Review

Synaptic plasticity mechanisms common to learning and alcohol use disorder

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Alcohol use disorders include drinking problems that span a range from binge drinking to alcohol abuse and dependence. Plastic changes in synaptic efficacy, such as long-term depression and long-term potentiation are widely recognized as mechanisms involved in learning and memory, responses to drugs of abuse, and addiction. In this review, we focus on the effects of chronic ethanol (EtOH) exposure on the induction of synaptic plasticity in different brain regions. We also review findings indicating that synaptic plasticity occurs in vivo during EtOH exposure, with a focus on ex vivo electrophysiological indices of plasticity. Evidence for effects of EtOH-induced or altered synaptic plasticity on learning and memory and EtOH-related behaviors is also reviewed. As this review indicates, there is much work needed to provide more information about the molecular, cellular, circuit, and behavioral consequences of EtOH interactions with synaptic plasticity mechanisms.

Different forms of synaptic plasticity

The most commonly studied forms of synaptic plasticity thought to contribute to learning and memory are long-term depression (LTD) and long-term potentiation (LTP). As the names imply, these changes involve long-lasting decreases and increases in synaptic efficacy, respectively. The mechanisms involved in LTD and LTP have been reviewed extensively, as have their potential roles in addiction (Collingridge et al. 2010; Grueter et al. 2012; Nestler 2013).

LTD measured in vitro

Different forms of LTD have been described at glutamatergic synapses, involving both pre- and postsynaptic mechanisms (Collingridge et al. 2010). The predominant mechanism underlying presynaptic LTD is decreased probability of neurotransmitter release (Upreti et al. 2013; Atwood et al. 2014b). Activation of a variety of G protein-coupled receptors (GPCRs) that signal through $G_{i/o}$-type G proteins can induce LTD at synapses throughout the brain (Atwood et al. 2014b).

Among the best-characterized forms of $G_{i/o}$-induced presynaptic LTD is that involving endocannabinoid (eCB) activation of the type 1 cannabinoid receptor (CB1) (Augustin and Lovinger 2018). The eCB–CB1 signaling system is present at a wide variety of synapses throughout the brain, where postsynaptic eCB production and release leads to activation of presynaptic CB1 receptors to initiate decreased probability of release. The eCB production and release usually involve increases in postsynaptic intracellular calcium and/or activation of G_q-coupled GPCRs (Castillo et al. 2012). In many cases, this synaptic depression outlasts CB1 activation, and this is defined at eCB–LTD (Castillo et al. 2012; Augustin and Lovinger 2018). Other signaling mechanisms have also been reported to produce presynaptic LTD (e.g., nitric oxide) (Upreti et al. 2013). The intra-terminal signaling mechanisms involved in $G_{i/o}$-induced presynaptic LTD expression appear to include decreased cAMP production and PKA activation, as well as protein translation involving presynaptic RNA (Yin et al. 2006; Castillo et al. 2012; Younts et al. 2016).

A widespread mechanism for postsynaptically expressed LTD is decreased function of synaptic AMPA-type glutamate ligand-gated ion channel-type receptors (GluAs or AMPARs) (Collingridge et al. 2010). This form of LTD is usually initiated by activation of NMDA-type glutamate receptors (GluNs or NMDARs) or other receptors/ion channels that can produce moderate increases in intracellular calcium concentration (Collingridge et al. 2010). This calcium increase activates intracellular signaling molecules including calmodulin, the calmodulin-activated protein phosphatase calcineurin (aka PP2B), protein phosphatase PP1, other signaling enzymes and receptor-associated proteins leading to reduced AMPAR levels at synapses (Collingridge et al. 2010). Alterations in AMPAR subunit content and decreases in NMDAR function have also been implicated in postsynaptic LTD (Dore et al. 2017). Postsynaptically expressed LTD has been observed in neurons throughout the brain and brainstem.

LTD also occurs at GABAergic synapses (McBain and Kauer 2009). The mechanisms underlying this plasticity involve some that are similar to those implicated in glutamatergic plasticity, but also some divergent intracellular cascades (McBain and Kauer 2009). Studies have shown that hippocampal eCB, $GABA_B$ and delta-opioid receptors can be involved in GABAergic LTD (for review, see Rozov et al. 2017). Endocannabinoid-dependent presynaptic GABAergic LTD is induced by high or low-frequency repetitive synaptic stimulation (Chevaleyre and Castillo 2003; Zhu and Lovinger 2007), L-type calcium channel activation (Adermark et al. 2009) or theta burst stimulation (Heifets et al. 2008; Jappy et al. 2016).

Postsynaptically expressed LTD also occurs at GABAergic brain synapses, with expression mechanisms that appear to involve decreased synaptic numbers and/or function of $GABA_A$-type ligand-gated ion channels (Kullmann and Lamsa 2011; Kodangattil et al. 2013). Theta-burst stimulation induces GABAergic LTD on hippocampal pyramidal neurons, with activation of $GABA_B$ receptors and suppression of AC/cAMP/PKA activity involved in LTD induction (Jappy et al. 2016). In addition, high-frequency stimulation at GABAergic synapses formed by parvalbumin-expressing interneurons in the hippocampus

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induces LTD that is mediated by delta-opioid, but not mu-opioid, receptors (Piskorowski and Chevaleyre 2013).

LTP measured in vitro

Presynaptically expressed LTP is less well characterized than other forms of synaptic plasticity. Nonetheless, there is evidence at a number of synapses that long-lasting increases in glutamate release are observed following certain patterns of afferent stimulation or pharmacological treatments (MacDougall and Fine 2014). A variety of different intra-terminal signaling cascades have been implicated in these increases, including increased cAMP/PKA signaling, nitric oxide actions on presynaptic enzymes, changes in presynaptic ion channel function, and increased phosphorylation of proteins involved in vesicle fusion (for review, see Yang and Calakos 2013). Perhaps the best characterized form of presynaptic LTP is observed at the glutamatergic synapses made by mossy fibers on CA3 pyramidal neurons in the hippocampus (Yeckel et al. 1999; Evstratova and Toth 2014). This LTP involves intra-terminal calcium increases, cAMP/PKA signaling and increased vesicle fusion/glutamate release.

Postsynaptically expressed LTP at glutamatergic synapses was the first type of synaptic plasticity to be discovered (Lomo 2018) and it is the best characterized form of plasticity, expressed in a wide variety of cortical and subcortical neurons. The cellular mechanisms that contribute to LTP are often the opposite of those underlying postsynaptic LTD, in this case involving increased, rather than decreased synaptic AMPAR function (Luscher et al. 2000; Herring and Nicoll 2016). Altered AMPAR subunit composition, sometimes associated with altered AMPAR single channel conductance, also appears to contribute to postsynaptic LTP (Benke et al. 1998; Beaulieu-Laroche and Harnett 2018). There is physiological and pharmacological evidence for transient synaptic expression of calcium-permeable AMPARs that lack GluA2 following LTP induction (Isaac et al. 2007). This transient expression is thought to help consolidate LTP expression. The molecular mechanisms underlying postsynaptic LTP begin with activation of NMDARs leading to relatively large increases in postsynaptic calcium. The calcium increase activates the calcium-calmodulin-dependent CamKII alpha protein kinase along with protein kinase C (Herring and Nicoll 2016). There is also increased cAMP production leading to activation of protein kinase A (Nguyen and Woo 2003). Activation of these kinases leads to phosphorylation of AMPARs that enhance synaptic localization and alter subunit structure. While alterations in AMPAR phosphorylation are implicated in both postsynaptic LTD (phosphorylation of GluA2, dephosphorylation of GluA1) and postsynaptic LTP (phosphorylation of GluA1), different amino acid residues appear to be involved in the phosphorylation changes that underlie the removal and insertion of receptors that is key to these forms of plasticity (Kessels and Malinow 2009).

LTP can also occur at GABAergic synapses, and both pre- and postsynaptic mechanisms have been implicated in this plasticity (Nugent and Kauer 2008; Maffei 2011). Theta frequency stimulation induces selective LTP of $GABA_A$ receptor-mediated synaptic responses that involves activation of $GABA_B$ and glutamate type I/II metabotropic receptors in hippocampus (Patenaude et al. 2003). GABA neurons in the ventral tegmental area (VTA) and accumbal GABAergic afferents also exhibit LTP after high frequency stimulation (Nugent et al. 2007; Simmons et al. 2017). However, much less is known about GABAergic LTP.

LTD and LTP measured in vivo

The mechanistic studies characterizing LTD and LTP discussed above were performed using brain slice preparations from various brain regions. However, there is ample evidence that LTD and LTP can be induced in the in vivo brain, beginning with the first characterization of LTP in the hippocampus (Bliss and Lomo 1973), and LTD in the cerebellum (Ito and Kano 1982), respectively. The reader is referred to studies showing in vivo LTP in different brain regions (Manahan-Vaughan 1997; Poschel and Manahan-Vaughan 2005; Chu et al. 2014).

Ex vivo indices of LTD and LTP

There is considerable interest in determining if synaptic plasticity occurs in vivo following environmental events, including learning and memory and exposure to drugs of abuse. Changes in synapse function, neuronal morphology/ultrastructure and molecular/biochemical responses in neurons (e.g., immediate-early gene expression) are involved in synaptic plasticity and have been used as ex vivo proxies for the occurrence of plasticity in vivo. Reviews have provided useful overviews of these approaches, including changes in dendritic spines and immediate early gene expression (Alvarez and Sabatini 2007; Minatohara et al. 2015). LTD and LTP involve changes in receptor expression or function that can be investigated by quantifying the expression levels of these ion channels or by several electrophysiological techniques. In this review we will focus on the electrophysiological indices of synaptic transmission most often used in these studies.

Investigators have used the "AMPA/NMDA ratio" as one index of plasticity, including following exposure to drugs of abuse (Citri and Malenka 2008; Kessels and Malinow 2009). This index is commonly measured by holding the membrane potential at positive potentials (for example, +40 mV), to completely relieve the Mg^{2+} block of NMDARs. A typical procedure is to record a dual component EPSC (mediated by both AMPAR and NMDAR) and then apply an NMDA antagonist to isolate the AMPA EPSC. The NMDA EPSC is obtained by digital subtraction of the AMPA EPSC from the dual component EPSC. Measurement of the AMPA EPSC can also be made at membrane potentials nearer to the resting level. The ratio can only be used to compare different conditions and the relative contributions of AMPA and NMDA receptors. This method can be affected by the adequacy of the neuronal space clamp and also assumes that there is no change in the calcium-impermeable AMPARs as rectification of these receptors can confound the measure (for review, see Kauer and Malenka 2007). Indeed, insertion of calcium-impermeable AMPARs is another index of plasticity and it can be estimated by examining rectification of EPSCs at different voltage-clamp steps and sensitivity to polyamine-based compounds that inhibit GluA2-lacking receptors (Isaac et al. 2007; Kessels and Malinow 2009).

Alterations in synaptic currents that report single-synapse responses have been used to determine the presence and locus of synaptic plasticity. Miniature postsynaptic currents (mPSCs) at GABAergic (mIPSCs) and glutamatergic (mEPSCs) synapses are measured in the absence of action potential firing and report the frequency, amplitude and kinetics of responses at individual synapses. The mPSC frequency generally provides an index of the combined effects of synapse number and probability of release (Kavalali 2015). Additionally, responses to local neurotransmitter application using chemical "uncaging" (Araya 2014) can be used to measure the amplitude and kinetics of single synapse currents, providing information about postsynaptic responsiveness.

Measurement of unitary PSCs induced by stimulation of a single presynaptic neuron (Bolshakov et al. 1997), which is best achieved with paired pre- and postsynaptic recordings are also used to determine the presence of pre- or postsynaptic plasticity. This latter technique allows the investigator to use quantal analysis and estimation of the success or failure to induce a synaptic response (method of failures) to determine probability of release at a single synapse.

Another related technique takes advantage of the fact that Sr^{2+} can substitute for Ca^{2+} in excitation/secretion-coupling, but with lower affinity for the relevant divalent cation binding sites (Oliet et al. 1996). The frequency, amplitude and kinetics of these asynchronous PSCs can then be used as in mPSC measurement to determine if pre- or postsynaptic plasticity has occurred. Using these techniques, investigators have determined if pre- or postsynaptically expressed LTD and LTP occur following in vivo experiences.

The relationship between intraterminal Ca^{2+} and probability of release leads to changes in responses to paired synaptic stimuli, as residual Ca^{2+} from the first stimulus will influence release in response to the second stimulus (Zucker and Regehr 2002). In general, an increase in this paired-pulse ratio, deemed paired-pulse facilitation (PPF), indicates decreased probability of release (larger effect of residual Ca^{2+} if levels are lower after the first pulse). In contrast, paired-pulse depression (PPD) is indicative of increased probability of release. These measures have been used to determine if presynaptically expressed LTD and LTP have occurred in vivo. However, it must be noted that changes in paired-pulse ratio generally occur over a restricted range of baseline probability of release values (Atzori et al. 2001; Zucker and Regehr 2002), and thus this technique has limited sensitivity.

Brief summary of current evidence for roles in learning and memory

Since the discovery of LTP over 40 yr ago, there has been a longstanding effort to determine if and how synaptic plasticity contributes to learning and memory. This subject has been reviewed extensively in recent years (Collingridge et al. 2010), and thus it will be discussed only briefly at present and the reader is referred to more comprehensive reviews.

Early experiments assayed if changes in synaptic efficacy observed in vivo coincided with learning. Most of these studies focused on the hippocampal formation as LTP was well characterized in that brain region. Evidence that training induces an LTP-like enhancement of synaptic efficacy in vivo has been observed in hippocampus using Pavlovian conditioning (Gruart et al. 2006) and in amygdala using fear conditioning (Rogan et al. 1997). Hippocampal LTD- and depotentiation-like synaptic changes have been reported using novelty detection and Pavlovian conditioning procedures (Manahan-Vaughan and Braunewell 1999; Abraham et al. 2002; Kemp and Manahan-Vaughan 2004; Li et al. 2005; Gruart et al. 2006), and altered hippocampal LTD is associated with stress-induced impairment of spatial memory retrieval (Wong et al. 2007). In the perirhinal cortex, an LTD-like change in synaptic transmission accompanies familiarity discrimination (Brown and Bashir 2002).

Other studies attempted to induce synaptic plasticity in key circuits to determine if these manipulations had effects on learning and memory. In the Barnes and McNaughton laboratories, investigators induced LTP in the dentate gyrus with electrical stimulation of the perforant pathway, and this manipulation produced a deficit in spatial learning and recall of recently acquired, but not previously acquired spatial memories (McNaughton et al. 1986). Disruption of Pavlovian conditioning was observed following strong LTP induction at CA3-CA1 hippocampal synapses (Gruart et al. 2006). This memory disruption has been suggested to involve saturation of the LTP process that prevents further learning-associated increases in synaptic efficacy, although other explanations such as induction of pathological neuronal synchrony have not been ruled out.

Optogenetics has also been used to determine if plasticity induction produces learning and/or memory. Nabavi and coworkers used a fear-conditioning paradigm coupled with optogenetic stimulation and found that induction of LTD by low-frequency stimulation of auditory inputs to amygdala inactivated fear memories (Nabavi et al. 2014). Induction of LTP could induce behaviors indicative of reactivation of the fear memory. Interestingly, LTP could not reverse extinction, consistent with the idea that different types of plasticity contribute to this form of learning (Izquierdo et al. 2016).

Alcohol use disorder and memory deficits

Among the psychiatric disorders, alcohol use disorder (AUD) is one of the leading causes of worldwide deaths, victimizing around 129 thousand people in 2015 (Global Health Estimates 2015: Deaths by Cause, Age, Sex, by Country and by Region, 2000–2015). Furthermore, the prospective epidemiology does not seem very positive, as the 2014 Global Health Observatory data repository (WHO Global Information System on Alcohol and Health) estimates that 14% of the world's 15–19-yr-old are drinkers and there is an increasing concern with excessive binge EtOH consumption particularly in this age group.

EtOH exposure triggers cognitive deficits that include mild cognitive impairment, blackouts during strong intoxication (Hermens and Lagopoulos 2018), memory deficits and executive dysfunction in EtOH-dependent individuals (Bates et al. 2002; Pitel et al. 2007; Chen et al. 2018). These changes are associated with neuroadaptations in brain regions implicated in learning and memory including, but not limited to, the amygdala complex, cortex, hippocampus, and striatum (Abrahao et al. 2017). These neuroadaptations also contribute to alterations in the rewarding and aversive effects of ethanol (EtOH), as well as changes in behaviors related to EtOH consumption (Abrahao et al. 2017). Indeed, these behavioral changes involve learning and memory-like processes.

There is growing evidence that prolonged EtOH exposure produces or alters synaptic plasticity (Lovinger and Roberto 2013; Zorumski et al. 2014; Abrahao et al. 2017; Morisot and Ron 2017). This review will describe current evidence for EtOH-induced alterations in the induction of synaptic plasticity in different brain regions. We will also comment on evidence from ex vivo examination of indices that in vivo EtOH exposure induces plasticity. Some discussion of the mechanisms underlying these plasticity changes will also be included. The potential roles that these changes in plasticity play in EtOH-related behaviors and cognitive disruption will be discussed.

Plasticity induced by chronic ethanol exposure or drinking

Studies examining EtOH effects on synaptic plasticity have been ongoing for decades. There is considerable evidence that acute application of EtOH reduces LTP (Zorumski et al. 2014). Acute EtOH effects on LTD have also been examined in different brain regions (Valenzuela et al. 2010; Zorumski et al. 2014). While these findings are interesting, especially in relation to the cognitive effects of EtOH, this review will focus on chronic effects of the drug that alter synaptic plasticity and ex vivo indices of plasticity.

Alterations in LTD and LTP

Experiments in which investigators compared induction of LTD and LTP in brain slices from control and chronic EtOH-exposed rodents constituted the bulk of early studies examining effects on glutamatergic and GABAergic synaptic plasticity (McCool 2011; Olsen and Spigelman 2012; Lovinger and Roberto 2013; Zorumski et al. 2014; Abrahao et al. 2017). Here, we pay

particular attention to the time course of the synaptic plasticity changes during early and protracted withdrawal and the different types of synaptic plasticity. While it is interesting to compare these plasticity changes to those induced by other drugs of abuse, this topic is not the focus of the present review. We refer readers to other outstanding reviews that cover this topic (Hyman et al. 2006; Kauer and Malenka 2007; Luscher and Malenka 2011).

Chronic EtOH exposure impairs LTD in hippocampus (Roberto et al. 2002; Thinschmidt et al. 2003; Coune et al. 2017), dorsal striatum (Cui et al. 2011; DePoy et al. 2013, 2015) the dopamine D1 receptor-containing neurons of the nucleus accumbens (NAc) shell (Jeanes et al. 2011; Spiga et al. 2014; Renteria et al. 2018b) and the NAc core (Abrahao et al. 2013). Both NMDA and CB1-dependent LTD are impaired by chronic EtOH exposure. In addition, recent work observed blunted mGluR5-induced LTD in the hippocampus shortly after cessation of EtOH exposure (Wills et al. 2017). Chronic EtOH exposure also induces loss of CB1-dependent presynaptic LTD in the dorsolateral striatum (DLS) (Xia et al. 2006; Adermark et al. 2011; DePoy et al. 2013). At GABAergic synapses, eCB-dependent LTD in striatum is also impaired following chronic EtOH drinking, facilitating a long-lasting potentiation of striatal output in response to glutamatergic transmission (Adermark et al. 2011).

EtOH exposure reversibly inhibits postsynaptically expressed LTP (Roberto et al. 2002) in hippocampus (Durand and Carlen 1984; Thinschmidt et al. 2003; Stephens et al. 2005), basolateral amygdala (BLA) (Stephens et al. 2005), and the bed nucleus of the stria terminalis (Francesconi et al. 2009). Enhanced expression of NMDA-receptor mediated spike-timing-dependent LTP is observed in medial PFC (Kroener et al. 2012), orbitofrontal cortex (OFC) (Nimitvilai et al. 2016), and GluN2B-NMDAR-dependent LTP is enhanced in the DMS (Wang et al. 2012).

The changes in synaptic plasticity induction produced by in vivo EtOH exposure follow different time-courses following withdrawal depending on the brain region as described in the following paragraph and in Figure 1. These changes can result from either a direct inhibition of the induction of plasticity or from occlusion of plasticity induction by plasticity that occurred prior to the recording.

Figure 1 summarizes specific changes in LTP and LTD during early or protracted withdrawal for four brain regions implicated in learning and memory and EtOH-related behaviors. Although deficits in LTD and LTP in hippocampus seem to be stable during early and protracted withdrawal, striatal plasticity deficits often reach their maximum level within 48 h of the last EtOH exposure (Xia et al. 2006; Wang et al. 2012). In addition, while LTD changes in the NAc shell occur early in EtOH withdrawal (Jeanes et al. 2014; Renteria et al. 2017), LTD alterations in the NAc core occur in late withdrawal (Abrahao et al. 2013; Renteria et al. 2018b), but only in those mice that developed behavioral sensitization (Abrahao et al. 2013). Increased LTP expression occurs in both the lateral orbitofrontal cortex (OFC) (Nimitvilai et al. 2016) and the medial prefrontal cortex (mPFC) (Kroener et al. 2012) following chronic EtOH exposure, but as yet there is little information on the time course of these changes, and the effects of different exposure protocols.

GABAergic synapses also appear to regulate EtOH effects on cortical plasticity. In humans, very low doses of EtOH (BECs < 5 mM), but not GABAergic hypnotic drugs, suppress LTP-like plasticity, measured by paired associative transcranial magnetic stimulation (PAS–LTP) used in healthy subjects (Lucke et al. 2014). Binge EtOH exposure also impairs PAS–LTP in the motor cortex of EtOH binge drinkers (Loheswaran et al. 2016). In contrast, EtOH enhances PAS–LTD plasticity in human cortex (Fuhl et al. 2015). Both effects may be associated with EtOH enhancement of extrasynaptic $GABA_A$ receptor-mediated tonic inhibition. Studies in laboratory animals would be necessary to identify the specific role of GABAergic tonic inhibition in regulating EtOH effects on plasticity at synapses on cortical neurons.

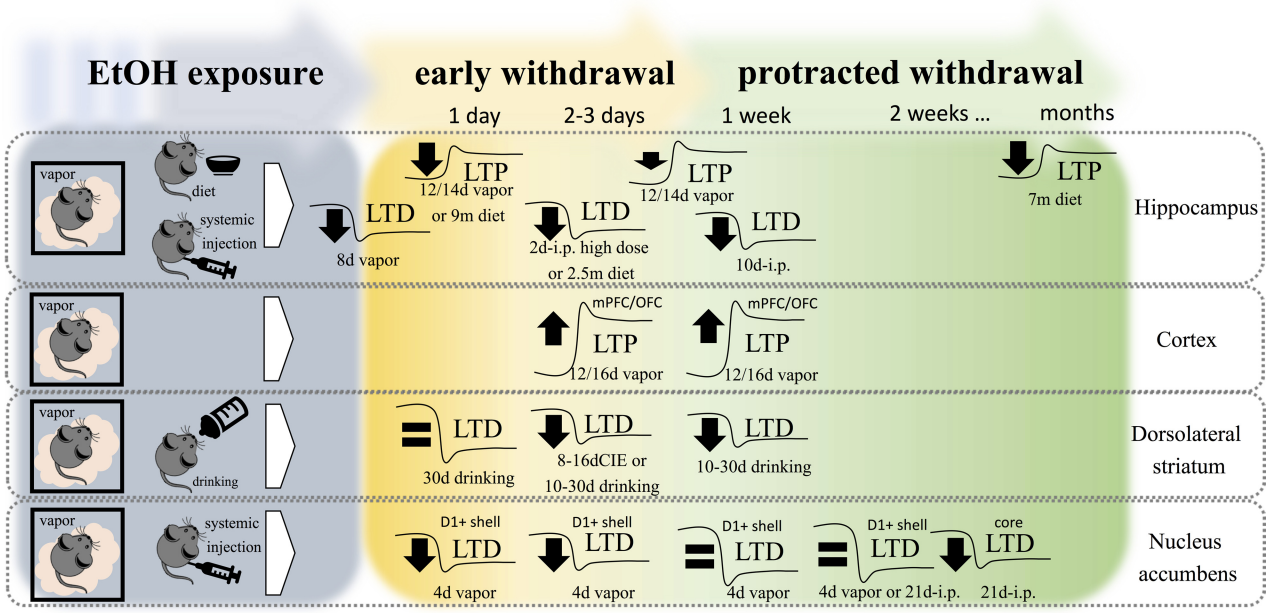

Figure 1. Plasticity changes during withdrawal after chronic ethanol exposure in four brain regions important for learning and memory processes: hippocampus, cortex (medial prefrontal cortex, mPFC, and orbital frontal cortex, OFC), dorsolateral striatum, and nucleus accumbens (shell and core). Experiments used vapor chambers, ethanol liquid diet or systemic injections (intra-peritoneal. i.p.) and measures of long-term depression (LTD) or long-term potential (LTP). The length of ethanol treatment is represented under each plasticity change: (d) days, (m) months. Blue = EtOH exposure paradigm, yellow = early withdrawal (1–3 d) and in green = protracted withdrawal (1 wk up to months).

Alterations in ex vivo indices of synaptic plasticity

Several studies have reported evidence of plasticity at GABAergic and glutamatergic synapses after chronic EtOH exposure, and these have been reviewed in depth recently (Lovinger and Kash 2015; Abrahao et al. 2017; Morisot and Ron 2017). Thus, we will focus on those changes that are most indicative of in vivo LTD and LTP.

Increased NMDAR function following chronic EtOH exposure has been observed in several brain regions (Floyd et al. 2003; Carpenter-Hyland and Chandler 2007; Wang et al. 2007, 2011; Morisot and Ron 2017). The increased function of this receptor could set up conditions in which LTP is more readily induced in vivo. In the dorsomedial striatum (DMS) it appears that this sequence of events occurs following EtOH exposure and consumption. The process of increasing NMDAR function begins during acute EtOH exposure. Brain slice recordings in DMS show that application of EtOH inhibits NMDA–EPSCs (Popp et al. 1998; Wang et al. 2007; Yin et al. 2007), as observed in other brain regions (Lovinger et al. 1989). This inhibition is maintained throughout EtOH application, but when EtOH is washed from the slice the NMDA–EPSC is increased in amplitude above the original pre-EtOH amplitude. This EPSC increase persists for the duration of recordings and thus has been termed long-term facilitation (LTF) (Wang et al. 2007). The mechanisms underlying this LTF process involve Fyn kinase-mediated phosphorylation of the GluN2B NMDA subunit. Enhanced function of GluN2B-containing NMDARs has also been observed in DMS brain slices examined following several days of EtOH exposure or after weeks of voluntary EtOH consumption in an intermittent access paradigm (Wang et al. 2011). The mechanisms underlying this increase appear to be the same as LTF.

The initial LTF observed following acute exposure is not accompanied by any change in AMPA-EPSCs. However, following chronic EtOH consumption or noncontingent in vivo exposure increased AMPA-EPSCs are observed (Wang et al. 2012). Thus, it was proposed that LTF of NMDA–EPSCs induces an LTP-like process that enhances AMPAR function if given enough drug exposure and time in vivo. The enhanced GluN2B-NMDAR function appears to have a role in initiating this LTP-like process. This AMPAfication occurs mainly at glutamatergic synapses onto striatal medium spiny projection neurons (MSNs) that are part of the "direct" striatonigral pathway (Wang et al. 2015). This provides a mechanism through which chronic EtOH enhances striatal output that eventually enhances cortical activation that may favor enhanced drug seeking.

The majority of studies analyzed GluN expression or currents in early withdrawal after chronic EtOH exposure. Protracted withdrawal may modulate glutamate receptors levels differently. One week after the last exposure to EtOH, GluN mRNA levels are decreased in central amygdala, which is accompanied by decreased PPF of NMDA–EPSCs (Roberto et al. 2006). In the NAc, 2 wk of withdrawal from EtOH treatment resulted in less expression of GluN1, but no significant change in the surface expression of GluN2A, GluN2B, or GluA2/3 AMPA channels in the neuronal membrane, which was associated with impaired NMDA-dependent LTD in EtOH-sensitized mice (Abrahao et al. 2013). In PFC, the increased GluN1 and GluN2B expression observed in early withdrawal is not present after 1 wk of withdrawal (Kroener et al. 2012).

There is also evidence for LTP-like alterations at synapses in several other brain regions based on increases in AMPAR function and changes in AMPA/NMDA ratios and rectification of AMPA-EPSCs. Analysis of glutamatergic transmission in VTA dopaminergic neurons revealed evidence of increased postsynaptic AMPAR function during a short (12–24 h) withdrawal period following weeks of intermittent EtOH drinking (Stuber et al. 2008). While the increased AMPA/NMDA ratio observed in this study does not provide definitive evidence of increased AMPAR function, this conclusion was supported by increased amplitude of AMPAR-mediated mEPSCs, with no change in paired-pulse facilitation. Increased AMPAR-mediated glutamatergic synaptic responses are observed in NAc MSNs following weeks of EtOH exposure via gavage (Marty and Spigelman 2012). A similar increase in AMPAR-mediated glutamatergic transmission was observed in periaqueductal gray neurons after withdrawal following 4 d of EtOH exposure in a paradigm that fosters withdrawal seizures (Long et al. 2007).

Biochemical studies have revealed ample evidence of increased AMPAR subunit expression in different brain regions following chronic EtOH exposure (for reviews, see Holmes et al. 2013; Hwa et al. 2017), although some studies found no changes in hippocampus (Ferreira et al. 2001; Puglia and Valenzuela 2010). A recent study indicates that EtOH increases the rectification of AMPAR-mediated EPSCs in NAc MSNs, a change generally associated with increased expression of receptors lacking the GluA2 subunit (Laguesse et al. 2017). The intracellular signaling pathway implicated in this synaptic plasticity involves Prosapip1-dependent postsynaptic protein interactions and signaling through the mammalian target of rapamycin complex (Laguesse et al. 2017). This study also provides evidence that this signaling pathway can regulate EtOH reward, seeking, and drinking.

There is also evidence of presynaptic glutamatergic plasticity following chronic EtOH exposure or drinking (for review, see Lovinger 2017). In rat BLA principal neurons paired pulse-facilitation of EPSCs was decreased and frequency of mEPSCs increased following chronic intermittent EtOH exposure and withdrawal (Lack et al. 2007). A similar decrease in paired pulse-ratio of EPSCs was observed in GABAergic neurons of the CeA in one study (Zhu et al. 2007), but not in another (Roberto et al. 2004b). Increased mEPSC frequency was also observed in serotonergic neurons of the dorsal raphe nucleus (Lowery-Gionta et al. 2015). In the monkey putamen, mEPSC frequency is increased following long-term EtOH consumption interspersed with periods of forced abstinence, and this physiological change is accompanied by increased dendritic spine density on putamen MSNs (Cuzon Carlson et al. 2011). Thus, chronic EtOH appears to produce a presynaptic LTP-like change at glutamatergic synapses in several brain regions, but it is not yet clear if this involves increased probability of release, increased synaptic numbers, or both.

There is much less information about chronic EtOH effects on GABAergic transmission that is indicative of in vivo plasticity, but in general the findings provide evidence of presynaptic LTD-like changes following chronic exposure or drinking. Increased paired-pulse facilitation was observed at GABAergic synapses of lateral/paracapsular neurons onto principal neurons in the BLA following chronic EtOH exposure (Diaz et al. 2011). Interestingly, synapses made by local interneurons were not affected by this treatment (Diaz et al. 2011). A similar paired-pulse facilitation increase was observed at GABAergic synapses in dentate gyrus granule neurons from monkeys that consumed EtOH for 18 mo (Ariwodola et al. 2003). In rat hippocampal CA1 pyramidal neurons, the frequency of mIPSCs was decreased following chronic intermittent EtOH exposure (Cagetti et al. 2003). Decreased mIPSC frequency is observed when recording from MSNs in the mouse DLS and DMS and monkey caudate and putamen following chronic EtOH consumption (Cuzon Carlson et al. 2011, 2018; Wilcox et al. 2014). These findings indicate that several GABAergic synapses show decreased probability of release or numbers of synapses following chronic EtOH exposure or drinking. One exception is synapses in the CeA that show decreased paired-pulse ratios and increased mIPSC frequency in EtOH-dependent rats (Roberto et al. 2004a).

Changes in $GABA_A$ receptor subunit expression and some evidence of changes in postsynaptic receptor function have also been observed following chronic exposure or drinking, and these findings have been nicely summarized in recent reviews (Lovinger and Roberto 2013; Roberto and Varodayan 2017). These postsynaptic changes could signal LTD or LTP-like changes at GABAergic synapses in several brain regions.

Researchers are now using optogenetic tools to identify specific synapses that are affected by EtOH. For example, excessive EtOH intake potentiates AMPA- and NMDA-mediated synaptic transmission at the medial PFC input and increases the probability of glutamate release at the basal lateral amygdala (BLA) afferents to the DMS (Ma et al. 2017). These changes could explain the effect of chronic EtOH exposure on striatal LTP, as paired activation of the medial PFC and BLA inputs using dual-channel optogenetics induced robust LTP of the corticostriatal input to the DMS (Ma et al. 2017).

The idea that synaptic efficacy is adjusted to maintain an optimal level for proper neuronal and circuit function (Hengen et al. 2013; Keck et al. 2013) fostered research on plasticity mechanisms involved in this process. These forms of plasticity are termed homeostatic synaptic plasticity (HSP) (Turrigiano 2012). Experimental evidence for HSP comes from studies in which strong perturbations of neuronal or synaptic function such as blockade of neuronal firing or ionotropic receptors are applied to neurons (often primary cultures) for days. These treatments generally elicit changes in synaptic efficacy that are opposite to those produced by the treatment itself (e.g., increased synaptic AMPAR function following chronic TTX treatment) (Turrigiano 2012). While these studies are instructive, this concept is nothing new in the drug abuse research field. There has been ample evidence for some time that drugs of abuse produce homeostatic changes in synaptic transmission that compensate for changes in synaptic function or altered circuit function.

In the case of EtOH, the most obvious examples of homeostatic changes in transmission are the increases in NMDAR, and especially GluN2B-containing NMDAR activity following chronic exposure, as discussed earlier in this review (for reviews, see Carpenter-Hyland and Chandler 2007; Morisot and Ron 2017). This increased activity is presumably triggered by acute EtOH inhibition of NMDARs, and we have already discussed how activation of protein kinases and phosphorylation of GluN2B is involved in this plasticity (Wang et al. 2007).

Compensatory changes in GABAergic transmission are also observed following chronic EtOH exposure at synapses where acute exposure increases GABAergic transmission. Potentiation by acute EtOH can involve increases in firing of GABAergic neurons, increased GABA release from terminals or increased $GABA_AR$ function (for reviews, see Abrahao et al. 2017; Roberto and Varodayan 2017). Homeostatic compensation usually involves decreased $GABA_AR$ function with changes in expression of specific receptor subunits.

There is less information about how synaptic efficacy changes in response to EtOH effects alter excitability within microcircuits or circuits. Exposure to EtOH or NMDAR antagonists induces enlargement of dendritic spines in hippocampal neurons in culture (Carpenter-Hyland and Chandler 2006). Changes in expression and function of calcium-activated potassium channels also appear to compensate for EtOH effects on neuronal function in the hippocampus and VTA (for review, see Mulholland et al. 2009).

Many of the molecular and synaptic changes induced by chronic EtOH exposure would tend to restore levels of synaptic, neuronal, and circuit function to predrug exposure levels when the drug itself is present (e.g., increased glutamatergic transmission that compensates for NMDAR inhibition). However, when EtOH is removed during forced or voluntary abstinence these homeostatic changes can drive neuronal and circuit function to levels higher or lower than those observed prior to drug exposure. Thus, what is initially homeostatic may well become pathological, especially following the sort of repeated withdrawal episodes characteristic of AUD.

Possible roles in Alcohol Use Disorders

Ultimately, it will be crucial to understand how the plastic changes at synapses in different brain regions contribute to alterations in learning and memory and EtOH-related behaviors. Most studies have focused on examining different subregions of the striatum and the afferents that innervate these areas.

The NAc has well characterized roles in reward-driven behavior, cue-driven drug self-administration, and a variety of drug-related associative learning processes including conditioned place preference and sensitization (McBride et al. 1999; Gardner 2011; Camarini and Pautassi 2016; Scofield et al. 2016). The Prosapip-1-dependent changes in AMPAR-mediated synaptic transmission in NAc appear to play a role in controlling EtOH self-administration (Laguesse et al. 2017). LTD impairment in the accumbens core is also associated with behavioral sensitization: while blunted NMDA dependent accumbal LTD is associated with the development of sensitization (Abrahao et al. 2013), blunted hippocampal LTD is observed only in sensitization-resistant mice (Coune et al. 2017).

Plasticity within the dorsal striatum appears to be implicated in control of EtOH seeking and drinking, and also in cognitive and behavioral consequences of chronic exposure to the drug (Corbit et al. 2012; Gremel and Lovinger 2017). Potentiation of glutamatergic synapses onto direct-pathway MSNs in the DMS appears to play an important role in driving goal-directed EtOH drinking. Injection of Fyn kinase or Glun2B–NMDA antagonists into DMS reduces EtOH seeking and drinking in an operant paradigm in which these processes are driven by goal-directed strategies (Wang et al. 2010). Intra-DMS injection of AMPAR and D1 dopamine receptor antagonists have similar effects (Wang et al. 2012, 2015). Overall, these findings indicate that an LTP-like process that enhances output from the DMS direct pathway is an important step in the development of goal-directed EtOH seeking and drinking.

Recent evidence indicates that in vivo induction of LTD and LTP in mice after exposure to EtOH can modulate EtOH-seeking behavior (Ma et al. 2018). This work showed that application of an LTP-inducing protocol in the DMS caused a long-lasting increase in EtOH-seeking behavior, while the LTD protocol decreased this behavior in mice previously exposed to EtOH (Ma et al. 2018). Additional studies of this type will be useful in determining if and how plasticity in different brain regions can alter EtOH-related behaviors. With the increasing application of optogenetic techniques, these studies can target specific afferent inputs to brain regions of interest.

EtOH seeking and drinking can also involve non-goal-directed/habitual aspects depending on the circumstances of drug exposure (Corbit et al. 2012; O'Tousa and Grahame 2014). The DLS has important roles in control of habitual and inflexible behaviors (Yin and Knowlton 2006). There is growing evidence that chronic EtOH exposure enhances habit learning (Corbit et al. 2012; Renteria et al. 2018a), and other behaviors that involve the DLS, and altered LTD in DLS appears to be involved in these behavioral changes (DePoy et al. 2013).

Studies have related plastic changes in synaptic transmission within the amygdala to changes in anxiety and rewarding drug effects following chronic EtOH exposure. The pre- and postsynaptic changes in AMPAR-mediated glutamatergic synaptic responses in the BLA appear to have roles in the anxiogenic behavior observed

during withdrawal (Lack et al. 2007). Extinction of conditioned fear responses is another behavior that is altered by chronic EtOH exposure (Tipps et al. 2014; Butler et al. 2016), and altered NMDAR-dependent synaptic plasticity at PFC-BLA synapses appears to have a role in this learning alteration (Holmes et al. 2012). Conditioned place preference for EtOH appears to involve changes in AMPAR-mediated synaptic transmission in the CeA (Zhu et al. 2007).

Future directions

Ultimately, we hope to make the case that additional work is needed to establish the mechanisms underlying EtOH effects on synaptic plasticity. In the following paragraphs, we suggest a few general directions for future research in addition to the more specific ideas presented earlier in this review.

It has been hypothesized that different drugs of abuse induce similar deficits in synaptic plasticity in the reward system (Luscher and Malenka 2011; Mameli and Luscher 2011). Indeed, investigators have reported similarities in psychostimulant- opioid- and EtOH-induced deficits in plasticity (Korpi et al. 2015), especially changes in AMPA/NMDA ratio after short-term withdrawal (Luscher and Malenka 2011). However, there are particular effects of each drug of abuse, including primary molecular targets, time courses of drug action and withdrawal, and circuit/behavioral changes produced by the different drugs that must be taken into account to better understand how altered synaptic plasticity contributes to use disorders for the different drugs. For example, loss of endocannabinoid-dependent LTD is observed following exposure to several drugs in addition to ethanol (Mato et al. 2005; Xia et al. 2006; Adermark et al. 2011; Atwood et al. 2014a). However, the mechanisms underlying these effects are likely to be different, as cannabinoid drugs down-regulate receptor function, while EtOH may have a more general effect on intraterminal signaling mechanisms involved in presynaptic LTD (Hoffman et al. 2003; Mato et al. 2005; Lovinger 2017). Given the different primary molecular targets of ethanol and other drugs of abuse, it is likely that compensatory plasticity involving changes in these target molecules would also differ for the different substances. Acute ethanol-induced increases in GABA release are often followed by decreased release after chronic exposure as discussed earlier in this review, and these effects may differ with drugs that do not directly target presynaptic GABAergic terminals. Chronic cocaine administration produces changes in GABAergic transmission in the ventral pallidum and VTA (Bocklisch et al. 2013; Kupchik et al. 2014) but as yet there is no direct comparison to EtOH effects in these regions. For these reasons, the alcohol research field should not only look for effects that are similar to and different from those of other drugs of abuse, but also develop new strategies to understand the sequence of neuroadaptations following acute and chronic EtOH exposure and withdrawal.

More attention should be given to different withdrawal time points after EtOH exposure. As observed in Figure 1, deficits in plasticity in the striatal regions and hippocampus can change with time after the last ethanol exposure. Much less is known in the cortex and other brain regions. It is postulated, for example, that withdrawal-dependent plasticity leads to incubation of psychostimulant craving/relapse (summarized in Dong et al. 2017), but similar data are lacking for EtOH. A comprehensive understanding of the dynamic changes in plasticity during withdrawal following EtOH exposure is necessary to better investigate molecular targets potentially important for the treatment of craving and relapse. It is also important to investigate different types of plasticity as they may have different functions in the behavioral effects of EtOH.

We also consider very important that future studies examine how, where and when GABAergic plasticity occurs and how these synaptic changes interact with glutamatergic plasticity. The effect of EtOH on the GABAergic system involves changes in neurotransmitter release, GABA receptor function and GABAergic neuron intrinsic excitability (for review, see Abrahao et al. 2017). Furthermore, there is a large literature indicating that ethanol effects on GABAergic synaptic transmission are involved in the behavioral actions of the drug (for review, see Abrahao et al. 2017). However, much less is understood about how EtOH can interfere with plasticity at GABAergic synapses.

While the findings described in this review represent a good start, more work is clearly needed to understand the many ways in which synaptic plasticity contributes to the cognitive and addictive effects of EtOH.

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