Presynaptic Ethanol Actions: Potential Roles in Ethanol Seeking

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Abstract

Ethanol produces intoxication through actions on numerous molecular and cellular targets. Adaptations involving these and other targets contribute to chronic drug actions that underlie continued and problematic drinking. Among the mechanisms involved in these ethanol actions are alterations in presynaptic mechanisms of synaptic transmission, including presynaptic protein function and excitation-secretion coupling. At synapses in the central nervous system (CNS), excitation-secretion coupling involves ion channel activation followed by vesicle fusion and neurotransmitter release. These mechanisms are altered by presynaptic neurotransmitter receptors, and prominently by G-protein coupled receptors (GPCRs). Studies over the last 20–25 years have revealed that acute ethanol exposure alters neurotransmitter secretion, with especially robust effects on synapses that use the neurotransmitter gamma-aminobutyric acid (GABA). Intracellular signaling pathways involving second messengers such as cyclic AMP and calcium are implicated in these acute ethanol actions. Ethanol-induced release of neuropeptides and small molecule neurotransmitters that act on presynaptic GPCRs also contribute to presynaptic potentiation at synapses in amygdala and hippocampus, and inhibition of GABA release in the striatum. Prolonged exposure to ethanol alters neurotransmitter release at many CNS GABAergic and glutamatergic synapses, and changes in GPCR function are implicated in many of these neuroadaptations. These presynaptic neuroadaptations appear to involve compensation for acute drug effects at some synapses, but "allostatic" effects that result in long-term resetting of synaptic efficacy occur at others. Current investigations are determining how presynaptic neuroadaptations contribute to behavioral changes at different stages of alcohol drinking, with increasing focus on circuit adaptations underlying these behaviors. This chapter will discuss the acute and chronic presynaptic effects of ethanol in the CNS, as well as some of the consequences of these effects in amygdala and corticostriatal circuits that are related to excessive seeking/drinking and ethanol abuse.

Keywords

Alcohol; Addiction; Synaptic transmission; GABA; Glutamate; Endocannabinoid; Synaptic Plasticity; Amygdala; Cortex; Striatum; Long-term depression

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Excitation-Secretion Coupling and Modulation at CNS Synapses

Communication between neurons generally occurs at synapses in which neurotransmitters are stored in and released from vesicles. When a neuronal action potential reaches the presynaptic terminal, the depolarization activates voltage-gated calcium channels (VGCCs) that allow calcium to enter the terminal. The increased intraterminal calcium stimulates vesicle fusion in a process known as excitation-secretion coupling (Catterall and Few 2008). Low rates of vesicle fusion also occur in the absence of excitation-secretion coupling, and this fusion appears to involve vesicle and plasma membrane-associated proteins (Kavalali 2015). Upon release, the neurotransmitter is available to bind to receptor proteins that either directly gate ion flux (ligand-gated ion channels, LGICs) or act through intracellular GTP/GDP-binding proteins (G proteins) that alter signaling processes (G protein-coupled receptors, GPCRs) (Betke et al. 2012; Latek et al. 2012).

While postsynaptic receptors are well known to transduce the signals necessary for anterograde transmission, presynaptic receptors have important roles in feedback alterations in the released neurotransmitter (via "autoreceptors") or crosstalk to alter release of other neurotransmitters (via "heteroreceptors"). Both LGICs and GPCRs serve as presynaptic receptors. The LGICs directly influence excitability of terminals (Engelman and MacDermott 2004; Pinheiro and Mulle 2008), and although these effects are interesting they will not be considered in any detail in the remainder of this chapter given the relative lack of information on ethanol interaction with these presynaptic receptors. The presynaptic GPCRs work through a variety of heterotrimeric G-proteins and signaling pathways. The heterotrimeric G-proteins consist of obligate α, β and γ subunits, with the latter forming stable β/γ complexes. The G-proteins are generally classified according to the type of α subunit present in the complex, and there are several major α subtypes. In this review the focus will be on three subtypes, Gαi/o, Gαq and Gαs/olf. Upon GPCR activation the heterotrimeric complex separates into free α and β/γ components that then bind to intracellular signaling proteins to alter many aspects of cell biochemistry, gene expression and physiology (Oldham and Hamm 2006).

Activation of GPCRs that couple to Gi/o generally inhibits excitation-secretion coupling and vesicle fusion, and hence neurotransmitter release (Atwood et al. 2014; Miller 1998). The predominant mechanism involved in this modulation is inhibition of the VGCCs that mediate excitation-secretion coupling (Herlitze et al. 1996; Ikeda 1996). However, there is also strong evidence for direct G-protein inhibition of vesicle release (Blackmer et al. 2001). It must be emphasized that the Gβ/γ subunit produces these actions by direct binding to channels and vesicle associated proteins. The Gαi/o subunit inhibits adenylyl cyclase (AC), and thus reduces intracellular cyclic AMP levels (Oldham and Hamm 2006). Inhibition of this enzyme is also implicated in inhibition of neurotransmitter release, especially in long-lasting inhibition (Atwood et al., 2014; Seino and Shibasaki, 2005).

A wide variety of Gi/o-coupled GPCRs exist, with a subtype for almost every major neurotransmitter and neuromodulator. Many of these receptors will be discussed throughout this review, with a strong emphasis on the type 1 cannabinoid receptor (CB1). The CB1 receptor is the target of Δ9-tetrahydrocannabinol, the major psychoactive

ingredient in preparations of cannabis sativa. This receptor is normally activated by the endocannabinoid (eCB) fatty acid derivatives produced by hydrolysis of arachidonoyl membrane lipids (namely arachidonoyl ethanolamide, or AEA also known as anandamide, and 2-arachidonoylglycerol, or 2-AG) (Araque et al. 2017). Functions of the gamma-aminobutyric acid B (GABA$_B$) receptor and the metabotropic glutamate receptor type 2 (mGluR2) will also be discussed in some detail.

The GPCRs that couple to Gq-containing GPCRs activate the hydrolysis of membrane phospholipids by phospholipases, a mechanism activated by the Gαq subunit (Oldham and Hamm 2006). The best-known pathway is activation of phospholipase C to catalyze the generation of diacylglycerol (DAG) and inositol phosphates. Among the many responses to Gαq actions are neuronal excitation through inhibition of voltage-gated potassium channels and activation of transient receptor potential (TRP) channels. These effectors may contribute to increased VGCC activation and increased neurotransmitter release (reviewed in Brown and Sihra 2008). However, Gβ/γ liberated by dissociation of heterotrimeric Gαq-containing proteins can inhibit VGCCs and neurotransmitter release (Brown and Sihra 2008). In addition, the DAG liberated by PLC-mediated hydrolysis can be further metabolized to the eCB 2-AG. Activation of Gαs/olf G-proteins leads to stimulation of AC activity and cAMP production, leading to stimulation of protein kinase A (PKA) and the exchange protein activated by cAMP (EPAC) proteins. GPCRs that activate Gαs/olf regulate a diverse array of biochemical, protein trafficking and genetic regulation pathways. The direct physiological consequences of this signaling are not widely known, but it has generally been observed that activation of some Gαs/olf-coupled receptors stimulates neurotransmitter release (reviewed in Brown and Sihra 2008). Forskolin, an AC activator, also increases neurotransmitter release at a variety of synapses, via a mechanism that involves cAMP and PKA activation.

GPCRs, Heterotrimeric G-Proteins, and Synaptic Plasticity

Activation of presynaptic Gi/o-coupled GPCRs can produce either short- or long-lasting decreases in neurotransmitter release (Atwood et al. 2014). Inhibition of VGCCs and vesicle fusion are generally responsible for the short-lasting effects (persisting for seconds-10s of seconds). The longer lasting effects (termed long-term depression or LTD) persist at least for hours, and generally for as long as the preparation survives. It is not entirely clear what mechanisms contribute to Gi/o-LTD, but it is most likely that these mechanisms take place within the presynaptic neuronal elements with the axon terminal being the most likely site of action. LTD is observed in slice preparations in which the presynaptic soma is not present (e.g. at glutamatergic synapses in striatum in slices in which axons have been severed, as in Yin et al. 2006). Within the axon terminal, inhibition of AC is a prominent mechanism implicated in Gi/o-LTD, but long-lasting inhibition of VGCCs may also contribute (Atwood et al. 2014; Pelkey et al. 2008). Inhibition of AC will inhibit the activity of PKA, and this mechanism may also contribute to LTD. One PKA substrate, the Rim1 protein, has been implicated in presynaptic LTD (Heifets and Castillo 2009; Grueter et al. 2010). This phosphoprotein is associated with vesicles and implicated in control of vesicle fusion. Thus, it is thought that reducing PKA-catalyzed phosphorylation of Rim1 leads to a decrease in rates of fusion and neurotransmitter release. Presynaptic protein synthesis via translation also appears to have a key role in some forms of presynaptic Gi/o-LTD (Yin et al. 2006;

Younts et al. 2017). An elegant recent study indicates that presynaptic GABAergic terminals in the hippocampus contain ribosomal elements that can mediate protein translation, and this process appears to be necessary for the expression of Gi/o-LTD at these synapses (Younts et al. 2017).

Presynaptic long-term potentiation (LTP) also appears to involve Gs/olf-mediated processes (Evans and Morgan 2003; Waltereit and Weller 2003). For example, increased cAMP and PKA activation are implicated in the increased glutamate release observed during LTP at mossy fiber-CA3 pyramidal neuron synapses in the hippocampus (reviewed in Estratova and Tóth 2014).

Acute Ethanol Effects on Neurotransmitter Release

Ethanol acts through a variety of molecular targets to produce acute intoxication. The stages of intoxication range from euphoria, anxiolysis and enhanced movement (which can be quite variable across individuals) to motor and cognitive impairment, sedation, anesthesia, coma and even death from respiratory depression (Abrahao et al. 2017; Mihic and Harris 2011). The blood and brain ethanol concentrations generally associated with these lower dose effects range from 5–10 mM at the low end, through 18 mM (the legal intoxication level in the USA up to ~100 mM which is the lethal range for average non-tolerant humans). Thus, in understanding the molecular and cellular bases of intoxication it is important to examine effects of these relevant concentrations. The behavioral manifestations of intoxication are driven by effects on neurons (and possibly glia) in a number of brain regions and circuits that control everything from reward and movement to respiratory control (Abrahao et al. 2017). Thus, there is a need to understand actions on different cells in different regions to gain a fuller picture of how intoxication develops. It is also becoming clear that ethanol alters neuronal and synaptic activity via different mechanisms at different sites within the brain, and thus the field can no longer assume that effects involving one molecular target in one brain region will necessarily generalize to other regions (chapters in this volume, including: Anderson et al. 2017; Cannady et al. 2017; Chandler et al. 2017; Coleman and Crews 2017; Cuzon Carlson 2017; Dopico et al. 2017; Finn and Jimenez 2017; Hopf and Mangieri 2017; Klenowski and Tapper 2017; N'Gouemo 2017; Roberto et al. 2017; Schreiber and Gilpin 2017; Siciliano et al. 2017).

In this chapter the focus is on presynaptic ethanol effects. While ethanol has clear actions on targets within the postsynaptic elements of neurons, including a number of ligand-gated ion channels and potassium channels, these effects will not be discussed at present. The reader is referred to recent reviews that cover these subjects in detail (Abrahao et al. 2017; Harris et al. 2008; Lovinger and Roberto 2013; Roberto and Varodayan 2017).

GABA

Ethanol has its clearest acute presynaptic effects at GABAergic synapses in many brain regions. Early neurochemical studies showed both inhibitory and stimulatory effects of acute ethanol on GABA release in synaptosomal and brain slice preparations (Howerton and Collins 1984; Strong and Wood 1984; Seilicovich et al. 1988). It is not clear what accounted for these different findings, but they may be due to differences in the

methods for stimulating release (mostly assayed with stimulation of release by increasing extracellular potassium concentrations) or the brain regions examined (e.g. as in Peris et al. 1992). Electrophysiological studies beginning in the 1990s began to establish that ethanol potentiation of GABAergic transmission at intact synapses is one of the clearest acute effects of the drug (Wan et al. 1996; Weiner et al. 1997). However, it was often assumed these ethanol effects only involved changes in $GABA_A$ receptor function. The first clear evidence of increased GABA release within particular brain regions came from studies in which the ethanol-induced potentiation was accompanied by decreased paired-pulse facilitation, changes in the frequency of miniature synaptic events, and other signs of presynaptic facilitation (Ariwodola and Weiner 2004; Nie et al. 2004; Roberto et al. 2003). Such effects were first reported at synapses made by GABAergic neurons in the hippocampus (Ariwodola and Weiner 2004; Sanna et al. 2004). Subsequently, similar effects have been observed in the basolateral amygdala, central amygdala, cerebellum, dorsal striatum, nucleus accumbens, spinal cord and ventral tegmental area (Bajo et al. 2008; Criswell et al. 2008; Kelm et al. 2008; Richardson and Rossi 2017; Silberman et al. 2008; Talani and Lovinger 2015; Theile et al. 2008; Wilcox et al. 2014; Ziskind-Conhaim et al. 2003). Ethanol also enhances GABA release onto cerebellar Purkinje neurons, although this effect appears to be due mainly to increased firing of Golgi-type interneurons (Carta et al. 2004). Within the BLA ethanol potentiates GABAergic synapses, with presynaptic mechanisms involved at one population of synapses and adrenergic-dependent postsynaptic mechanisms at another synaptic population (Silberman et al. 2008, 2012). Evidence for ethanol potentiation of glycine release has also been observed (Richardson and Rossi 2017; Ziskind-Conhaim et al. 2003).

Interestingly, some of the earliest reports of the presynaptic GABA release-enhancing ethanol effects also noted that these effects could be reduced by activation of the Gi/o-coupled $GABA_B$-type GPCR (Figure 1A) (Ariwodola and Weiner 2004; Wan et al. 1996). This finding provided one of the first clues about the signaling pathways implicated in ethanol potentiation of GABA release. Subsequent studies have implicated the cyclic adenosine monophosphate (cAMP) intracellular signaling pathway in this ethanol action (Figure 1A). Inhibition of adenylyl cyclase (the enzyme that catalyzes cAMP formation) and protein kinase A (PKA, the cAMP-activated protein kinase) has been shown to prevent this ethanol potentiation (Zhu and Lovinger 2006; Kelm et al. 2008; Talani and Lovinger 2015). The actions of Gi/o-GPCRs that prevent ethanol potentiation likely involve AC inhibition, which is a common consequence of activation of such receptors. Indeed, different Gi/o-GPCRs have now been shown to have this ethanol-inhibiting action at GABAergic synapses in several brain regions (Figure 1A) (Kelm et al. 2008; Roberto et al. 2010; Talani and Lovinger 2015). This raises the possibility that such receptors may be used to alter ethanol effects, and indeed there is evidence that CB1, $GABA_B$ and mGluR2 receptor-targeted ligands may be useful in this context (Agabio and Colombo 2014; Meinhardt et al. 2013; Pava and Woodward 2012).

Additional mechanisms may also be involved in the presynaptic GABA-enhancing ethanol action. Knocking out the protein kinase C epsilon (PKCε) isoform appears to prevent ethanol effects in the central amygdala (CeA) (Figure 1A) (Bajo et al. 2008). There may also be a role for stimulation of intracellular calcium release that could enhance excitation/

secretion coupling in the cerebellum and VTA (Figure 1A) (Kelm et al. 2007; Theile et al. 2009), and P/Q-type VGCCs appear to be involved in ethanol potentiation in the CeA (Figure 1A) (Varodayan et al. 2017). At several synapses, ethanol has been shown to increase the frequency of action potential- and calcium-entry-independent miniature inhibitory postsynaptic curents (mIPSCs) (Hirono et al. 2009; Kelm et al. 2007; Roberto et al. 2003; Talani et al. 2015; Theile et al. 2008; Zhu and Lovinger 2006), and thus mechanisms downstream of VGCC function are likely involved in this effect (Figure 1A). The function of vesicle- and plasma membrane-associated proteins involved in fusion could be targets for ethanol actions, e.g. through changes in phosphorylation, but this has not yet been examined in detail.

The ethanol-induced increases in GABA release observed in brain slices could involve indirect effects due to release of neuromodulators that stimulate GABAergic terminals (Figure 1A,B). In the CeA, ethanol potentiation of GABA release appears to involve activation of receptors for corticotrophin-releasing factor (CRF), presumably secondary to release of CRF itself (Figure 1A,B) (Nie et al. 2004). Serotonin actions at the 5-HT2C receptor are implicated in ethanol potentiation in VTA (Theile et al. 2009). Application of the nociceptin peptide decreases GABA release in the CeA, and prevents potentiation by ethanol when the peptide is applied before the drug (Roberto and Siggins 2006). Thus, increased release or decreased reuptake of small molecules or neuropeptides may underlie some of these ethanol actions.

However, experiments examining ethanol effects in an isolated "neuron-bouton" preparation provided evidence for a direct effect of ethanol on GABAergic presynaptic terminals (Zhu and Lovinger 2006; Kelm et al. 2007). These neurons are isolated mechanically such that pinched-off presynaptic boutons remain attached to the postsynaptic neuron. These boutons still release GABA and thus spontaneous GABAergic IPSCs (sIPSCs) can be observed independent of the firing of GABAergic neurons and influences of any neurons other than the postsynaptic neuron (Jun et al. 2011). In this preparation, ethanol produces a rapid increase in the frequency of sIPSCs and mIPSCs, indicating a direct effect on GABAergic boutons that appears to be independent of known modulatory or retrograde signals form postsynaptic neurons (Zhu and Lovinger 2006).

It must also be noted that ethanol reduces GABAergic synaptic transmission at some CNS synapses. In the dorsolateral striatum (DLS) acute ethanol application produces such a reduction at synapses onto the medium spiny projection neurons (MSNs) made by both other MSNs and by parvalbumin-positive fast-spiking interneurons (FSIs) (Wilcox et al. 2014; Patton et al. 2016). The inhibition at FSI-MSN synapses appears to involve a presynaptic decrease in GABA release brought about through activation of delta opiate receptors (Figure 1A) (Patton et al. 2016). This finding suggests increased production or release of yet another neuromodulatory peptide by acute ethanol, in this case an enkephalin (Figure 1B). The emerging trend of ethanol modulatory effects through neuropeptide release opens up the possibility that the drug has a variety of actions at different synapses depending on the local peptide expression pattern.

Interactions at GABAergic synapses between the acute presynaptic effects of ethanol and endocannabinoids that act through the CB1 receptor have been especially noteworthy. Within the nervous system eCBs are produced by postsynaptic elements in response to intense neuronal activity. These compounds travel retrogradely across the synaptic cleft to act on presynaptic CB1 receptors, Gi/o-GPCRs that inhibit neurotransmitter release (Figure 1B). At synapses in the CeA and basolateral amygdala (BLA), CB1 activation prevents ethanol potentiation of GABA release (as described previously for other Gi/o-GPCRs) (Figure 1A) (Kelm et al. 2008; Roberto et al. 2010; Talani and Lovinger 2015). There is also evidence that acute ethanol exposure can reduce retrograde eCB signaling at GABAergic synapses in the BLA (Talani and Lovinger 2015). In contrast, acute exposure to ethanol appears to enhance eCB-mediated LTD at glutamatergic synapses in the dorsomedial striatum (Yin et al. 2007). It is not yet clear what mechanisms account for the interaction of ethanol with eCB retrograde signaling. Interactions between ethanol and eCB/CB1 signaling may contribute to the alterations in the *in vivo* actions of ethanol produced by eCB-targeted drugs (Pava and Woodward 2012), a subject that will be discussed in greater detail in considering the effects of chronic ethanol exposure on the eCB signaling system.

Glutamate and Other Neurotransmitters

Acute ethanol exposure-induced alterations in glutamate release at CNS synapses have not been observed as frequently as effects on GABA release, but a few synapses show some sensitivity, with decreased release being the most common finding (Basavarajappa et al. 2008; Gioia and McCool 2017; Gioia et al. 2017; Li et al. 2013; Maldve et al. 2004; Silberman et al. 2015; Zhu et al. 2007). In the basolateral amygdala (BLA), Ethanol inhibits glutamate release leading to decreased posttetanic potentiation, and reduced synaptic vesicle recycling appears to be the underlying mechanism (Gioia and McCool 2017). The vesicle-associated protein Munc13–2 is implicated in this effect (Gioia et al. 2017). Ethanol decreases glutamatergic synaptic transmission in CeA and this effect is prevented by a CB1 agonist (Kirson et al. 2017), and may also involve N-type VGCCs (Zhu et al. 2007). While it is presumed that this effect involves presynaptic mechanisms there is as yet no direct evidence that this is the case. Potentiation of glutamate release by ethanol has also been reported (e.g. Xiao et al. 2009; Deng et al. 2009), but less frequently than inhibitory actions.

The reasons for the differential effects of ethanol on GABA and glutamate release remain unclear. It is possible that presynaptic molecules that regulate intracellular calcium release and/or vesicle fusion differ at the different synaptic types. In addition, the effects on release secondary to increases in neuromodulator levels and subsequent activation of GPCRs may underlie these differential ethanol actions. This area should be a rich source of important new findings in the future.

There is evidence that presynaptic effects of ethanol alter release of other neurotransmitters, but in many cases it is unclear if these effects involve direct drug actions on presynaptic terminals (Lovinger and Roberto 2013). In the striatum, ethanol inhibits DA release at relatively high concentrations in preparations where DAergic axon terminals are disconnected from their somata (Budygin et al. 2001). While this may still reflect an indirect modulatory action, the findings indicate a local effect on terminal DA release.

Presynaptic Neuroadaptations to Ethanol Exposure and Drinking

Prolonged exposure to ethanol, whether through forced exposure or ethanol drinking, produces neuroadaptations that often compensate for the acute drug actions. However, some adaptations are not always clearly compensatory, and sometimes appear to produce stable alterations that have an "allostatic" effect on neural function.

GABA

Both compensatory and allostatic neuroadaptations to ethanol have been observed at GABAergic synapses in different brain regions. While this chapter focuses on the presynaptic changes at GABAergic synapses, postsynaptic neuroadaptations have also been observed in many brain regions (e.g. Diaz et al. 2011, Abrahao et al. 2017; Roberto and Varodayan 2017). In the CeA, increased GABAergic transmission is observed following prolonged ethanol administration via vapor inhalation (Figure 2) (Roberto et al. 2004a 2010). While there is a prominent postsynaptic component to this neuroadaptation, there is also evidence that the probability of GABA release and/or the number of GABAergic synapses contributes to this effect. Reduced function of $GABA_B$ presynaptic autoreceptors is one factor that appears to contribute to this increase in release (Figure 2) (Roberto et al. 2008). Disrupted eCB/CB1 modulation of GABA release may also contribute to the increased release following chronic ethanol exposure (Varodayan et al. 2016). Alterations in CRF levels and function could well play a role in the chronic ethanol actions on CeA GABAergic transmission given the CRF potentiation involved in the acute drug action that was discussed previously (Figures 1, 2). Indeed, CRF levels are increased in the amygdala following withdrawal after chronic ethanol exposure, as measured with *in vivo* microdialysis (Merlo Pich et al. 1995). The ability of CRF to enhance GABA release in CeA is augmented in ethanol-dependent rats. The acute ethanol-induced potentiation of GABAergic transmission on CeA neurons remains intact following chronic exposure, indicating a lack of tolerance to ethanol. Withdrawal following chronic ethanol intake results in increased extracellular CRF levels in the BNST (Olive et al. 2002), but it is not clear if the increase alters GABAergic transmission in this region. Overall, GABAergic neuroadaptations in the CeA, and perhaps other parts of the extended amygdala, are not compensatory but rather induce a general enhancement of inhibition within CeA that is exacerbated during intoxication.

GABA release at hippocampal synapses may also be altered through changes in presynaptic function and modulation. In the dentate gyrus hippocampal subfield there is evidence of decreased probability of GABA release following chronic ethanol intake in monkeys (Figure 2) (Weiner et al. 2005). Evidence for decreased GABA release has also been observed in the CA1 subfield (Cagetti et al. 2003). These effects would appear to compensate for the increased GABA release during acute ethanol exposure. However, decreased $GABA_B$ receptor function has been implicated in increased GABA release in the CA1 subfield *in vivo*, and this may be an allostatic type of neuroadaptation (Peris et al. 1997). Decreased GABAergic transmission, involving both pre- and postsynaptic mechanisms has also been observed in the BLA following chronic ethanol drinking, and this neuroadaptation likely contributes to negative affective states that develop during withdrawal (Diaz et al., 2011).

GABAergic synaptic transmission onto serotonergic neurons in the dorsal raphe nucleus is not altered by acute ethanol exposure in naïve mice of the DBA1/J strain. However, following chronic ethanol exposure, acute application of the drug produces a robust enhancement of GABA release (Figure 2) (Lowery-Gionta et al. 2015). This illustrates a case where a change in transmission does not directly compensate for an acute drug effect, but instead chronic exposure induces a hypersensitivity to ethanol that may alter the pattern of intoxication during subsequent encounters with the drug.

In the DLS, long-term changes at GABAergic synapses onto MSNs are mainly allostatic. Decreased frequency of GABAergic mIPSCs has been observed in both mouse DLS and the monkey putamen nucleus (roughly equivalent to rodent DLS) following chronic ethanol drinking protocols (Wilcox et al. 2014; Cuzon Carlson et al. 2011). These findings indicate that the effect of chronic ethanol exposure is similar to that of acute exposure, with the net effect being a loss of inhibition of MSN activity/striatal output (Figure 2). In mouse DLS the effect of acute ethanol is lost after chronic drinking (Wilcox et al. 2014), and thus the effect of chronic ethanol consumption sets a new level of GABAergic inhibition that appears to be stable.

Chronic ethanol drinking leads to depression of DMS GABAergic synapses, i.e. decreased mIPSC frequency, similar to that observed in DLS (Figure 2) (Wilcox et al. 2014). This decrease is accompanied by a change from acute ethanol potentiation of GABA release to a slight depression. In the monkey caudate nucleus GABAergic synaptic transmission exhibits smaller changes following chronic drinking than those observed in the putamen, but decreased mIPSC frequency is the most consistent observation (Cuzon Carlson et al. 2017). Thus, the general effect of ethanol on striatal GABAergic transmission is a decrease that would generally allow for increased striatal output driven by synaptic activation of MSNs.

In the VTA, a single *in vivo* ethanol exposure appears to produce increased GABA release at synapses on dopaminergic neurons (Melis et al. 2002; Wanat et al. 2009). This potentiation may involve impaired function of GABA$_B$ autoreceptors (Melis et al. 2002). However, effects of more prolonged ethanol exposure remain to be determined.

Glutamate and Dopamine

Prolonged ethanol exposure or drinking has generally been proposed to produce an increase in extracellular glutamate levels (Figure 2) (Dahchour and De Witte 1999, 2003; Griffin et al. 2014; Meinhardt et al. 2013; Rossetti and Carboni 1995; Roberto et al. 2004b; Knackstedt and Kalivas 2009). The main evidence supporting this idea comes from microdialysis data demonstrating increases in extracellular glutamate in cortex, dorsal striatum, NAc and other brain regions (Dahchour and De Witte 1999, 2003; Knackstedt and Kalivas 2009; Meinhardt et al. 2013; Rossetti and Carboni 1995). However, it is not clear that the glutamate measured with this approach is of synaptic origin (e.g. Baker et al. 2002). Indeed, changes in the function of the cystine-glutamate transporter accounts for some of this increase (Baker et al. 2002; Knackstedt and Kalivas 2009). Nonetheless, there is evidence for presynaptic changes at glutamatergic synapses that would promote increased glutamate release and direct evidence for increased glutamate release at some brain synapses (Cuzon Carlson et al. 2011; Lack et al. 2007; Lowery-Gionta et al. 2015; Ma et al. 2017;

Meinhardt et al. 2013; Zhu et al. 2007; Roberto et al. 2004b). There is also evidence for decreased glutamate uptake in the NAc following chronic ethanol drinking (Melendez et al. 2005). It should also be noted that synaptic glutamate release appears to be decreased in the lateral CeA following chronic ethanol exposure and a 48 hour withdrawal (Pleil et al. 2015). Thus, with some exceptions, it appears that ethanol produces increased glutamate release at synapses in many brain regions.

Another synaptic change that appears to contribute to increased glutamate levels is the loss of regulation of release by presynaptic Gi/o-coupled receptors (Figure 2). In the NAc and DS mGluR2 acts presynaptically as an autoreceptor to reduce glutamate release (Lovinger and McCool 1995; Manzoni et al. 1997). Chronic ethanol exposure decreases mGluR2 expression and function (Meinhardt et al. 2013), and this study supports the idea that loss of the mGluR2 autoreceptor function contributes to enhanced glutamate levels state in NAc. Interestingly, mGluR2 is not expressed by the ethanol-preferring P rats and is prevalent in other rat lines selected for high ethanol drinking preference (Zhou et al. 2013; Wood et al. 2017). The impact of this receptor on ethanol seeking and drinking will be discussed later in this chapter.

Dopamine release in the nucleus accumbens is also altered following chronic ethanol exposure or drinking in rats and mice and in chronic ethanol-consuming rhesus monkeys (Siciliano 2017). Some of these changes appear to reflect direct neuroadaptations in dopamine release mechanisms such as decreased release in brain slices (Karkhanis et al. 2015; Melchior and Jones 2017), while others indicate increased dopamine clearance, most likely due to changes in function of the dopamine transporter (Karkhanis et al. 2015, 2016). It is notable that dopamine release in male monkey NAc slices is increased following chronic drinking (Siciliano et al. 2015), in contrast to the findings in rodent. For a more in-depth discussion of these findings, the reader is referred to the excellent chapter by Siciliano and coworkers (2017) in this volume. Inhibition of dopamine release by the Gi/o-coupled kappa opioid receptor is also enhanced after chronic ethanol exposure in rodent NAc (Karkhanis et al. 2016; Rose et al 2016), contributing to a possible hypodoaminergic state after this exposure. A similar enhancement of kappa receptor function is observed in NAc and caudate nucleus of chronic ethanol consuming monkeys (Siciliano et al 2015, 2016). Overall, several factors contribute to an overall decrease in synaptic dopamine levels following chronic ethanol exposure, particularly during the early stages of abstinence (Hirth et al. 2016). However, increased DA levels have been observed following protracted abstinence in rat, and molecular changes that could contribute to increased extracellular dopamine have been observed in postrmortem tissue from patients with AUD (Hirth et al. 2016). These findings indicate that changes in factors controlling extracellular DA levels may depend on the period of drug withdrawal.

Endocannabinoids and LTD

The CB1 receptor is another presynaptic Gi/o-coupled GPCR whose function is decreased following long-term ethanol exposure (Figure 2) (Xia et al. 2006; Depoy et al. 2013; Adermark et al. 2011a,b). As mentioned previously, retrograde signaling by postsynaptically-released eCBs normally activates presynaptic CB1 receptors inducing

either short-term synaptic depression or Gi/o-LTD at GABAergic and glutamatergic synapses throughout the brain (Araque et al. 2017; Heifets and Castillo 2009).

Chronic ethanol exposure or drinking produces decreased CB1 expression and function and loss of the LTD induced by activation of this receptor (Basavarajappa et al. 1998; Xia et al. 2006; Adermark et al. 2011a; DePoy et al. 2013). In the dorsal striatum, depression at glutamatergic synapses induced by a CB1 agonist is lost following chronic ethanol drinking (Adermark et al. 2011a). The loss of CB1-mediated LTD persists for 7 days following the last drug exposure (Xia et al. 2006). At GABAergic synapses, eCB-dependent LTD also occurs, and this synaptic depression indirectly produces a long-lasting increase in neuronal activation by glutamatergic synapses (Adermark et al. 2009). This type of LTD is also impaired following chronic ethanol drinking, facilitating a long-lasting potentiation of striatal output in response to glutamatergic transmission (Adermark et al. 2011b). These changes in eCB-dependent plasticity combine with the decrease in GABAergic transmission to increase striatal output in ethanol-exposed animals.

Roles of Presynaptic Changes in Ethanol-Related Behaviors: Focus on Cortico-Basal Ganglia and Amygdala Circuitry

As the preceding sections indicate we now know a great deal about the acute and chronic ethanol effects on neurotransmitter release as well as presynaptic modulation and plasticity. However, less is known about the roles played by these ethanol actions in the behavioral alterations induced by ethanol. Regarding the consequences of altered GABA release, there are well known interactions between the acute effects of ethanol and many drugs that act at GABAergic synapses (Mihic and Harris 2011). However, these interactions have been mainly ascribed to ethanol effects on $GABA_A$ receptors. Thus, it will be important to investigate if presynaptic changes at GABAergic synapses contribute to the drug interactions. This is certainly an important topic, because ethanol drinking in conjunction with drugs that target GABAergic transmission can result in profound acute toxicity, including death.

There has been considerable recent attention on ethanol-induced alterations in presynaptic modulation at synapses in different regions of the striatum. This topic is of interest to investigators examining ethanol seeking and drinking because different cortico-basal ganglia circuits involving specific striatal subregions are implicated in these behaviors. Large regions of the striatum are part of at least three different cortico-basal ganglia circuits, with the DMS/caudate being part of an "associative" circuit, the DLS/putamen participating in the "sensorimotor" circuit, and the NAc being incorporated into the "limbic" circuit (Yin and Knowlton 2006). As discussed in the previous sections of this chapter, ethanol has effects on aspects of presynaptic function in striatal components of all these circuits.

The behavioral consequences of ethanol actions in NAc are widely appreciated (Koob and Volkow 2016). It is clear that this region and the associated limbic circuit have crucial roles in the rewarding effects of the drug (as shown using conditioned place preference and ethanol self-administration procedures). Indeed, alterations within the NAc/limbic circuit are likely to impact affective states, Pavlovian conditioning and Pavlovian-to-instrumental

transfer conditioning, as well as responses to stress, withdrawal and other factors that contribute to negative affect that helps to drive relapse to drinking. A decrease in mGluR2 modulation of glutamate release at prefrontal cortical inputs to the NAc contributes to excessive seeking and drinking following chronic ethanol exposure (Meinhardt et al. 2013). Rats and mice lacking mGluR2 also show enhanced ethanol seeking and drinking (Zhou et al. 2013; Wood et al. 2017), although it is clear thatloss of mGluR2 is only one of several genetic and molecular factors that influence these behaviors in alcohol-preferring rats (Zhou et al. 2013). The consequences of mGluR2 absence or hypofunction presumably reflect loss of a crucial feedback control that normally prevents the hyperglutamatergic state thought to drive excessive drinking. Treatment with mGluR2/3 agonists reduces ethanol seeking in rodent models (Backstrom and Hyytia 2005; Rodd et al. 2006; Sidhpura et al. 2010; Zhao et al. 2006). However, considerable additional work is needed to determine the contributions of other presynaptic mechanisms in NAc (e.g. alterations in other presynaptic Gi/o-coupled GPCRs or altered GABA release) to ethanol actions *in vivo*.

Striatal function within the associative and sensorimotor circuits also has the potential to contribute to a variety of acute and chronic ethanol actions. The major focus of research in this area has been the dissociation of effects on "goal-directed" and "habitual" behaviors, including ethanol seeking and drinking (Lovinger and Alvarez 2017; Corbit and Janak 2016; Gremel and Lovinger 2017). Indeed, the DMS/caudate is implicated in goal-directed behaviors while the DLS has a key role in habit learning, especially in self-paced "free-choice" instrumental tasks and response learning tasks. However, this facile dichotomy has overshadowed important roles of these regions and the larger circuits in behavioral control and ethanol actions.

For example, the associative striatum receives strong synaptic inputs from many regions of frontal cortex, including orbitofrontal and medial prefrontal areas (Haber et al. 2006; Hintiryan et al. 2016; Hunnicutt et al. 2016). These cortical regions show structural and functional alterations following long-term ethanol exposure, both in experimental animals and in humans (reviewed in Barker et al. 2015; Sullivan and Pfefferbaum 2005). The caudate nucleus also shows reduced volume after heavy drinking in adolescents (Squeglia et al. 2014). Thus, the associative circuit is likely to be strongly compromised by this type of ethanol exposure. Given the key role of the DMS/caudate within this circuitry, it is very likely that altered cortical communication to this striatal region contributes to this dysfunction. The evidence that acute and chronic ethanol produce presynaptic alterations in the DMS and caudate has already been discussed. The "hypofrontality" and altered DMS/caudate function induced by ethanol are likely to contribute to deficits in cognitive function and altered decision making induced by ethanol abuse. The loss of conscious executive control during intoxication and following chronic ethanol abuse is likely to contribute to poor decision making and preservation in drinking and other associated maladaptive behaviors. There is a growing literature showing that manipulation of the DMS alters ethanol seeking and drinking (Cheng et al. 2017; Corbit et al. 2012; Nam et al. 2013; Wang et al. 2012), but more work is needed to determine the mechanisms within this striatal region that contribute to this behavioral change.

The sensorimotor circuit has important roles in performance of well-learned actions. Inputs from sensory and motor cortices drive neurons in the DLS/putamen (Haber et al. 2006; Hintiryan et al. 2016; Hunnicutt et al. 2016) allowing for output of automatized movements in appropriate contexts. This circuitry also has key roles in reinforcement-driven "stimulus-response" learning and behavior, especially in self-paced operant tasks that do not include a clear Pavlovian component (Yin and Knowlton 2006). Repeated performance of actions for an outcome in a particular context leads to development of associations between the external context, the internal state of the animal and the action, driven by the history of reinforcement (Dickinson 1985). Indeed, this form of instrumental learning, now sometimes referred to as "habit" learning, received the strongest attention prior to characterization of action-outcome "goal-directed" instrumental learning (Colwill and Rescorla 1990; Dickinson 1985). A number of studies have now shown that chronic ethanol drinking or exposure enhances this type of behavior in both experimental animals and humans (Barker et al. 2010; Corbit et al. 2012; Dickinson et al. 2002; Gladwin and Wiers 2012; Hogarth et al. 2012; Ostlund et al. 2010; Hay et al. 2013; Mangieri et al. 2012; Sjoerds et al. 2013 although see Sebold et al. 2014, 2017), as well as other behaviors that involve the DLS (DePoy et al. 2013).

A number of presynaptic changes in the DLS/putamen have been discussed, including decreased GABA release and decreased Gi/o modulation of cortical/glutamatergic inputs to this striatal subregion. The general consequence of these alterations is to decrease modulatory and inhibitory controls on the activation of MSNs, producing the potential for enhanced DLS/putamen output after chronic ethanol exposure. This would help to foster the learning and performance mediated by the sensorimotor circuit, including increased S-R learning. It remains to be determined what other presynaptic changes occur in other parts of the circuitry that could also contribute to these behavioral changes.

While the focus of the work on ethanol and sensorimotor circuitry has been on how enhanced "habit formation" might contribute to ethanol seeking and drinking, it is important not to lose sight of how the drug effects on sensorimotor circuitry will alter all behaviors related to this circuitry. For example, the fact that ethanol increases S-R learning reinforced by food is part of the pattern of impaired decision making produced by the drug. This effect has consequences across the entire spectrum of behaviors altered by ethanol abuse. In combination with impairment of associative circuit function, enhanced potential for sensorimotor circuit function likely contributes to loss of executive control and behavioral flexibility with enhanced control of behavior by the immediate context. It is worth noting that this effect does not depend on having ethanol as the reinforcer driving learning, as S-R learning is enhanced by forced ethanol exposure when a food reinforcer is used in training (Corbit et al. 2012). Thus, it is unlikely that the enhanced S-R learning is driven by the reinforcement history per se. Rather, it appears to be the effect of ethanol is on the circuitry that influences how reinforcement drives behavior.

The implications of these presynaptic changes in particular circuit changes for ethanol seeking and drinking and other drug-related behaviors can be debated, but there is evidence from studies in both experimental animals and humans that that they have important roles. Multiple circuits contribute to intoxication, binge and excessive ethanol drinking, withdrawal effects, relapse to drinking and excessive drinking following relapse.

Acute exposure to ethanol initiates the processes that contribute to escalation of drinking. Presynaptic inhibitory changes in the BLA, CeA and VTA likely contribute to the rewarding effects of ethanol. Enhanced inhibition in the associative circuit may play a part in impairment of cognitive control and executive function that contributes to lack of ability to consciously control drinking as well as poor decisions made under the influence of ethanol. Disinhibition of sensorimotor striatum most likely fosters excessive drinking and poor decision making by fostering more automatized action patterns. Chronic ethanol effects will exacerbate many of these changes, particularly the presynaptic effects on amygdala and sensorimotor circuitry. Presynaptic changes within the limbic circuitry may also begin to have a larger influence with increasing duration and amount of chronic ethanol exposure. Increased inhibition in the hippocampal CA1 region can impair spatial memory and other aspects of episodic learning and memory (Berry et al. 2009; Gibson 1985; Givens 1995; Hunt et al. 2009; Matthews et al. 2002; Ryabinin 1998; Ryabinin et al. 2002). Long-term effects of changes in this limbic region may also underlie the influence of context on relapse to ethanol seeking and taking. Clearly ethanol has strong effects on GABA release in the CeA, with CRF participating in both the acute and chronic drug actions. There is now considerable evidence for participation of these neurotransmitters and this brain region in relapse driven by stress and negative affect (Koob and Volkow 2016). The BLA plays important roles in signaling the relative positive or negative valence of environmental events within the associative and limbic circuits (Johansen et al. 2011; Wassum and Izquierdo 2015). Presynaptic ethanol effects at both GABAergic and glutamatergic synapses likely alter the contribution of this brain region to reward- and punishment-driven behavior, as well as responses to stress. Presynaptic effects of ethanol that alter serotonergic neuronal function will also alter limbic circuit responses to stress, in addition to affecting affective states.

The alterations in all three cortico-basal ganglia circuits, including presynaptic changes, will ultimately participate in a vicious circle of behavioral changes similar to that proposed by Koob and others (Barker et al. 2015; Koob and Volkow 2016). Prolonged ethanol exposure combined with conditioning related to ethanol intake will promote loss of associative circuit-based mechanisms that normally support decisions to limit drinking. Ethanol will alsopromote transition from associative/limbic-based reward-driven actions to sensorimotor reinforcement-based actions that will promote excessive drinking, especially in environments previously associated with heavy drinking. This will drive further neuroadaptations including impairment in prefrontal cortex contributions to associative and limbic circuits leading to compromised executive control and conscious decision making. Parallel changes in other limbic cortical areas will promote excessive responding to negative emotions and stressful/negative environmental events, especially during abstinence. These limbic changes will help to promote relapse. In the proper environmental/social contexts relapse will be fostered by a strengthened sensorimotor circuit, and once drinking has begun, the dominant sensorimotor circuit and impaired associative circuit will likely contribute to continued drinking due to automatization of behavior. Often drinking will then proceed well beyond levels needed to simply overcome negative consequence of abstinence. It will be interesting to determine more about how components of each of these circuits contribute to different stages of alcohol abuse. For example, little is known about how acute and chronic ethanol exposure alters sensory and motor cortex function, and how these actions

might contribute to altered circuit function. Even less is known about ethanol actions on the thalamic elements of the three circuits, or effects on basal ganglia regions downstream of the striatum. Presynaptic ethanol actions may occur in many of these brain regions, and discovery of these effects may add to the list of potential targets for treatment of alcohol use disorders.

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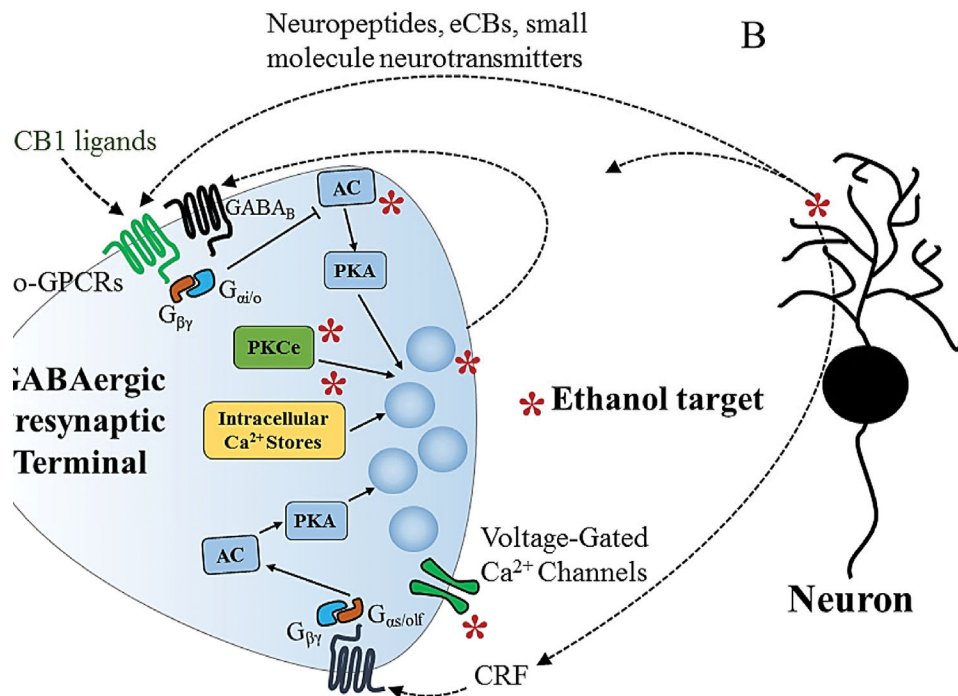
Figure 1.

Molecular targets and neuromodulators involved in acute presynaptic ethanol actions at GABAergic synapses. A) Schematic diagram of a presynaptic terminal showing suspected sites of ethanol actions that enhance GABA release (*). The main suspected targets are voltage-gated calcium channels, AC, vesicle fusion, PKCε and intracellular Ca^{2+} stores. Neuropeptides, including CRF, eCBs and small molecule neurotransmitters (including feedback vesicular GABA release) can contribute to or modulate ethanol actions on presynaptic GABA release through actions on presynaptic GPCRs. Note that ethanol enhances GABA release in many brain regions, but inhibits release in others. B) Ethanol is thought to stimulate release of neuropeptides (including enkephalins and CRF) and eCBs, presumably from neurons, and these neuromodulators act on presynaptic GPCRs to alter GABA release. Arrows indicate stimulation, cross-ended lines indicate inhibition. AC = adenylyl cyclase, CB1 = cannabinoid type 1 receptor, CRF = corticotrophin-releasing factor, eCB = endocannabinoid, GABA = gamma-aminobutyric acid, GPCR = G protein-coupled receptor, Gαi/o = alpha i/o G protein subunit, Gαs/olf = alpha s/olf subunit of G protein, Gβγ = beta/gamma dimer subunit of G protein, PKA = protein kinase A, PKCε = protein kinase C epsilon,
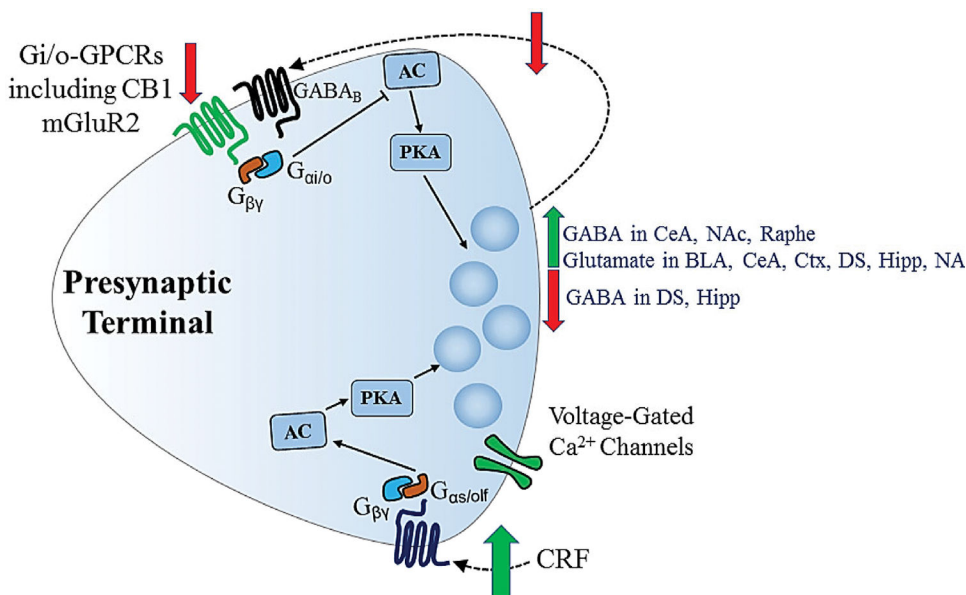
Figure 2.
Presynaptic neuroadaptations to chronic ethanol exposure/consumption. Green arrows
indicate increases in GABA and glutamate release observed in several brain regions,
as well as increased CRF that drives increased GABA release in CeA. Red arrows
indicate decreases in Gi/o-GPCR expression/function that occur at both GABAergic and
glutamatergic synapses (including decreased GABA/GABA$_B$R feedback onto GABAergic
terminals), as well as decreased GABA release observed in some brain regions. Decreases in
GABA release are thought to compensate for ethanol-induced increases in neurotransmitter
release at GABAergic synapses, while activation of GABA$_B$ Gi/o-GPCRs participates
in compensatory negative feedback that produces tolerance to the direct ethanol action
on release (dashed arrow). At glutamatergic synapses, increased neurotransmitter release
and decreased Gi/o-GPCR function may compensate for ethanol-induced decreases in
glutamatergic transmission. Neuroadaptations that have a more allostatic role include
increased GABA release and increased CRF signaling that enhances GABA release. AC
= adenylyl cyclase, BLA = basolateral amygdala, CB1 = cannabinoid type 1 receptor,
CeA = central amygdala, CRF = corticotrophin-releasing factor, Ctx = cortex, DS = dorsal
striatum, GABA = gamma-aminobutyric acid, GABA$_B$ = GABA type B receptor, GPCR = G
protein-coupled receptor, Gαi/o = alpha i/o G protein subunit, Gαs/olf = alpha s/olf subunit
of G protein, G$\beta\gamma$ = beta/gamma dimer subunit of G protein, Hipp = hippocampus, NAc =
nucleus accumbens, DRN = dorsal raphe nucleus, PKA = protein kinase A.