Exploration of Astrocyte-Induced Cognitive Enhancements

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ABSTRACT

Many, if not all, neurodegenerative diseases are associated with cognitive impairments. From learning deficits to memory impairments, reduced cognitive abilities contribute to the decline in the quality of life experienced by affected individuals. Advances in technology have allowed researchers to understand neurodegenerative disease pathology in terms of what cells are being affected and how they are being affected. Researchers have used synaptic plasticity and long-term potentiation (LTP) as an experimental model to uncover learning and memory mechanisms.

Astrocytes are star-shaped glial cells in close contact with neurons and envelope synapses. They have been recognized as supportive cells for years with functions in neurotrophic factor excretion, toxin clearance, and glucose metabolism maintenance. However, advances in technology have accelerated research regarding the role of astrocytes in neural networks. In vitro studies have identified the importance of astrocytes in synaptic maintenance. This review will compare two studies exploring the role of astrocytic activation on LTP and memory performance. Specifically, this review will assess the methodology used to experimentally assess astrocytes and compare the results of astrocytic influence on memory.

(Keywords: neurological disorders, memory deficits, long-term potentiation, LPT, astrocytes, neurotrophic functions)

INTRODUCTION

Global concern regarding population aging has accelerated research focusing on improving the quality of life as individuals age. Notably, the increasing prevalence of Alzheimer's and Parkinson's disease with age has emphasized the need to characterize their pathologies (GBD 2015 Neurological Disorders Collaborator Group, 2017; Lobo, *et al.*, 2000). Many, if not all, neurodegenerative diseases are associated with cognitive impairments (Alzheimer's Association, 2013; Goldstein and Abrahams, 2013; Svenningsson, *et al.*, 2012; Walker, 2007). From learning deficits to memory impairments, reduced cognitive abilities contribute to the decline in the quality of life experienced by affected individuals.

Advances in technology have allowed researchers to understand neurodegenerative disease pathology in terms of what cells are being affected and how they are being affected. Researchers have used synaptic plasticity and long-term potentiation (LTP) as an experimental model to uncover learning and memory mechanisms.

Neurons communicate through synapses. Synaptic plasticity characterizes changes in synapses over time and underlies the process of various cognitive functions. According to the synaptic plasticity and memory hypothesis, "activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation and is both necessary and sufficient for the information storage underlying the type of memory mediated by the brain area in which that plasticity is observed" (Martin, *et al*. 2000). Precisely, memories are formed when neurons establish new or strengthen existing synapses. High-frequency or repeated signal transmission leads to the persistent strengthening of synapses and elevated synaptic transmission between neurons. This process of synaptic strengthening is referred to as LTP and serves as the cellular basis for memory formation.

LTP is well studied within glutamatergic synapses in the hippocampus. Stimulation of glutamatergic neurons triggers glutamate release into the synaptic cleft where it then binds to either α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) or N-methyl-D-aspartate (NMDA) receptors on the post-synaptic neuron (Goncalves-Ribeiro, *et al*., 2019). Upon weak stimulation, the pre-synaptic neuron releases minimal glutamate leading to activation of AMPA receptors (AMPARs) and depolarization induced by sodium influx into the post-synaptic neuron. NMDA receptors (NMDARs) remain closed due to blockage by magnesium ions. However, following strong or repeated stimulations, the pre-synaptic neuron releases more glutamate which leads to prolonged activation of AMPARs and increased sodium influx.

The increased sodium influx expels magnesium from the NMDAR and allows calcium (Ca2+) into the cell which serves as a mediator for LTP induction. Early LTP underlies short-term memory and involves Ca2+ activating several protein kinases that enhance synaptic communication through two mechanisms: phosphorylation of existing AMPA receptors to increase sodium conductance and transportation of AMPA receptors from intracellular stores to the post-synaptic membrane. Late phase LTP involves the synthesis of AMPAR and the expression of other proteins to develop new dendritic spines and synaptic connections. Late-phase LTP has been associated with long-term memory (Goncalves-Ribeiro, *et al.*, 2019). Interestingly, many experiments have attempted to explore other potential mediators of LTP, with astrocytes at the forefront of recent literature.

Astrocytes are star-shaped glial cells in close contact with neurons and envelope synapses. Although these cells were observed in 1921, a lack of methodology has hindered research regarding their importance in neural functions (del-Rio Hortega, 1921). Hence, they have been recognized as supportive cells for years with functions in neurotrophic factor excretion, toxin clearance, and glucose metabolism maintenance (Turner and Adamson, 2011). However, advances in technology have accelerated research regarding the role of astrocytes in neural networks. *In vitro* studies have identified the importance of astrocytes in synaptic maintenance.

Kucukdereli, *et al*. (2011) established the involvement of astrocytes in synaptogenesis; upon blockage of astrocyte-neuron communication, synaptogenesis was impaired. Astrocytes seem to critically modulate synaptic structure and function. Considering LTP at the synaptic level and its involvement in memory formation, researchers have become curious as to whether astrocytes influence LTP and memory processes. This review will compare two studies exploring the role of astrocytic activation on LTP and memory performance. Specifically, this review will assess the methodology used to experimentally assess astrocytes and compare the results of astrocytic influence on memory.

Forebrain Engraftment by Human Glial Progenitor Cells Enhances Synaptic Plasticity and Learning in Adult Mice

Han, *et al*. (2013) designed human chimeric mice brains to assess whether human astrocytes influence activity-dependent plasticity in a different neural network. They tested their hypothesis that human astrocytes enhance synaptic plasticity and learning relative to murine mice. To study human astrocytes in live adult mice brains, Han, *et al.* (2013) xenografted immunodeficient mice with isolated human glial progenitor cells (GPCs) that were transfected to express an enhanced green fluorescent protein (EGFP).

The xenografted GPCs matured into astroglia in a cell-autonomous manner and were linked to gap junctions in the mice neural network. Preliminary analysis revealed xenografted astrocytes exhibited a higher input resistance and 3-fold accelerated intracellular calcium signal propagation compared to host murine astrocytes.

Effect of Human Astrocytes on Synaptic Plasticity: Following two trains of high-frequency stimulation, Han, *et al*. (2013) recorded field excitatory postsynaptic potentials (fEPSPs) in hippocampal slices and noticed potentiation of the fEPSP slope to 151.2% of baseline in chimeric mice (138.6% in control littermates). Notably, the potentiation of fEPSP slope persisted for 60 minutes in chimeric mice, unlike both unengrafted and allografted mice.

To determine the mechanism behind the observed potentiation of fEPSPs in chimeric mice, Han, *et al.* (2013) assessed the contribution of NMDARs and adenosine by

blocking their actions with their respective inhibiting agents. However, they concluded NMDARs and adenosine did not contribute to the previously observed potentiation of fEPSPs in chimeric mice. Astrocytes also release D-serine which is an NMDA co-agonist. Han, *et al*. (2013) administered D-serine to brain slices of control mice and reported no effects of D-serine on fEPSP slopes. Moreover, immunolabelling for D-serine and its synthetic enzyme, serine racemase, did not differ between chimeric and uninjected control mice.

Astrocytes release tumor necrosis factor-alpha (TNFα) which increases AMPAR concentration at neuronal membranes (Leonoudakis, *et al*., 2004). Upon administration of TNFα, Han, *et al*. (2013) reported an increase in fEPSPs and increased levels of AMPA glutamate receptor 1 (GluR1) subunits in unengrafted mice. They proceeded to confirm increased human TNFα and GluR1 expression in chimeric mice compared to unengrafted mice.

Furthermore, the administration of thalidomide, an inhibitor of TNFα production, led to attenuation of fEPSPs and LTP in chimeric mice compared to those receiving vehicle (control substance). Immunolabelling analysis revealed reduced GluR1 in thalidomide chimeric mice. Further quantitative immunohistochemistry revealed a significant increase in phosphorylation of the Ser831 PKC-site on GluR1 subunits in human glial chimeric mice. Phosphorylation of GluR1 at the Ser831-PKC site is critical for synaptic membrane insertion of AMPARs (Jenkins and Traynelis, 2012).

Taken together, Han, *et al*. (2013) suggested human astrocytes facilitate synaptic insertion of the GluR1 subunit in murine neurons through a TNFα-dependent PKC/CaMKII-mediated pathway which decreases the threshold for LTP induction in human glial chimeric mice.

Effect of Human Glial Progenitor Cells on Learning in Mice: Han, *et al.* (2015) assessed whether human glial chimeric mice exhibited enhanced performance in the following learning tasks: auditory fear conditioning (AFC), contextual fear conditioning (CFC), Barnes maze, and Object-Location Memory Task (OLT). In the AFC task, chimeric mice demonstrated enhanced learning of the tone foot-shock pairing measured by their increased levels of freezing in response to the conditioned tone. Similarly, the human glial chimeric mice exhibited enhanced learning in the CFC task. In the Barnes maze spatial learning task, the human glial chimeras persistently made fewer errors and displayed a shorter latency in finding the escape/dropbox compared to their littermate controls. In testing the ability of the mice to recognize a familiar object in a novel location, chimeric mice performed significantly better on the OLT by displaying a greater preference for objects in novel locations than their controls. Overall, Han, *et al*. (2013) show human astrocytes enhance learning in chimeric mice.

Critique of Studying Human Astrocytes in Chimeric Mice: Han, *et al.* (2013) studied the involvement of astrocytes on neurons by comparing neural function between human astrocyte chimeric mice to allografted or unengrafted mice. Their justification stems from the more complex morphological features of human astrocytes compared to mice astrocytes. Previous studies have suggested this greater complexity reflects a greater functional role of human astrocytes in synaptic modulation and cortical circuitry (Oberhein, *et al*., 2006; Oberheim, *et al*., 2009). Based on this suggestion, Han, *et al.* (2013) believed human astrocytes should induce greater synaptic potentiation and cognitive enhancements in mice neural networks compared to mice astrocytes.

When Han, *et al*. (2013) were investigating the mechanism behind astrocyte-induced LTP, they observed increases in fEPSP and GluR1 expression after TNFα administration. Although their subsequent experiment showed increased TNFα in chimeric mice, Han, *et al*. (2013) verified TNFα as the mediator for LTP by using thalidomide to inhibit TNFα production in chimeric mice which led to their expected result of reducing GluR1 expression and LTP. This confirmative analysis strengthens the results of their study. However, Han, *et al*. (2013) neglect the analysis of AMPA influencing LTP. They state NMDA receptors have a higher affinity for glutamate than AMPARs and proceed to only evaluate the effect of NMDAR blockage on LTP.

Han, *et al*. (2013) demonstrated enhanced cognitive abilities of human glial chimeric mice across multiple behavioral tests. However, they did not consider any statistical corrections for the extensive number of comparisons made. The use

of the Bonferroni Correction procedure would have allowed Han, *et al*. (2013) to adjust their α value with respect to the number of comparative tests they conducted and reduce the risk for false positives (Armstrong, 2014).

Astrocytic Activation Generates *de novo* Neuronal Potentiation and Memory Enhancement

Adamsky, *et al.* (2018) investigated the effect of activating CA1 hippocampal astrocytes on synaptic potentiation and cognitive behavior. To chemo-genetically activate astrocytes, they delivered an adeno-associated virus serotype 8 (AAV8) vector encoding the G1-coupled designer receptor hM3Dq fused to mCherry under the control of a glial-fibrillary acidic protein (GFAP) promoter (AAV8-GFAP::hM3Dq-mCherry). The use of hM3Dq in astrocytes allows for time-restricted activation by clozapine-N-oxide (CNO).

Long-Term Potentiation Induced by Astrocytic Activation: Adamsky, *et al*. (2018) first verified their experimental activation of CA1 astrocytes. Two-photon Ca2+ imaging in brain slices revealed elevated Ca2+ levels in hM3Dq expressing CA1 astrocytes following CNO administration. Further imaging analysis displayed CNO application inducing increased Ca2+ transients produced by hM3Dq-GCaMP6f astrocytes that lasted over 40 minutes.

Adamsky, *et al*. (2018) proceeded to characterize the effect of astrocytic activation on spontaneous synaptic release events (SSREs) in CA1 hippocampal neurons. They recorded SSREs in neurons from voltage clamps under tetrodotoxin (TTX; a neurotoxin that blocks stimulatory inputs from other neurons) allowing them to examine the effects of only astrocytes on spontaneous synaptic release events in CA1 hippocampal neurons. Interestingly, they reported astrocytic activation inducing significant increases in both frequency and amplitude of miniature excitatory postsynaptic currents (mEPSCs; EPSCs).

Given the effects of astrocytic activation on spontaneous synaptic events, Adamsky, *et al*. (2018) assessed whether astrocytic activation is sufficient to induce *de novo* potentiation. They stimulated Schaffer collaterals (SCs) and noticed a 50% potentiation of the EPSC amplitude in response to the same stimulus in GFAP::hM3Dq slices treated with CNO, but not in the same mice exposed to artificial cerebrospinal fluid (ACSF). Moreover, after 20 minutes of CNO washout, there was a significantly greater increase in fEPSP amplitude compared to ACSF-treated slices.

Identification of this astrocyte-induced LTP led Adamsky, *et al*. (2018) to explore the mechanism underlying this process. They replicated the previous experiment using SC stimulation under the presence of the following blocking agents: metabotropic glutamate receptors (mGluRs) blockers, NMDA receptor blockers, and NMDA D-serine site blockers. Adamsky, *et al*. (2018) reported no contribution of mGluRs in potentiation as CNO application in the presence of the mGluRs blockers still significantly potentiated fEPSPs. Interestingly, potentiation was not noticed under the NMDA receptor blocker. Moreover, in the presence of elevated magnesium levels (an NMDAR blocker), more SC stimulations were required to reach the full potentiation effect. Administration of the NMDA D-serine site blocker completely blocked potentiation.

Taken together, Adamsky, *et al*. (2018) demonstrated the synaptic potentiation induced by astrocytic activation is mediated by the NMDA receptor and involves the NMDA co-agonist D-serine. Lastly, Adamsky, *et al*. (2018) confirmed astrocyte-induced synaptic potentiation is mediated by increased intracellular Ca2+ in astrocytes after fEPSPs were minimally potentiated when astrocytes were filled with Ca2+ chelators.

Effect of Astrocytic Activation on Spatial Memory and Fear Condition: To generally assess the effect of astrocytic activation on memory, Adamsky, *et al*. (2018) compared T-maze performance between mice injected with saline or CNO 30 minutes prior to the training session. Mice injected with CNO demonstrated an increased preference for the novel arm when re-introduced to the T-maze, indicating an enhanced memory for the two other arms they were initially exposed to. Adamsky, *et al*. (2018) investigated the specific stage of memory processing that astrocytic activation enhances by administering CNO or saline 30 minutes before the training (acquisition) or 30 minutes before the recall of CFC and AFC. Interestingly, Adamsky, *et al.* (2018) reported astrocytic activation

improving memory acquisition but not recall abilities.

Adamsky, *et al.* (2018) questioned whether the memory enhancing-effects are simply due to increases in general neural activity. However, when they directly activated the CA1 hippocampal neurons, the mice exhibited reduced contextual freezing a day after their CFC training, indicating impaired memory abilities. Adamsky, *et al*. (2018) proceeded to assess the effect of astrocytic versus neural activation in either home-caged or fear-conditioned mice. Mice with their neurons directly activated experienced similar levels of increased neural activity in both conditions. However, when Adamsky, *et al*. (2018) activated the mice astrocytes, neural activity only increased in mice undergoing fear conditioning. Hence, they concluded astrocytic activation enhances neuronal activity in a task-dependent way which leads to enhanced acquisition and memory.

Lastly, Adamsky, *et al*. (2018) used optogenetic activation of CA1 astrocytes to confirm that astrocytic activation only enhances the acquisition stage of memory processing. They activated CA1 astrocytes only during the 5-minute fear-conditioning training session which led to increased contextual freezing by 89% the next day.

Assessment of Astrocytic Activation and its Behavioral Outcomes: Adamsky, *et al.* (2018) experimentally activated astrocytes in mice and assessed whether it can induce LTP and enhance memory. Their use of an AAV8-GFAP::hM3Dq-mCherry is a strong, selective way of activating CA1 hippocampal astrocytes. The employment of two-photon Ca2+ imagining verifying astrocytic activation by hM3Dq strengthens their use of the viral vector. However, when Adamsky, *et al*. (2018) evaluated the effect of astrocytic activation on SSREs in CA1 hippocampal neurons, they used TTX to block stimulation of their target neuron from other neural inputs. TTX also blocks the target neuron itself from firing action potentials which led Adamsky, *et al*. (2018) to measure neural activity through mEPSCs (Lee and Ruben, 2008).

It is important to recognize that mEPSCs are not action potentials. Therefore, it remains unclear whether astrocytic activation alone can increase action potential firing, or if they simply alter the electrophysiology of neurons which then enhances or depletes the effects of incoming neural inputs.

Adamsky, *et al.* (2018) reported that astrocytic activation led to improvements in memory performance. Their study only explores spatial memory and associative memory in the context of fear conditioning. Therefore, their results regarding astrocytic activation and memory enhancement cannot be generalized to all forms of memory. Interestingly, Adamsky, *et al.* (2018) concluded astrocytic activation enhances the acquisition stage of memory but not the recall phase. They initially used pharmacogenetic administration of CNO to activate astrocytes during the acquisition phase, however, Adamsky, *et al.* (2018) noted that CNO may not have been eliminated from the system prior to the early consolidation stage. To ensure early consolidation was not affected by astrocytic activation, they used optogenetics to only activate astrocytes during the training sessions thereby targeting acquisition. However, Adamsky, *et al.* (2018) did not rule out astrocytic activation affecting early consolidation as they did not opto-genetically activate astrocytes during the consolidation phase to see whether memory performance is affected.

CONCLUSION

Han, *et al*. (2013) and Adamsky, *et al*. (2018) provide strong methodological procedures to assess the influence of astrocytes on neural functioning. Future studies can implement their procedures to investigate the role of astrocytes in other behavioral functions including sensorimotor and locomotor abilities. Despite minor limitations, both studies also present strong evidence for astrocytes enhancing synaptic potentiation and enhancing memory.

Their results highlight the potential need to maintain astrocyte health throughout life to promote stable cognitive abilities. However, both studies assume that the enhanced memory performance is caused by the potentiation induced by astrocytes. This assumption can be empirically evaluated using *in vivo* Ca2+ imagining of astrocytes in mice. In an experiment with a condition that inhibits the expression of factors involved in plasticity, experimental activation of astrocytes can be verified through *in vivo* two-photon laser scanning fluorescence microscopy imaging (Ding, 2012; Harlow, *et al*.,

2010; He, *et al*., 2019). If mice with functional plasticity show memory enhancements whereas mice with the plasticity inhibition do not, then it can be concluded that astrocytes induce synaptic potentiation that then leads to memory enhancements.

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