie the hyperexcitability observed in these mice?

To further explore this, we investigated markers of glial cell activation associated with neuroinflammation, as well as the presence of soluble A β and amyloid plaques, in brain endothelial LRP1KO mice. Our findings revealed evidence of astro- and microgliosis in these mice, but no significant changes in brain soluble A β levels or amyloid plaque deposition. These results suggest that in this transgenic model, epileptogenesis is primarily driven by gliosis-related mechanisms rather than by brain A β accumulation. Astro- and microgliosis, along with the release of neuroinflammatory factors, are well-established contributors to hyperexcitability and epileptogenesis in both AD [87, 88] and epilepsy [89, 90]. Glia-mediated neuronal hyperexcitability can be inflammatory, but also non-inflammatory, and also caused by inflammation, often exacerbating each other in a vicious cycle [91]. Notably, silencing radial glial LRP1 *in vivo* activates microglia and astrocytes [54]. Similarly, neuronal LRP1 deletion *in vivo* activates microglia and astrocytes

leading to the release of neuroinflammatory factors such as TNF- α , IL-6, and IL-1 β [92]. Additionally, *in vitro* studies have demonstrated that LRP1 deletion increases the expression of proinflammatory cytokines and chemokines [93]. Pro-inflammatory cytokines enhance excitatory neurotransmission by promoting exocytosis of calcium-permeable glutamate receptors and decreasing inhibitory neurotransmission by promoting endocytosis of GABA receptors resulting in fewer surface receptors [94, 95]. This glial activation plays a pivotal role in epileptogenesis, as illustrated by the fact that genetically induced astrogliosis has been shown to cause epileptic seizures in mice [96], while suppressing microglial activation reduces seizure susceptibility [97]. Moreover, hippocampal microglial proliferation and reactive phenotypical changes, induced via activation of the mTOR pathway, have been reported to induce seizures [98].

Although LRP1KO-induced changes in brain A β levels are reported at younger ages in 5xFAD mice [20, 99], those effects may have been masked in our study by the overwhelming presence of abundant soluble A β and A β plaques in the hippocampus at older ages [20, 100, 101]. Potentially due to the similar reason, no differences between seizure and spike frequency were observed between 5xFAD WT and 5xFAD LRP1KO mice groups. Despite high A β levels in all animals, seizures were not evident in all animals. This is consistent with observations in other AD models [29]. Furthermore, astro- and microgliosis were also evident in 5xFAD WT mice and 5xFAD LRP1KO mice, but not different between the two groups. This is consistent with previous studies [20]. This is likely because gliosis has already peaked at this age in 5xFAD mice [100, 102], leaving no room for further increases.

Despite high levels of gliosis and/or A β levels, we observed a low seizure frequency in 5xFAD WT mice and 5xFAD LRP1KO mice. Although these factors may contribute to the induction of spikes (epileptogenesis), they may not be decisive in triggering seizures. Seizures may arise when other critical elements, such as blood-brain barrier dysfunction, come to the forefront [66, 78]. In the epileptogenic brain, reactive astrocytes produce pro-epileptogenic inflammatory factors that are often linked to BBB dysfunction in epilepsy [66, 78, 90, 103-105] and AD [49, 67, 106]. However, no significant BBB leakage was detected using albumin as a marker in LRP1KO mice, confirming findings from a previous study [20], nor in the 5xFAD WT and 5xFAD LRP1KO mice. Although subtle BBB leakage at earlier ages has been detected using more sensitive techniques in global endothelial LRP1KO mice [107], BBB dysfunction has been observed in brain endothelial LRP1KO mice only at a much older age (20 months) [108]. Furthermore, preserved microvascular function has been found in 7-11 month old 5xFAD mice [109]. Thus, in addition to high A β levels and gliosis, pronounced BBB leakage may play an important role in ictogenesis, and its lack in our study cohort may explain why we did not observe frequent seizures.

5.1.2 LRP1's role in cognitive decline

In **Chapter 4**, we investigated the effects of inducible knockout of brain endothelial LRP1 on cognition in transgenic mice. Our results showed that brain endothelial LRP1KO impairs spatial learning in control mice. This is consistent with earlier studies reporting cognitive deficits following global endothelial LRP1 inactivation in young mice [107] and in mice with reduced brain capillary LRP1 expression due to GLUT1 deficiency [21]. Similarly, hippocampal interictal spikes impair cognition in epileptic rats [110] and epilepsy patients [111, 112].

Several mechanisms may explain these cognitive deficits, likely operating in tandem. First, hippocampal epileptiform spikes during sleep may interfere with memory consolidation, as observed in AD patients [5, 9, 10] and in animal models [113-115]. Conversely, sleep-disordered breathing, often associated with poor sleep quality, further exacerbates cognitive issues, as it has been linked to earlier onset of mild cognitive impairment [116].

Second, a role for gliosis in cognitive decline was suggested by various studies [117-119] and aligns with our finding of increased gliosis in LRP1KO mice. Microglia are crucial for learning and memory functions, because of their role in synapse formation [120]. However, when microglia become overactive they may excessively prune synapses, leading to the loss of neural connections vital for proper cognition functioning [119]. Similarly, astrocytes are essential for maintaining synaptic and network balance, and disruptions in their signaling can result in cognitive impairments [117, 118]. Studies in dementia patients have linked cognitive decline to astrogliosis [121, 122] and microglial activation [123], both of which are also evident in epilepsy [89, 90, 124]. Moreover, gliosis can lead to the release of inflammatory cytokines, which damage neurons and synapses, thereby exacerbating cognitive decline [125, 126].

Interestingly, we observed spatial learning and cognitive flexibility were impaired in 5xFAD mice, but these deficits were not exacerbated by additional brain endothelial LRP1KO. The effect of adjunctive brain LRP1KO was probably masked by the already abundant existing cognitive defect in 5xFAD mice, as these mice already have excessive brain gliosis [100, 102]. Previous studies have shown that targeting gliosis can improve cognition in neurodegenerative models: blocking microglial proliferation enhanced cognitive function in APP/PS1 [127] and 5xFAD mice [128], while inhibiting astrocyte activation rescued cognitive impairments in 5xFAD mice [129]. These findings further underscore the critical role of glial cell activation in the pathways underlying cognitive decline.

Neuronal activity induces DNA double-strand breaks in the promoter of the *Fos* gene, enhancing its expression [130]. Increased DNA damage was observed in

5xFAD mice [131]. Δ FosB, an activity-dependent transcription factor from the Fos gene family, may serve a protective role by supporting cell survival and reducing excitability in hippocampal CA1 neurons [132, 133]. In **Chapter 4**, we observed high hippocampal Δ FosB and low calbindin expression as markers of epileptiform activity and cognitive decline in 5xFAD mice, unaffected by LRP1KO. These findings are consistent with other studies linking Δ FosB and calbindin alterations to epilepsy and AD, for Δ FosB see [134-142], and for calbindin see [29, 141, 143-150]. Δ FosB's remarkable stability, with a half-life exceeding eight days [151], allows it to sustain long-term changes in gene expression, making it a key regulator in epileptogenesis. For instance, Δ FosB induces *GFAP* expression [132] and epigenetically downregulates calbindin through histone deacetylation of its promoter [141]. Calbindin, a calcium-binding protein, is critical for maintaining intracellular calcium homeostasis and protecting neurons from calcium-mediated neurotoxicity during hyperexcitability [152, 153]. Its role in stabilizing neural circuits supports normal cognitive functions and guards against neurodegeneration [154-156].

5.2 Novel therapeutic strategies for epilepsy and AD

Currently, there are no cures for epilepsy and AD, and available treatment options have notable limitations. Therefore, the search for novel therapeutic strategies is ongoing. In recent years, novel therapeutic strategies for epilepsy and AD were mainly focused on targeting neuroprotective, neuroinflammatory, and neurodegenerative processes through both pharmacological and non-pharmacological interventions [157, 158] as well as on repurposing of drugs. Restoring LRP1 expression in blood vessels was recently suggested as novel therapeutic approach for AD [159], which may also be useful in reducing epileptogenesis. Peripheral treatment with recombinant LRP1 ligand binding domain IV (LRP-IV), resembling soluble LRP1, reduces brain A β levels and improves cognitive function in Tg2576 mice [160]. Furthermore, targeting LRP1 to regulate homeostasis during vascular complications through multiple signaling pathways, including the TGF- β pathway, has been suggested to be promising [161].

5.2.1 Restoring LRP1 expression in blood vessels as a novel therapeutic target

Various interventions have highlighted the therapeutic potential of restoring LRP1 expression at the BBB. For instance, gene therapy aimed at restoring LRP1 at the BBB successfully reversed cognitive impairment and BBB dysfunction in global endothelial LRP1 knockout mice [107]. Antioxidants counteract inflammation-induced A β accumulation through an LRP1-dependent mechanism at the BBB [162], and oleocanthal (a natural phenolic component in extra-virgin olive oil) boosts brain capillary LRP1 expression to facilitate A β clearance [163]. Magnesium enhances LRP1 expression in an *in vitro* human BBB model and accelerates A β clearance [25], and *Withania somnifera* (a nightshade family member) root extract increases

LRP1 expression in brain microvessels, reversing AD pathology in APP/PS1 mice [164]. Similarly, the antibiotic rifampicin upregulates LRP1 in brain endothelial cells to enhance A β clearance [165] and has been shown to slow cognitive decline in AD patients [166]. Furthermore, targeting several microRNAs rescue copper-induced decreases in LRP1 expression in human primary microvascular endothelial cells [167]. Another strategy to modulate LRP1 expression involves targeting the peroxisome proliferator-activated receptor gamma (PPAR- γ). For example, PPAR- γ agonist rosiglitazone increases LRP1 expression in adipocytes [168] and in human brain microvascular endothelial cells, thereby enhancing A β uptake [169]. Similarly, pioglitazone, another PPAR- γ agonist, elevates LRP1 expression in hippocampal endothelial cells, reduces hippocampal soluble A β levels, and improved cognitive function in a mouse model of sporadic AD [170]. Additionally, pioglitazone decreases the severity of PTZ-induced seizures [171], while rosiglitazone protects against cognitive decline, reduces astrogliosis, and mitigates oxidative stress in rats with pilocarpine-induced SE [172]. The beneficial effects of PPAR- γ agonists may partly result from their ability to upregulate excitatory amino acid transporter 2 (EAAT2), responsible for extracellular glutamate uptake, thereby preventing excitotoxicity [173]. PPAR- γ also enhances astrocytic defense mechanisms against reactive oxygen species (ROS) [174, 175], contributing to neuroprotection. Interestingly, rosiglitazone improves cognitive decline in ApoE4-negative patients with mild-to-moderate AD, but was ineffective in ApoE4 carriers [176]. A subsequent Phase III trial, however, failed to confirm cognitive benefits in AD patients, regardless of ApoE4 status [177]. Thus, although some studies suggest that targeting LRP1 through PPAR- γ agonists could offer a novel approach to mitigate epileptogenesis and cognitive decline, further research is necessary to validate their efficacy and understand the underlying mechanisms, particularly in the context of ApoE isoforms.

Statins, widely used cholesterol-lowering drugs, have been shown to reduce AD risk [178] and exhibit antiepileptic effects in mice [179]. Their action may involve the suppression of sterol regulatory element binding protein-2 (SREBP2), a transcriptional repressor of LRP1 [180], which is suppressed by sterols like cholesterol [181]. As a result, simvastatin and lovastatin upregulate LRP1 in human brain endothelial cells [182], and fluvastatin increases LRP1 levels at the BBB in a mouse model of AD [183]. Similarly, non-statin cholesterol-lowering drugs like probucol enhance hippocampal LRP1 expression and reduce glial activation in aged rats [184], while anti-PCSK9 antibodies prevent LRP1 degradation, reducing A β pathology and preserving cognitive function in an AD mouse model [99]. Vitamin D receptor agonism also upregulates LRP1 through SREBP2 inhibition, leading to reduced A β burden and cognitive deficits in APP/PS1 mice [185]. Moreover, vitamin D increases LRP1 expression in mouse brain endothelial cells [186]. Lower levels of GLUT1, the transporter responsible for glucose transport across the BBB, may also

lead to transcriptional inhibition of LRP1 through SREBP2 in brain endothelial cells [21]. GLUT1 deficiency syndrome, caused by heterozygous mutations in *SLC2A1*, the gene which encodes GLUT1, is characterized by infantile-onset seizures [187]. These findings underscore the therapeutic potential of targeting SREBP2 to restore LRP1 expression at the BBB, mitigating pathological processes in both AD and epilepsy.

Lifestyle and dietary interventions also influence LRP1 levels: cognitive and physical stimulation increased brain LRP1 levels in an AD mouse model [188], while ketone bodies (which are produced during a ketogenic diet, a treatment for epilepsy) rescued seizure-like behavior in LRP1-deficient *Drosophila* [189]. Several lifestyle factors have been identified as playing a role in reducing the risk of both epilepsy and cognitive deterioration, and taking these into account may contribute to healthier aging and cognitive preservation. Furthermore, sleep deprivation reduces hippocampal LRP1 expression in rats [190], suggesting an important role for sleep in the proper functioning of LRP1. Similarly, the importance of sleep is illustrated by the fact that treatment of sleep-disordered breathing with continuous positive airway pressure delayed the age at MCI onset [116]. Interventions that prioritize physical activity, balanced nutrition, cardiovascular health, quality sleep, and cognitive stimulation could be beneficial. Integrating these practices into public health strategies and personal health management could lead to improved (health) outcomes for individuals and communities. Altogether, these observations underscore the therapeutic value of targeting LRP1 expression at the BBB to potentially restore homeostasis, protect neuronal function, and mitigate the progression of epilepsy and AD.

While increasing the expression of LRP1 yields promising results in mitigating neuropathological processes that may contribute to epilepsy and AD, it is crucial to approach this strategy carefully. LRP1 expression differs across cell types and tissues and boosting it without specificity may have harmful effects. For example, while brain endothelial LRP1 levels are reduced in some neurological disorders, the expression levels of neuronal and glial LRP1 can already be elevated. Increasing it further in these cells may worsen pathology or even interfere with normal brain function. Outside the brain, LRP1 is involved in processes like lipid metabolism, meaning systemic therapies could cause unintended effects in organs such as the liver. Any treatment targeting LRP1 must carefully consider these risks and benefits, focusing on where and when to enhance its expression and how this affects cellular expression levels with caution towards potential harmful side effects caused by potential off target effects. Future research should prioritize methods to selectively increase LRP1 expression at the BBB without affecting other tissues or cell types.

5.3 Concluding remarks

Our findings indicate that LRP1 is downregulated at the BBB in both experimental epilepsy and patients with epilepsy. Additionally, we have shown that inducible knockout of LRP1 in brain endothelial cells in transgenic mice leads to epileptiform spikes and induced cognitive dysfunction, primarily associated with gliosis-related mechanisms rather than A β accumulation. A therapy aimed at restoring LRP1 specifically at the level of the BBB may therefore be a novel therapeutic approach. To explore this potential therapy, it is crucial to identify the most suitable delivery mechanisms, understand potential harmful off-target effects, and determine the optimal timing and dosing for treatment in a preclinical setting. Additionally, clinical studies will be required to evaluate whether such therapy impacts disease progression in humans and whether it can prevent the onset of disease. In summary, further investigation is essential to develop strategies that could ultimately slow down or halt disease progression, or ideally, even prevent it.

References

1. Deuschl, G., et al., *The burden of neurological diseases in Europe: an analysis for the Global Burden of Disease Study 2017*. Lancet Public Health, 2020. **5**(10): p. e551-e567.
2. Sen, A., et al., *Epilepsy in older people*. Lancet, 2020. **395**(10225): p. 735-748.
3. Kamondi, A., et al., *Epilepsy and epileptiform activity in late-onset Alzheimer disease: clinical and pathophysiological advances, gaps and conundrums*. Nat Rev Neurol, 2024. **20**(3): p. 162-182.
4. Romoli, M., et al., *Amyloid-beta: a potential link between epilepsy and cognitive decline*. Nat Rev Neurol, 2021. **17**(8): p. 469-485.
5. Lam, A.D., et al., *Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease*. Nat Med, 2017. **23**(6): p. 678-680.
6. Lam, A.D., et al., *Association of epileptiform abnormalities and seizures in Alzheimer disease*. Neurology, 2020. **95**(16): p. e2259-e2270.
7. Zhang, D., et al., *The clinical correlation between Alzheimer's disease and epilepsy*. Front Neurol, 2022. **13**: p. 922535.
8. Dun, C., et al., *Bi-directional associations of epilepsy with dementia and Alzheimer's disease: a systematic review and meta-analysis of longitudinal studies*. Age Ageing, 2022. **51**(3).
9. Vossel, K.A., et al., *Incidence and impact of subclinical epileptiform activity in Alzheimer's disease*. Ann Neurol, 2016. **80**(6): p. 858-870.
10. Horvath, A.A., et al., *Subclinical epileptiform activity accelerates the progression of Alzheimer's disease: A long-term EEG study*. Clin Neurophysiol, 2021. **132**(8): p. 1982-1989.
11. Yeh, W.C., et al., *Association between Subclinical Epileptiform Discharge and the Severity of Cognitive Decline in Alzheimer's Disease: A Longitudinal Cohort Study*. J Alzheimers Dis, 2022. **90**(1): p. 305-312.
12. Breuer, L.E.M., et al., *Accelerated Cognitive Ageing in Epilepsy: A Neuropsychological Evaluation of Cognitive Deterioration*. Arch Clin Neuropsychol, 2019. **34**(3): p. 301-309.
13. Potschka, H., *The aging brain and late onset drug-refractory epilepsies*. Seizure, 2024.
14. Kwan, P., et al., *Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies*. Epilepsia, 2010. **51**(6): p. 1069-77.
15. Tellez-Zenteno, J.F., et al., *A validation of the new definition of drug-resistant epilepsy by the International League Against Epilepsy*. Epilepsia, 2014. **55**(6): p. 829-34.
16. Tallis, R., et al., *Epilepsy in elderly people: management issues*. Epileptic Disord, 2002. **4 Suppl 2**: p. S33-9.
17. Cretin, B., *Pharmacotherapeutic strategies for treating epilepsy in patients with Alzheimer's disease*. Expert Opin Pharmacother, 2018. **19**(11): p. 1201-1209.
18. Cumbo, E. and L.D. Lorigi, *Levetiracetam, lamotrigine, and phenobarbital in patients with epileptic seizures and Alzheimer's disease*. Epilepsy Behav, 2010. **17**(4): p. 461-6.
19. Zhao, Z., et al., *Central role for PICALM in amyloid-beta blood-brain barrier transcytosis and clearance*. Nat Neurosci, 2015. **18**(7): p. 978-87.
20. Storck, S.E., et al., *Endothelial LRP1 transports amyloid-beta(1-42) across the blood-brain barrier*. J Clin Invest, 2016. **126**(1): p. 123-36.

21. Winkler, E.A., et al., *GLUT1 reductions exacerbate Alzheimer's disease vasculo-neuronal dysfunction and degeneration*. Nat Neurosci, 2015. **18**(4): p. 521-530.
22. Zlokovic, B.V., *Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders*. Nat Rev Neurosci, 2011. **12**(12): p. 723-38.
23. Shibata, M., et al., *Clearance of Alzheimer's amyloid-ss(1-40) peptide from brain by LDL receptor-related protein-1 at the blood-brain barrier*. J Clin Invest, 2000. **106**(12): p. 1489-99.
24. Deane, R., et al., *LRP/amyloid beta-peptide interaction mediates differential brain efflux of Abeta isoforms*. Neuron, 2004. **43**(3): p. 333-44.
25. Zhu, D., et al., *Magnesium Reduces Blood-Brain Barrier Permeability and Regulates Amyloid-beta Transcytosis*. Mol Neurobiol, 2018. **55**(9): p. 7118-7131.
26. Yamada, K., et al., *The low density lipoprotein receptor-related protein 1 mediates uptake of amyloid beta peptides in an in vitro model of the blood-brain barrier cells*. J Biol Chem, 2008. **283**(50): p. 34554-62.
27. Osgood, D., et al., *Aging alters mRNA expression of amyloid transporter genes at the blood-brain barrier*. Neurobiol Aging, 2017. **57**: p. 178-185.
28. Silverberg, G.D., et al., *Amyloid efflux transporter expression at the blood-brain barrier declines in normal aging*. J Neuropathol Exp Neurol, 2010. **69**(10): p. 1034-43.
29. Minkeviciene, R., et al., *Amyloid beta-induced neuronal hyperexcitability triggers progressive epilepsy*. J Neurosci, 2009. **29**(11): p. 3453-62.
30. Bres, E.E. and A. Faissner, *Low Density Receptor-Related Protein 1 Interactions With the Extracellular Matrix: More Than Meets the Eye*. Front Cell Dev Biol, 2019. **7**: p. 31.
31. Donahue, J.E., et al., *RAGE, LRP-1, and amyloid-beta protein in Alzheimer's disease*. Acta Neuropathol, 2006. **112**(4): p. 405-15.
32. Halliday, M.R., et al., *Accelerated pericyte degeneration and blood-brain barrier breakdown in apolipoprotein E4 carriers with Alzheimer's disease*. J Cereb Blood Flow Metab, 2016. **36**(1): p. 216-27.
33. Bell, R.D., et al., *SRF and myocardin regulate LRP-mediated amyloid-beta clearance in brain vascular cells*. Nat Cell Biol, 2009. **11**(2): p. 143-53.
34. Farrell, J.S., et al., *Postictal behavioural impairments are due to a severe prolonged hypoperfusion/hypoxia event that is COX-2 dependent*. Elife, 2016. **5**.
35. Bartolini, E., et al., *Glycaemic Imbalances in Seizures and Epilepsy of Paediatric Age: A Literature Review*. J Clin Med, 2023. **12**(7).
36. Yan, F.L., Y. Zheng, and F.D. Zhao, *Effects of ginkgo biloba extract EGb761 on expression of RAGE and LRP-1 in cerebral microvascular endothelial cells under chronic hypoxia and hypoglycemia*. Acta Neuropathol, 2008. **116**(5): p. 529-35.
37. Aroor, A., et al., *Assessment of tau phosphorylation and beta-amyloid pathology in human drug-resistant epilepsy*. Epilepsia Open, 2023. **8**(2): p. 609-622.
38. Thom, M., et al., *Neurofibrillary tangle pathology and Braak staging in chronic epilepsy in relation to traumatic brain injury and hippocampal sclerosis: a post-mortem study*. Brain, 2011. **134**(Pt 10): p. 2969-81.
39. Mackenzie, I.R. and L.A. Miller, *Senile plaques in temporal lobe epilepsy*. Acta Neuropathol, 1994. **87**(5): p. 504-10.
40. Tai, X.Y., et al., *Hyperphosphorylated tau in patients with refractory epilepsy correlates with cognitive decline: a study of temporal lobe resections*. Brain, 2016. **139**(Pt 9): p. 2441-55.

41. Gourmaud, S., et al., *Alzheimer-like amyloid and tau alterations associated with cognitive deficit in temporal lobe epilepsy*. *Brain*, 2020. **143**(1): p. 191-209.
42. Silva, J.C., et al., *Low prevalence of amyloid and tau pathology in drug-resistant temporal lobe epilepsy*. *Epilepsia*, 2021. **62**(12): p. 3058-3067.
43. Cirrito, J.R., et al., *P-glycoprotein deficiency at the blood-brain barrier increases amyloid-beta deposition in an Alzheimer disease mouse model*. *J Clin Invest*, 2005. **115**(11): p. 3285-90.
44. Hartz, A.M., D.S. Miller, and B. Bauer, *Restoring blood-brain barrier P-glycoprotein reduces brain amyloid-beta in a mouse model of Alzheimer's disease*. *Mol Pharmacol*, 2010. **77**(5): p. 715-23.
45. Storck, S.E., et al., *The concerted amyloid-beta clearance of LRP1 and ABCB1/P-gp across the blood-brain barrier is linked by PICALM*. *Brain Behav Immun*, 2018. **73**: p. 21-33.
46. van Vliet, E., et al., *Selective and persistent upregulation of *mdr1b* mRNA and P-glycoprotein in the parahippocampal cortex of chronic epileptic rats*. *Epilepsy Res*, 2004. **60**(2-3): p. 203-13.
47. Aronica, E., et al., *Expression and cellular distribution of multidrug resistance-related proteins in the hippocampus of patients with mesial temporal lobe epilepsy*. *Epilepsia*, 2004. **45**(5): p. 441-51.
48. Loscher, W., *Drug transporters in the epileptic brain*. *Epilepsia*, 2007. **48 Suppl 1**: p. 8-13.
49. Sweeney, M.D., et al., *Blood-Brain Barrier: From Physiology to Disease and Back*. *Physiol Rev*, 2019. **99**(1): p. 21-78.
50. Liu, Q., et al., *Amyloid precursor protein regulates brain apolipoprotein E and cholesterol metabolism through lipoprotein receptor LRP1*. *Neuron*, 2007. **56**(1): p. 66-78.
51. Li, D., et al., *Bioinformatics analysis reveals multiple functional changes in astrocytes in temporal lobe epilepsy*. *Brain Res*, 2024. **1831**: p. 148820.
52. Keck, M., et al., *Proteomic profiling of epileptogenesis in a rat model: Focus on cell stress, extracellular matrix and angiogenesis*. *Neurobiol Dis*, 2018. **112**: p. 119-135.
53. Liu, C.C., et al., *Astrocytic LRP1 Mediates Brain A β Clearance and Impacts Amyloid Deposition*. *J Neurosci*, 2017. **37**(15): p. 4023-4031.
54. Bres, E.E., et al., *Lipoprotein receptor loss in forebrain radial glia results in neurological deficits and severe seizures*. *Glia*, 2020. **68**(12): p. 2517-2549.
55. Qian, Z., et al., *Tissue-plasminogen activator is induced as an immediate-early gene during seizure, kindling and long-term potentiation*. *Nature*, 1993. **361**(6411): p. 453-7.
56. Iyer, A.M., et al., *Tissue plasminogen activator and urokinase plasminogen activator in human epileptogenic pathologies*. *Neuroscience*, 2010. **167**(3): p. 929-45.
57. Gorter, J.A., et al., *Potential new antiepileptogenic targets indicated by microarray analysis in a rat model for temporal lobe epilepsy*. *J Neurosci*, 2006. **26**(43): p. 11083-110.
58. Casse, F., et al., *Glutamate controls tPA recycling by astrocytes, which in turn influences glutamatergic signals*. *J Neurosci*, 2012. **32**(15): p. 5186-99.
59. Huang, S.S., et al., *Cellular growth inhibition by IGFBP-3 and TGF- β 1 requires LRP-1*. *FASEB J*, 2003. **17**(14): p. 2068-81.
60. Liu, Q., S.S. Huang, and J.S. Huang, *Function of the type V transforming growth factor beta receptor in transforming growth factor beta-induced growth inhibition of mink lung epithelial cells*. *J Biol Chem*, 1997. **272**(30): p. 18891-5.

61. Boucher, P., et al., *LRP1 functions as an atheroprotective integrator of TGFbeta and PDGF signals in the vascular wall: implications for Marfan syndrome*. PLoS One, 2007. **2**(5): p. e448.
62. Diniz, L.P., et al., *Astrocytes and the TGF-beta1 Pathway in the Healthy and Diseased Brain: a Double-Edged Sword*. Mol Neurobiol, 2019. **56**(7): p. 4653-4679.
63. Stipursky, J., D. Francis, and F.C. Gomes, *Activation of MAPK/PI3K/SMAD pathways by TGF-beta(1) controls differentiation of radial glia into astrocytes in vitro*. Dev Neurosci, 2012. **34**(1): p. 68-81.
64. Ferrari, G., et al., *Transforming growth factor-beta 1 (TGF-beta1) induces angiogenesis through vascular endothelial growth factor (VEGF)-mediated apoptosis*. J Cell Physiol, 2009. **219**(2): p. 449-58.
65. Bar-Klein, G., et al., *Losartan prevents acquired epilepsy via TGF-beta signaling suppression*. Ann Neurol, 2014. **75**(6): p. 864-75.
66. van Vliet, E.A., et al., *Blood-brain barrier leakage may lead to progression of temporal lobe epilepsy*. Brain, 2007. **130**(Pt 2): p. 521-34.
67. Liu, Y., C.C. Huber, and H. Wang, *Disrupted blood-brain barrier in 5xFAD mouse model of Alzheimer's disease can be mimicked and repaired in vitro with neural stem cell-derived exosomes*. Biochem Biophys Res Commun, 2020.
68. Aronica, E., et al., *Upregulation of metabotropic glutamate receptor subtype mGluR3 and mGluR5 in reactive astrocytes in a rat model of mesial temporal lobe epilepsy*. Eur J Neurosci, 2000. **12**(7): p. 2333-44.
69. Das, A., et al., *Hippocampal tissue of patients with refractory temporal lobe epilepsy is associated with astrocyte activation, inflammation, and altered expression of channels and receptors*. Neuroscience, 2012. **220**: p. 237-46.
70. Zhang, Y., et al., *Role of Elevated Thrombospondin-1 in Kainic Acid-Induced Status Epilepticus*. Neurosci Bull, 2020. **36**(3): p. 263-276.
71. Heinemann, U., D. Kaufer, and A. Friedman, *Blood-brain barrier dysfunction, TGFbeta signaling, and astrocyte dysfunction in epilepsy*. Glia, 2012. **60**(8): p. 1251-7.
72. Flanders, K.C., et al., *Altered expression of transforming growth factor-beta in Alzheimer's disease*. Neurology, 1995. **45**(8): p. 1561-9.
73. Wyss-Coray, T., et al., *Amyloidogenic role of cytokine TGF-beta1 in transgenic mice and in Alzheimer's disease*. Nature, 1997. **389**(6651): p. 603-6.
74. Ardestani, P.M., et al., *Modulation of neuroinflammation and pathology in the 5XFAD mouse model of Alzheimer's disease using a biased and selective beta-1 adrenergic receptor partial agonist*. Neuropharmacology, 2017. **116**: p. 371-386.
75. Romao, L.F., et al., *Glutamate activates GFAP gene promoter from cultured astrocytes through TGF-beta1 pathways*. J Neurochem, 2008. **106**(2): p. 746-56.
76. Kapoor, M. and S. Chinnathambi, *TGF-beta1 signalling in Alzheimer's pathology and cytoskeletal reorganization: a specialized Tau perspective*. J Neuroinflammation, 2023. **20**(1): p. 72.
77. Senatorov, V.V., Jr., et al., *Blood-brain barrier dysfunction in aging induces hyperactivation of TGFbeta signaling and chronic yet reversible neural dysfunction*. Sci Transl Med, 2019. **11**(521).
78. van Vliet, E.A. and N. Marchi, *Neurovascular unit dysfunction as a mechanism of seizures and epilepsy during aging*. Epilepsia, 2022. **63**(6): p. 1297-1313.

79. Kanekiyo, T., et al., *Neuronal clearance of amyloid-beta by endocytic receptor LRP1*. J Neurosci, 2013. **33**(49): p. 19276-83.
80. Van Gool, B., et al., *LRP1 Has a Predominant Role in Production over Clearance of Abeta in a Mouse Model of Alzheimer's Disease*. Mol Neurobiol, 2019. **56**(10): p. 7234-7245.
81. Rauch, J.N., et al., *LRP1 is a master regulator of tau uptake and spread*. Nature, 2020. **580**(7803): p. 381-385.
82. Chen, K., et al., *LRP1 is a neuronal receptor for alpha-synuclein uptake and spread*. Mol Neurodegener, 2022. **17**(1): p. 57.
83. Canet, G., et al., *Seizure activity triggers tau hyperphosphorylation and amyloidogenic pathways*. Epilepsia, 2022. **63**(4): p. 919-935.
84. Wang, X., et al., *Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression*. Cell Res, 2019. **29**(10): p. 787-803.
85. Li, Z., et al., *Seizure resistance without parkinsonism in aged mice after tau reduction*. Neurobiol Aging, 2014. **35**(11): p. 2617-2624.
86. Imbimbo, B.P., et al., *Initial failures of anti-tau antibodies in Alzheimer's disease are reminiscent of the amyloid-beta story*. Neural Regen Res, 2023. **18**(1): p. 117-118.
87. Sofroniew, M.V. and H.V. Vinters, *Astrocytes: biology and pathology*. Acta Neuropathol, 2010. **119**(1): p. 7-35.
88. Meraz-Rios, M.A., et al., *Inflammatory process in Alzheimer's Disease*. Front Integr Neurosci, 2013. **7**: p. 59.
89. Verhoog, Q.P., et al., *Astrocytes as Guardians of Neuronal Excitability: Mechanisms Underlying Epileptogenesis*. Front Neurol, 2020. **11**: p. 591690.
90. Vezzani, A., et al., *The role of inflammation in epilepsy*. Nat Rev Neurol, 2011. **7**(1): p. 31-40.
91. Devinsky, O., et al., *Glia and epilepsy: excitability and inflammation*. Trends Neurosci, 2013. **36**(3): p. 174-84.
92. Liu, Q., et al., *Neuronal LRP1 knockout in adult mice leads to impaired brain lipid metabolism and progressive, age-dependent synapse loss and neurodegeneration*. J Neurosci, 2010. **30**(50): p. 17068-78.
93. Mantuano, E., et al., *LDL receptor-related protein-1 regulates NFkappaB and microRNA-155 in macrophages to control the inflammatory response*. Proc Natl Acad Sci U S A, 2016. **113**(5): p. 1369-74.
94. Stellwagen, D., et al., *Differential regulation of AMPA receptor and GABA receptor trafficking by tumor necrosis factor-alpha*. J Neurosci, 2005. **25**(12): p. 3219-28.
95. Ren, S., et al., *TNF-alpha-mediated reduction in inhibitory neurotransmission precedes sporadic Alzheimer's disease pathology in young Trem2(R47H) rats*. J Biol Chem, 2021. **296**: p. 100089.
96. Robel, S., et al., *Reactive astrogliosis causes the development of spontaneous seizures*. J Neurosci, 2015. **35**(8): p. 3330-45.
97. Abraham, J., et al., *Minocycline attenuates microglia activation and blocks the long-term epileptogenic effects of early-life seizures*. Neurobiol Dis, 2012. **46**(2): p. 425-30.
98. Zhao, X., et al., *Noninflammatory Changes of Microglia Are Sufficient to Cause Epilepsy*. Cell Rep, 2018. **22**(8): p. 2080-2093.
99. Mazura, A.D., et al., *PCSK9 acts as a key regulator of Abeta clearance across the blood-brain barrier*. Cell Mol Life Sci, 2022. **79**(4): p. 212.

100. Forner, S., et al., *Systematic phenotyping and characterization of the 5xFAD mouse model of Alzheimer's disease*. *Sci Data*, 2021. **8**(1): p. 270.
101. Oblak, A.L., et al., *Comprehensive Evaluation of the 5XFAD Mouse Model for Preclinical Testing Applications: A MODEL-AD Study*. *Front Aging Neurosci*, 2021. **13**: p. 713726.
102. Oakley, H., et al., *Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation*. *J Neurosci*, 2006. **26**(40): p. 10129-40.
103. Broekaart, D.W.M., et al., *Activation of the innate immune system is evident throughout epileptogenesis and is associated with blood-brain barrier dysfunction and seizure progression*. *Epilepsia*, 2018. **59**(10): p. 1931-1944.
104. Gorter, J.A., E.A. van Vliet, and E. Aronica, *Status epilepticus, blood-brain barrier disruption, inflammation, and epileptogenesis*. *Epilepsy Behav*, 2015. **49**: p. 13-6.
105. van Vliet, E.A., E. Aronica, and J.A. Gorter, *Blood-brain barrier dysfunction, seizures and epilepsy*. *Semin Cell Dev Biol*, 2015. **38**: p. 26-34.
106. Hansen, C.E., et al., *Tension at the gate: sensing mechanical forces at the blood-brain barrier in health and disease*. *J Neuroinflammation*, 2024. **21**(1): p. 325.
107. Nikolakopoulou, A.M., et al., *Endothelial LRP1 protects against neurodegeneration by blocking cyclophilin A*. *J Exp Med*, 2021. **218**(4).
108. Storck, S.E., M. Kurtyka, and C.U. Pietrzik, *Brain endothelial LRP1 maintains blood-brain barrier integrity*. *Fluids Barriers CNS*, 2021. **18**(1): p. 27.
109. Zhukov, O., et al., *Preserved blood-brain barrier and neurovascular coupling in female 5xFAD model of Alzheimer's disease*. *Front Aging Neurosci*, 2023. **15**: p. 1089005.
110. Kleen, J.K., et al., *Hippocampal interictal spikes disrupt cognition in rats*. *Ann Neurol*, 2010. **67**(2): p. 250-7.
111. Horak, P.C., et al., *Interictal epileptiform discharges impair word recall in multiple brain areas*. *Epilepsia*, 2017. **58**(3): p. 373-380.
112. Kleen, J.K., et al., *Hippocampal interictal epileptiform activity disrupts cognition in humans*. *Neurology*, 2013. **81**(1): p. 18-24.
113. Kam, K., et al., *Interictal spikes during sleep are an early defect in the Tg2576 mouse model of beta-amyloid neuropathology*. *Sci Rep*, 2016. **6**: p. 20119.
114. Gureviciene, I., et al., *Characterization of Epileptic Spiking Associated With Brain Amyloidosis in APP/PS1 Mice*. *Front Neurol*, 2019. **10**: p. 1151.
115. Lisgaras, C.P. and H.E. Scharfman, *Interictal spikes in Alzheimer's disease: Preclinical evidence for dominance of the dentate gyrus and cholinergic control by the medial septum*. *Neurobiol Dis*, 2023. **187**: p. 106294.
116. Osorio, R.S., et al., *Sleep-disordered breathing advances cognitive decline in the elderly*. *Neurology*, 2015. **84**(19): p. 1964-71.
117. Reichenbach, N., et al., *P2Y1 receptor blockade normalizes network dysfunction and cognition in an Alzheimer's disease model*. *J Exp Med*, 2018. **215**(6): p. 1649-1663.
118. Santello, M., N. Toni, and A. Volterra, *Astrocyte function from information processing to cognition and cognitive impairment*. *Nat Neurosci*, 2019. **22**(2): p. 154-166.
119. Yu, Y., et al., *The Role of Glial Cells in Synaptic Dysfunction: Insights into Alzheimer's Disease Mechanisms*. *Aging Dis*, 2024. **15**(2): p. 459-479.
120. Parkhurst, C.N., et al., *Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor*. *Cell*, 2013. **155**(7): p. 1596-609.

121. Kashon, M.L., et al., *Associations of cortical astrogliosis with cognitive performance and dementia status*. J Alzheimers Dis, 2004. **6**(6): p. 595-604; discussion 673-81.
122. Verberk, I.M.W., et al., *Combination of plasma amyloid beta((1-42/1-40)) and glial fibrillary acidic protein strongly associates with cerebral amyloid pathology*. Alzheimers Res Ther, 2020. **12**(1): p. 118.
123. Edison, P., et al., *Microglia, amyloid, and cognition in Alzheimer's disease: An [11C](R)PK11195-PET and [11C]PIB-PET study*. Neurobiol Dis, 2008. **32**(3): p. 412-9.
124. Dobson, H., et al., *Elevated plasma neurofilament light and glial fibrillary acidic protein in epilepsy versus nonepileptic seizures and nonepileptic disorders*. Epilepsia, 2024.
125. Rogers, J.T., et al., *CX3CR1 deficiency leads to impairment of hippocampal cognitive function and synaptic plasticity*. J Neurosci, 2011. **31**(45): p. 16241-50.
126. Qiao, J., et al., *Regulation of astrocyte pathology by fluoxetine prevents the deterioration of Alzheimer phenotypes in an APP/PS1 mouse model*. Glia, 2016. **64**(2): p. 240-54.
127. Olmos-Alonso, A., et al., *Pharmacological targeting of CSF1R inhibits microglial proliferation and prevents the progression of Alzheimer's-like pathology*. Brain, 2016. **139**(Pt 3): p. 891-907.
128. Sosna, J., et al., *Early long-term administration of the CSF1R inhibitor PLX3397 ablates microglia and reduces accumulation of intraneuronal amyloid, neuritic plaque deposition and pre-fibrillar oligomers in 5XFAD mouse model of Alzheimer's disease*. Mol Neurodegener, 2018. **13**(1): p. 11.
129. Choi, M., et al., *Inhibition of STAT3 phosphorylation attenuates impairments in learning and memory in 5XFAD mice, an animal model of Alzheimer's disease*. J Pharmacol Sci, 2020. **143**(4): p. 290-299.
130. Madabhushi, R., et al., *Activity-Induced DNA Breaks Govern the Expression of Neuronal Early-Response Genes*. Cell, 2015. **161**(7): p. 1592-605.
131. Thadathil, N., et al., *DNA Double-Strand Break Accumulation in Alzheimer's Disease: Evidence from Experimental Models and Postmortem Human Brains*. Mol Neurobiol, 2021. **58**(1): p. 118-131.
132. Kurushima, H., et al., *Selective induction of DeltaFosB in the brain after transient forebrain ischemia accompanied by an increased expression of galectin-1, and the implication of DeltaFosB and galectin-1 in neuroprotection and neurogenesis*. Cell Death Differ, 2005. **12**(8): p. 1078-96.
133. Eagle, A.L., et al., *DeltaFosB Decreases Excitability of Dorsal Hippocampal CA1 Neurons*. eNeuro, 2018. **5**(4).
134. Corbett, B.F., et al., *DeltaFosB Regulates Gene Expression and Cognitive Dysfunction in a Mouse Model of Alzheimer's Disease*. Cell Rep, 2017. **20**(2): p. 344-355.
135. Morris, T.A., N. Jafari, and R.J. DeLorenzo, *Chronic DeltaFosB expression and increased AP-1 transcription factor binding are associated with the long term plasticity changes in epilepsy*. Brain Res Mol Brain Res, 2000. **79**(1-2): p. 138-49.
136. Stephens, G.S., et al., *Genes Bound by DeltaFosB in Different Conditions With Recurrent Seizures Regulate Similar Neuronal Functions*. Front Neurosci, 2020. **14**: p. 472.
137. Chartampila, E., et al., *Choline supplementation in early life improves and low levels of choline can impair outcomes in a mouse model of Alzheimer's disease*. bioRxiv, 2024.
138. Clasadonte, J., et al., *DeltaFosB is part of a homeostatic mechanism that protects the epileptic brain from further deterioration*. Front Mol Neurosci, 2023. **16**: p. 1324922.

139. Fu, C.H., et al., *Early Seizure Activity Accelerates Depletion of Hippocampal Neural Stem Cells and Impairs Spatial Discrimination in an Alzheimer's Disease Model*. Cell Rep, 2019. **27**(13): p. 3741-3751 e4.
140. Fu, C.H., et al., *Hippocampal DeltaFosB expression is associated with cognitive impairment in a subgroup of patients with childhood epilepsies*. Front Neurol, 2023. **14**: p. 1331194.
141. You, J.C., et al., *Epigenetic suppression of hippocampal calbindin-D28k by DeltaFosB drives seizure-related cognitive deficits*. Nat Med, 2017. **23**(11): p. 1377-1383.
142. Eagle, A.L., et al., *Experience-Dependent Induction of Hippocampal DeltaFosB Controls Learning*. J Neurosci, 2015. **35**(40): p. 13773-83.
143. Palop, J.J., et al., *Neuronal depletion of calcium-dependent proteins in the dentate gyrus is tightly linked to Alzheimer's disease-related cognitive deficits*. Proc Natl Acad Sci U S A, 2003. **100**(16): p. 9572-7.
144. Iacopino, A.M. and S. Christakos, *Specific reduction of calcium-binding protein (28-kilodalton calbindin-D) gene expression in aging and neurodegenerative diseases*. Proc Natl Acad Sci U S A, 1990. **87**(11): p. 4078-82.
145. Karadi, K., et al., *Correlation between calbindin expression in granule cells of the resected hippocampal dentate gyrus and verbal memory in temporal lobe epilepsy*. Epilepsy Behav, 2012. **25**(1): p. 110-9.
146. Sanchez, P.E., et al., *Levetiracetam suppresses neuronal network dysfunction and reverses synaptic and cognitive deficits in an Alzheimer's disease model*. Proc Natl Acad Sci U S A, 2012. **109**(42): p. E2895-903.
147. Gorter, J.A., et al., *Long-lasting increased excitability differs in dentate gyrus vs. CA1 in freely moving chronic epileptic rats after electrically induced status epilepticus*. Hippocampus, 2002. **12**(3): p. 311-24.
148. Carter, D.S., et al., *Long-term decrease in calbindin-D28K expression in the hippocampus of epileptic rats following pilocarpine-induced status epilepticus*. Epilepsy Res, 2008. **79**(2-3): p. 213-23.
149. Magloczky, Z., et al., *Loss of Calbindin-D28K immunoreactivity from dentate granule cells in human temporal lobe epilepsy*. Neuroscience, 1997. **76**(2): p. 377-85.
150. Abraham, H., et al., *Degree and pattern of calbindin immunoreactivity in granule cells of the dentate gyrus differ in mesial temporal sclerosis, cortical malformation- and tumor-related epilepsies*. Brain Res, 2011. **1399**: p. 66-78.
151. Chen, J., et al., *Chronic Fos-related antigens: stable variants of deltaFosB induced in brain by chronic treatments*. J Neurosci, 1997. **17**(13): p. 4933-41.
152. Mattson, M.P., et al., *Evidence for calcium-reducing and excito-protective roles for the calcium-binding protein calbindin-D28k in cultured hippocampal neurons*. Neuron, 1991. **6**(1): p. 41-51.
153. Sun, S., et al., *Calbindin-D28K inhibits apoptosis in dopaminergic neurons by activation of the PI3-kinase-Akt signaling pathway*. Neuroscience, 2011. **199**: p. 359-67.
154. Westerink, R.H., J.P. Beekwilder, and W.J. Wadman, *Differential alterations of synaptic plasticity in dentate gyrus and CA1 hippocampal area of Calbindin-D28K knockout mice*. Brain Res, 2012. **1450**: p. 1-10.
155. Molinari, S., et al., *Deficits in memory and hippocampal long-term potentiation in mice with reduced calbindin D28K expression*. Proc Natl Acad Sci U S A, 1996. **93**(15): p. 8028-33.

156. Jouvenceau, A., et al., *Decrease in calbindin content significantly alters LTP but not NMDA receptor and calcium channel properties*. *Neuropharmacology*, 2002. **42**(4): p. 444-58.
157. Yu, T.W., H.Y. Lane, and C.H. Lin, *Novel Therapeutic Approaches for Alzheimer's Disease: An Updated Review*. *Int J Mol Sci*, 2021. **22**(15).
158. Klein, P., et al., *New epilepsy therapies in development*. *Nat Rev Drug Discov*, 2024. **23**(9): p. 682-708.
159. Storck, S.E. and C.U. Pietrzik, *Endothelial LRP1 - A Potential Target for the Treatment of Alzheimer's Disease : Theme: Drug Discovery, Development and Delivery in Alzheimer's Disease Guest Editor: Davide Brambilla*. *Pharm Res*, 2017. **34**(12): p. 2637-2651.
160. Sagare, A., et al., *Clearance of amyloid-beta by circulating lipoprotein receptors*. *Nat Med*, 2007. **13**(9): p. 1029-31.
161. He, Z., et al., *The molecular mechanism of LRP1 in physiological vascular homeostasis and signal transduction pathways*. *Biomed Pharmacother*, 2021. **139**: p. 111667.
162. Erickson, M.A., K. Hansen, and W.A. Banks, *Inflammation-induced dysfunction of the low-density lipoprotein receptor-related protein-1 at the blood-brain barrier: protection by the antioxidant N-acetylcysteine*. *Brain Behav Immun*, 2012. **26**(7): p. 1085-94.
163. Qosa, H., et al., *Oleocanthal enhances amyloid-beta clearance from the brains of TgSwDI mice and in vitro across a human blood-brain barrier model*. *ACS Chem Neurosci*, 2015. **6**(11): p. 1849-59.
164. Sehgal, N., et al., *Withania somnifera reverses Alzheimer's disease pathology by enhancing low-density lipoprotein receptor-related protein in liver*. *Proc Natl Acad Sci U S A*, 2012. **109**(9): p. 3510-5.
165. Qosa, H., et al., *Enhanced brain amyloid-beta clearance by rifampicin and caffeine as a possible protective mechanism against Alzheimer's disease*. *J Alzheimers Dis*, 2012. **31**(1): p. 151-65.
166. Loeb, M.B., et al., *A randomized, controlled trial of doxycycline and rifampin for patients with Alzheimer's disease*. *J Am Geriatr Soc*, 2004. **52**(3): p. 381-7.
167. Hsu, H.W., et al., *Copper-Induced Upregulation of MicroRNAs Directs the Suppression of Endothelial LRP1 in Alzheimer's Disease Model*. *Toxicol Sci*, 2019. **170**(1): p. 144-156.
168. Gauthier, A., et al., *Adipocyte low density lipoprotein receptor-related protein gene expression and function is regulated by peroxisome proliferator-activated receptor gamma*. *J Biol Chem*, 2003. **278**(14): p. 11945-53.
169. Moon, J.H., et al., *The effect of rosiglitazone on LRP1 expression and amyloid beta uptake in human brain microvascular endothelial cells: a possible role of a low-dose thiazolidinedione for dementia treatment*. *Int J Neuropsychopharmacol*, 2012. **15**(1): p. 135-42.
170. Seok, H., et al., *Low-dose pioglitazone can ameliorate learning and memory impairment in a mouse model of dementia by increasing LRP1 expression in the hippocampus*. *Sci Rep*, 2019. **9**(1): p. 4414.
171. El-Megiri, N., et al., *Pioglitazone Ameliorates Hippocampal Neurodegeneration, Disturbances in Glucose Metabolism and AKT/mTOR Signaling Pathways in Pentylentetrazole-Kindled Mice*. *Pharmaceuticals (Basel)*, 2022. **15**(9).
172. Hong, S., et al., *The PPARgamma agonist rosiglitazone prevents cognitive impairment by inhibiting astrocyte activation and oxidative stress following pilocarpine-induced status epilepticus*. *Neurol Sci*, 2012. **33**(3): p. 559-66.

173. Romera, C., et al., *Ischemic preconditioning reveals that GLUT1/EAAT2 glutamate transporter is a novel PPARgamma target gene involved in neuroprotection*. *J Cereb Blood Flow Metab*, 2007. **27**(7): p. 1327-38.
174. Di Cesare Mannelli, L., et al., *PPAR- gamma impairment alters peroxisome functionality in primary astrocyte cell cultures*. *Biomed Res Int*, 2014. **2014**: p. 546453.
175. Aguirre-Rueda, D., et al., *WIN 55,212-2, agonist of cannabinoid receptors, prevents amyloid beta1-42 effects on astrocytes in primary culture*. *PLoS One*, 2015. **10**(4): p. e0122843.
176. Risner, M.E., et al., *Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease*. *Pharmacogenomics J*, 2006. **6**(4): p. 246-54.
177. Gold, M., et al., *Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study*. *Dement Geriatr Cogn Disord*, 2010. **30**(2): p. 131-46.
178. Haag, M.D., et al., *Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study*. *J Neurol Neurosurg Psychiatry*, 2009. **80**(1): p. 13-7.
179. Hanin, A., et al., *Repurposing of cholesterol-lowering agents in status epilepticus: A neuroprotective effect of simvastatin*. *Epilepsy Behav*, 2023. **141**: p. 109133.
180. Llorente-Cortes, V., et al., *Sterol regulatory element-binding protein-2 negatively regulates low density lipoprotein receptor-related protein transcription*. *J Mol Biol*, 2006. **359**(4): p. 950-60.
181. Bengoechea-Alonso, M.T. and J. Ericsson, *SREBP in signal transduction: cholesterol metabolism and beyond*. *Curr Opin Cell Biol*, 2007. **19**(2): p. 215-22.
182. Deane, R., Z. Wu, and B.V. Zlokovic, *RAGE (yin) versus LRP (yang) balance regulates alzheimer amyloid beta-peptide clearance through transport across the blood-brain barrier*. *Stroke*, 2004. **35**(11 Suppl 1): p. 2628-31.
183. Shinohara, M., et al., *Reduction of brain beta-amyloid (Abeta) by fluvastatin, a hydroxymethylglutaryl-CoA reductase inhibitor, through increase in degradation of amyloid precursor protein C-terminal fragments (APP-CTFs) and Abeta clearance*. *J Biol Chem*, 2010. **285**(29): p. 22091-102.
184. Champagne, D., et al., *The cholesterol-lowering drug probucol increases apolipoprotein E production in the hippocampus of aged rats: implications for Alzheimer's disease*. *Neuroscience*, 2003. **121**(1): p. 99-110.
185. Fan, Y.G., et al., *Paricalcitol accelerates BACE1 lysosomal degradation and inhibits calpain-1 dependent neuronal loss in APP/PS1 transgenic mice*. *EBioMedicine*, 2019. **45**: p. 393-407.
186. Guo, Y.X., et al., *1,25-Dihydroxyvitamin D3 regulates expression of LRP1 and RAGE in vitro and in vivo, enhancing Abeta1-40 brain-to-blood efflux and peripheral uptake transport*. *Neuroscience*, 2016. **322**: p. 28-38.
187. Suls, A., et al., *Early-onset absence epilepsy caused by mutations in the glucose transporter GLUT1*. *Ann Neurol*, 2009. **66**(3): p. 415-9.
188. Herring, A., et al., *Environmental enrichment counteracts Alzheimer's neurovascular dysfunction in TgCRND8 mice*. *Brain Pathol*, 2008. **18**(1): p. 32-9.
189. Zhang, J.M., et al., *Ketone Body Rescued Seizure Behavior of LRP1 Deficiency in Drosophila by Modulating Glutamate Transport*. *J Mol Neurosci*, 2022. **72**(8): p. 1706-1714.
190. da Luz, M.H.M., et al., *Sleep deprivation modulates APOE and LDL receptor-related protein 1 through thyroid hormone T4 and impairs Abeta clearance in hippocampus of rats*. *Biochim Biophys Acta Mol Basis Dis*, 2023. **1869**(6): p. 166729.