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Review

Synaptic Plasticity and its Modulation by Alcohol

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Abstract. Alcohol is one of the oldest pharmacological agents used for its sedative/hypnotic effects, and alcohol abuse and alcohol use disorder (AUD) continues to be major public health issue. AUD is strongly indicated to be a brain disorder, and the molecular and cellular mechanism/s by which alcohol produces its effects in the brain are only now beginning to be understood. In the brain, synaptic plasticity or strengthening or weakening of synapses, can be enhanced or reduced by a variety of stimulation paradigms. Synaptic plasticity is thought to be responsible for important processes involved in the cellular mechanisms of learning and memory. Long-term potentiation (LTP) is a form of synaptic plasticity, and occurs via N-methyl-D-aspartate type glutamate receptor (NMDAR or GluN) dependent and independent mechanisms. In particular, NMDARs are a major target of alcohol, and are implicated in different types of learning and memory. Therefore, understanding the effect of alcohol on synaptic plasticity and transmission mediated by glutamatergic signaling is becoming important, and this will help us understand the significant contribution of the glutamatergic system in AUD. In the first part of this review, we will briefly discuss the mechanisms underlying long term synaptic plasticity in the dorsal striatum, neocortex and the hippocampus. In the second part we will discuss how alcohol (ethanol, EtOH) can modulate long term synaptic plasticity in these three brain regions, mainly from neurophysiological and electrophysiological studies. Taken together, understanding the mechanism(s) underlying alcohol induced changes in brain function may lead to the development of more effective therapeutic agents to reduce AUDs.

Keywords: LTP, ethanol, dorsal striatum, cortex, hippocampus

LEARNING AND SYNAPTIC PLASTICITY

The ability to remember is likely the most significant and distinctive feature of our existence. We are largely defined by what we have learned and what we can remember. Conversely, impairments in the ability to remember can lead to devastating memory losses, that are the hallmark of several neurodegenerative disorders [1] and alcohol use disorders (AUD; [2]). Learning may be described as the mechanism by which new information about the individual's environment is acquired, and memory as the mechanism by which that knowledge is retained [3]. Storage of memories in the brain almost certainly involves some form of synaptic modifications. Ramón y Cajal originally hypothesized that information storage relies on the changes in the strength of synaptic connections between connected pairs of neurons [4]. The guiding principle for such neuronal interactions was later proposed by Donald Hebb in his book, 'The Organization of Behavior' [5], where he states "When an axon of cell A is near enough to excite cell B or repeatedly or consistently takes part in firing it, some growth or metabolic changes takes place in one

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or both cells such that A's efficiency, as one of the cells firing B, is increased". Hebb also postulates that if two neurons are active at the same time, the synaptic efficiency of the appropriate synapse will be strengthened [5]. It took almost 25 years to discover a process by which strengthening of synaptic connections can be achieved, and the importance of one model that seemed to fit Hebb's idea. This model is known as a long-term potentiation (LTP). Based on several groundbreaking studies, it has been conceptualized that, (1) LTP is an enhancement of synaptic efficiency that can be induced by high frequency, or by low frequency stimulation; (2) LTP can last for an extended period of time (from weeks to months) *in vivo*; (3) It is most prominent in regions of the brain that are strongly implicated in learning and memory (e.g. neocortex and hippocampus); (4) LTP is specific to tetanized inputs: the non-tetanized inputs are not potentiated; (5) LTP has Hebbian-like properties, in that it requires conjoint pre-and post-synaptic activity for its generation; (6) There is the requirement for cooperativity amongst afferent fibers to induce LTP; (7) Associativity amongst afferents can also be demonstrated, i.e. a tetanus too weak to elicit LTP will do so, if paired with a strong tetanus; (8) Drug treatments that selectively block the induction of LTP also selectively impair learning and memory [6–9]. It is important to note that these conceptualizations are historical and that more recent work has determined that there are exceptions to these rules [10, 11].

Supporting the role of LTP, synaptic connections and plasticity in learning and memory functions, Scoville and Milner reported that bilateral medial temporal-lobe resection, including a structure called the hippocampus, causes a persistent impairment of recent memory [12]. These findings supported the hypothesis that the hippocampus is critically involved in the retention of current experience. What was striking about their study is that hippocampus-independent cognitive functions were preserved, and this aspect of preservation of certain cognitive functions in subjects with hippocampal lesions is supported in the famous patient H. M. [13]. For example, H. M.' s language and reasoning abilities were unchanged, his performance on an IQ test was increased, and remote memories were intact. More recent anatomical studies of H. M., and other human patients with amnesic syndromes, as well as studies in animals, suggest that the memory deficits in H. M. arose most probably from damage to the hippocampus and cortical structures immediately surrounding the medial temporal lobe [14]. Follow up studies by Anderson and Lomo reported that a single, short test shock, following an initial period of conditioning test shocks to the perforant path in the hippocampus, elicited a potentiated response in the dentate gyrus region of the hippocampus [15]. Furthermore, Lynch et al reported that a tetanic stimulation of one pathway in the CA1 region of the hippocampus depresses the effectiveness of the other synapses in the hippocampus [16]. They called this phenomenon a heterosynaptic long-term depression (LTD) which can be observed in the dentate gyrus and in the CA1 region of the hippocampus *in vitro*. In support of this phenomena, Dudek and Bear reported that several hundred stimuli delivered at low frequency (1–3 Hz) produced a sustained depression of a modest, but significant amplitude. This phenomenon is known as homosynaptic LTD, and is much harder to demonstrate *in vivo* compared with heterosynaptic LTD [17].

Taken together, the different forms of synaptic plasticity, namely LTP and LTD are thought to contribute significantly to learning and memory, and involve long lasting changes in the efficacy of glutamatergic synaptic activity. The potential role of these forms of plasticity in addiction has been reviewed extensively [18–20]. The remainder of the review will briefly focus on the cellular mechanisms of synaptic plasticity in dorsal striatal, neocortical, as well as hippocampal synapses based on several electrophysiological studies, and will discuss the effect of ethanol (EtOH) on synaptic plasticity in these brain regions. We restricted our focus on these three regions of the brain, as they are proposed to be significantly involved in the binge/intoxication (dorsal striatum) and preoccupation/anticipation (neocortex and hippocampus) stages of AUD [21].

Synaptic plasticity in the dorsal striatum

Corticostriatal and midbrain projections originate from several areas of the cerebral cortex and the midbrain [22], and release neurotransmitters including glutamate, dopamine and gamma-aminobutyric acid (GABA) into the dorsal striatum [23–25]. Both LTP and LTD have been found at corticostriatal synapses on medium-sized spiny neurons, *in vitro* and *in vivo* [26–28]. While LTD was reported to be the major form of corticostriatal plasticity, it has been reported that LTP and LTD can be induced by the high frequency stimulation (HFS) of corticostriatal fibers [29]. Notably, several factors have been implicated in modulating LTP and LTD at corticostriatal synapses. For example, in the presence of physiological

concentration of magnesium, HFS can induce LTD *in vitro* [30]. Next, at low magnesium concentrations, HFS in the lateral striatum produces NMDA receptor (NMDAR)-dependent LTP as it is blocked by DL-2-amino-5-phosphonovaleric acid (AP-5), an NMDAR antagonist [29]. Furthermore, the anatomical location of the synapses within the dorsal striatum seems to influence the polarity of the observed corticostriatal plasticity. For instance, if the HFS is conducted in the dorsolateral striatum, which receives input primarily from sensorimotor cortex, the major form of plasticity is LTD. However, if HFS is conducted in the dorsomedial striatum, the major form of plasticity is LTP [26, 31–33]. The mechanisms underlying this distinct and varied effect in the striatal sub-regions is currently unknown, but could be due to the differential expression patterns of dopamine D2-like receptors [34]. Perhaps, reduced expression of D2-like receptors in dorsomedial striatum could favor the induction of LTP vs. LTD. Nevertheless, the presence or absence of magnesium and the anatomical location are not the only factors influencing the induction of LTP and LTD. Additional cellular mechanisms underlying the regional difference in the form of plasticity in the dorsal striatum include differences in presynaptic release in neurotransmitters, such as GABA vs. glutamate or dopamine. Indeed LTP is increased medially with HFS, and the effect is dependent on the blockade of $GABA_A$ receptors, as well as the elimination of dopaminergic input from nigrostriatal synapses [35]. Next, the age of the animal is also an important factor for the switch between the induction of LTP and LTD in corticostriatal synapses. For example, the dorsolateral region of the striatum tends to express LTP in animals that are 12–14 days old, whereas LTD was found in slices from rats aged 15–34 days [26]. Interestingly, these authors also found that the type of synaptic plasticity is not altered by age in dorsomedial striatum, as NMDA-dependent LTP was found in both age groups. Lastly, the location of the stimulating electrode used for HFS to activate corticostriatal afferents influences the degree of synaptic plasticity in the striatum. For instance, if the stimulating electrode is located near the white matter it can directly cause the release of certain neurotransmitters such as dopamine or GABA. This may induce an LTD in the corticostriatal afferents. Conversely, if the stimulating electrode is located dorsally to the dorsomedial striatum on the cortical side, LTP is easily induced. This minimal current spread into the striatum is believed to minimize the release of large dopamine transients that bias toward LTD [27, 36]. Taken together, the varied and distinct forms of synaptic plasticity in the dorsal striatum and its modulation by EtOH (discussed in the later sections) may therefore be important for understanding the cellular mechanisms underlying the behavioral deficits seen in alcoholics and AUDs [2].

Synaptic plasticity in the neocortex

LTP and LTD forms of synaptic plasticity are evident in the neocortex [37–41]. As demonstrated in various *in vitro* studies, both NMDAR dependent and independent mechanisms contribute to LTD in the neocortex. For example, the NMDAR-mediated LTD is dependent on activation of calcineurin, and the resulting internalization of AMPA type glutamate receptors [42]. One form of NMDAR independent LTD occurs via activation of metabotropic glutamate receptors [43, 44]. A second form of NMDAR independent LTD occurs via activation of cannabinoid type 1 (CB1) receptors, which causes a long-lasting decrease in release probability [45, 46]. Additionally, HFS-induced LTD in the PFC requires $GABA_A$ receptor functioning and can be inhibited by dopamine receptor antagonists [47]. With respect to the mechanisms underlying LTP in the neocortex, most studies reveal a role for NMDARs [48]. Notably, NMDAR-mediated LTP occurs in concert with activity of several protein kinases, including, CaMKII, PKC and PKA, which alter AMPA-type glutamate receptor phosphorylation, and insertion of GluR1-containing AMPA receptors into synapses [48]. Learning and memory functions dependent on the neocortex are impaired in subjects with moderate to severe AUDs, and rodent studies have demonstrated aberrant metaplasticity of NMDAR dependent form of synaptic plasticity in the neocortex *in vitro* [49]. In addition, studies in human subjects have demonstrated impaired LTP-like neuroplasticity in the neocortex *in vivo* in intoxicated individuals [50]. Together these findings suggest the hypothesis that EtOH-induced alterations in both forms of synaptic plasticity in the neocortex (discussed in later sections) could contribute to the behavioral deficits seen in individuals with AUDs.

Synaptic plasticity in the Hippocampus

The phenomena of LTP and LTD are extensively studied in synapses located in the hippocampus [51–54]. Whereas LTP was originally induced in the hippocampus by stimulation of axons of the perforant

path and potentiation of the postsynaptic potentials in the dentate gyrus [55], the potentiation was found to be input-specific. That is, stimulation of the medial perforant path did not potentiate the lateral perforant path and *vice versa*. Later, Collingridge *et al.* made the key observation that the selective NMDAR antagonist AP-5 blocks the induction of LTP in the Schaffer collateral-commissural pathway of the hippocampus [56], indicating a direct role for NMDARs in mediating hippocampal LTP. At the same time, Lynch *et al.* illustrated that intracellular injection of the calcium chelator N,N,N',N'-tetraacetic acid (EGTA) into pyramidal cells of the CA1 region of the hippocampus blocked the induction of LTP suggesting that NMDARs are the source of calcium that supports this form of LTP [16]. Additional mechanistic studies have demonstrated that both GluN2A and GluN2B subunits of NMDARs play a significant role in induction of hippocampal LTP [57–59]. More notable is that GluN2A subunits selectively play a role in induction of hippocampal LTP without affecting induction of LTD [59]. Therefore, in the hippocampus it is clear that NMDAR subunits are critical factors that determine the polarity of synaptic plasticity. Additional studies indicate that low-frequency stimulation induced LTD in the hippocampus also requires NMDAR activation [17, 60]. In addition, mechanistic studies have revealed a role for GluN2A and GluN2B subunits in induction of hippocampal LTD, indicating that the two distinct forms of plasticity in the hippocampus share a common molecular mechanism [61, 62]. Lastly, there are reports of NMDAR independent mechanisms for induction of LTP and LTD in the hippocampus, indicating that other neurotransmitter systems are involved in these phenomena [53, 60]. Taken together, hippocampal LTP has been widely studied since it is believed that the mechanisms involved in its induction, expression, and maintenance are fundamental to learning and memory, including those that may contribute to relapse to alcohol seeking behaviors [6, 63].

MODULATION OF SYNAPTIC PLASTICITY BY ALCOHOL

Alcohol is widely used and abused and produces profound deficits in learning and memory [64–67]. Alcohol abuse and eventual dependence is a chronic relapsing disorder characterized by compulsive alcohol-drinking and alcohol-seeking behaviors [21, 68, 69]. The National Survey on Drug Use and Health estimated that 22.6 million Americans of age 12 or older, or 9.2% of the population, can be considered to have AUD, indicating that AUDs continue to be major economic, social and public health issue [70]. The precise molecular mechanisms by which EtOH produces its effects within central nervous system are only now beginning to be understood [2]. One way to better understand EtOH's effect on learning and memory is to study its acute and chronic effects on synaptic plasticity in different brain structures, including the hippocampus, neocortex and dorsomedial striatum, as these regions play critical roles in the distinct stages of alcohol addiction cycle [21, 71]. Mechanistic studies have convincingly shown that excitatory NMDARs in the brain are important sites for EtOH's actions [72–74]. Concurrently, NMDARs play an important role in learning and memory, and provide a unique role in maintaining and regulating synaptic plasticity [75–77]. Therefore, it appears that EtOH's actions via the NMDARs could be facilitating the EtOH-induced deficits in synaptic plasticity and learning and memory functions [2, 74, 78, 79]. A number of studies have demonstrated that EtOH alters synaptic plasticity in the dorsal striatum, neocortex and hippocampus [49, 80–84]. The following paragraphs will briefly discuss the effects of EtOH on synaptic plasticity in the dorsal striatum, neocortex and the hippocampus.

Alcohol and synaptic plasticity in the striatum

The dorsal striatum is a brain region that controls movement, is implicated in mediating the formation of goal-directed responses and behavioral habits, and plays a role in the binge/intoxication phase of the addiction cycle [21, 32, 85]. Recent studies have demonstrated that superfusion of EtOH and alcohol experience leads to disruption of synaptic plasticity in the dorsal striatum [82, 83, 86, 87] and ventral striatum [88, 89]. Mechanistic studies have shown that HFS induced LTD in the dorsal striatum in the presence of EtOH, and that this occurred independent of NMDAR activity, and was however, dependent on dopamine D2 and cannabinoid CB1 receptor activation [82]. With respect to NMDARs, these receptors consist of an obligatory GluN1 subunit and GluN2 (A-D) subunits [90]. GluN2A and GluN2B subunits are expressed in the striatum. A report demonstrates that superfusion of EtOH decreased NMDAR-mediated synaptic transmission in the striatum, indicating that acute EtOH

Table 1
Summary of EtOH's effects on synaptic plasticity in the neocortex, dorsal striatum and hippocampus

Alcohol (EtOH) and synaptic transmission and plasticity			
	Neocortex	Dorsal striatum	Hippocampus
Acute EtOH	↓	↓	↓
EtOH washout	NA	↑	NA
in vivo EtOH	–/↑	↑	↓/↑
Withdrawal from *in vivo* EtOH	NA	↑	↓
Abstinence from *in vivo* EtOH	–	↑	–/↑

Acute EtOH, EtOH on slices; EtOH washout, washout of acute EtOH on slices; *in vivo* EtOH, animals experiencing EtOH via injections, oral self-administration or EtOH vapor inhalation; withdrawal from *in vivo* EtOH, cessation of *in vivo* EtOH for a period of 5 to 20 hours; abstinence from *in vivo* EtOH, cessation of *in vivo* EtOH for a period of 48 hours and beyond. Up arrow indicates increase, down arrow indicates decrease, line indicates no change, NA indicates that data is not available.

induces immediate depressive effect on NMDAR activity. However, washout after acute EtOH conditions induces long-term facilitation via GluN2B NMDARs, particularly in the dorsal striatum [83]. Furthermore, washout of EtOH's effect on long-term facilitation is mediated through Fyn-mediated phosphorylation of GluN2B subunits [83]. More recent findings show that washout after acute EtOH and repeated systemic administration of EtOH followed by acute withdrawal facilitated LTP in the dorsal striatum in a GluN2B dependent manner [87]. More notable is that the induction of LTP is mediated by the synaptic localization of AMPARs in the dorsomedial striatum [87]. Few studies have investigated whether protracted consumption of EtOH affects synaptic transmission and plasticity in the dorsal striatum. A recent study used the intermittent-access two bottle choice alcohol drinking procedure and measured synaptic transmission in the dorsal striatum 24 hours after the last drinking session. They demonstrated that the intermittent-access procedure produced unregulated EtOH consumption, and that repeated cycles of unregulated EtOH consumption altered neurotransmission in the dorsomedial striatum, evident as strengthening of glutamatergic transmission in direct pathway neurons [91]. In addition, months of EtOH consumption leads to opposing effects on synaptic transmission in the dorsomedial versus dorsolateral striatum, with increased transmission in the dorsomedial striatum and reduced transmission in the dorsolateral striatum [92, 93]. Furthermore, the increased synaptic transmission observed after months of EtOH consumption in the dorsomedial striatum is not restored by abstinence, indicating that the effects are long-lasting [93]. Taken together, these studies demonstrate that the effects of EtOH (acute and *in vivo*) and washout/withdrawal from EtOH on synaptic transmission and synaptic plasticity in the dorsal striatum are multifaceted, and particularly the dorsomedial striatum is bidirectional [82, 87].

Alcohol and synaptic plasticity in the neocortex

The neocortex is involved in execution of cognitive function, and chronic alcohol exposure causes deficits in executive function dependent on the prefrontal cortex (PFC) and these deficits correlate with altered microstructure of the white and grey matter, disruption of glial homeostasis and dysregulated neuroplasticity in the PFC [94–96]. Recent *ex vivo* studies in the PFC have shown that chronic *in vivo* alcohol exposure leads to persistent increases in NMDA/AMPA current ratio via NMDARs, enhances LTP and alters glutamatergic neurotransmission [49, 97, 98]. Supporting the findings with *in vivo* alcohol exposure, studies with superfusion of EtOH in the PFC show that EtOH produces profound alterations in NMDAR mediated excitability of PFC neurons [99, 100]. More notable is that superfusion of EtOH also produces synaptic depression in the PFC and this effect is not modulated in animals that consumed EtOH over months during adulthood [93]. Overall these mechanistic studies have demonstrated that EtOH exposure (both acute and *in vivo* conditions) dysregulate glutamatergic transmission in the PFC which might contribute to the impairment of learning and memory that is seen in alcohol dependent subjects.

Alcohol and synaptic plasticity in the hippocampus

The hippocampus is involved in long and short-term spatial memory and declarative memory, and acute and chronic alcohol exposure causes deficits in these functions dependent on the hippocampus

[66, 101–105]. These deficits correlate with altered microstructure of the grey matter, disruption of glial homeostasis and dysregulated neuroplasticity in the hippocampus [79, 106–109]. EtOH (acute and *in vivo*) inhibits LTP in the hippocampus, and mechanistic studies show that NMDARs are involved [80, 110–116]. Further evaluation indicates that the dose of EtOH (acute studies) and protocols used for LTP induction may influence how EtOH affects LTP in the hippocampus [113, 114]. For example, whereas acute EtOH treatment causes disruption of LTP, chronic *in vivo* alcohol experience, in some cases, enhances NMDAR activity and induces LTP in CA1 region of the hippocampus. This differential effect on LTP is hypothesized to be influenced by the differential expression of GABARs and NMDARs with alcohol experience [111, 117, 118]. It is also possible that chronic alcohol consumption reduces GABAergic transmission which in turn provides enough depolarization to activate NMDARs during or after tetanus thus leading to induction of LTP [111]. Furthermore, it is possible that blood ethanol levels achieved during chronic alcohol experience might significantly influence the effect of EtOH on synaptic plasticity [116, 119]. Lastly, given that LTD is also evident with activation of NMDARs, it is interesting to note that EtOH enhances the induction of NMDA receptor-dependent LTD in the CA1 region of the hippocampus [120]. Taken together, results from studies in the hippocampus have demonstrated that EtOH exposure (both acute and *in vivo* conditions) dysregulates glutamatergic transmission, and that this effect of EtOH may produce impairments in hippocampal dependent learning and memory functions in alcohol dependent subjects.

In conclusion, review of the literature indicates that EtOH exposure (acute and *in vivo*) produces neuroplasticity in distinct brain subregions that play a role in binge/intoxication and preoccupation/anticipation stage of alcohol addiction. Based on these findings we hypothesize that these neuroadaptations by EtOH may further contribute to escalated drinking patterns of alcohol intake seen in moderate to severe AUD.

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DECLARATIONS OF INTEREST

The authors declare no conflict of interest.

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