Synaptic Effects Induced by Alcohol

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Abstract

Ethanol (EtOH) has effects on numerous cellular molecular targets, and alterations in synaptic function are prominent among these effects. Acute exposure to EtOH activates or inhibits the function of proteins involved in synaptic transmission, while chronic exposure often produces opposing and/or compensatory/homeostatic effects on the expression, localization, and function of these proteins. Interactions between different neurotransmitters (e.g., neuropeptide effects on release of small molecule transmitters) can also influence both acute and chronic EtOH actions. Studies in intact animals indicate that the proteins affected by EtOH also play roles in the neural actions of the drug, including acute intoxication, tolerance, dependence, and the seeking and drinking of EtOH. This chapter reviews the literature describing these acute and chronic synaptic effects of EtOH and their relevance for synaptic transmission, plasticity, and behavior.

Keywords

1 Acute Ethanol Actions

Ethanol (EtOH) produces intoxication through actions on the central nervous system (CNS) at concentrations ranging from low to ~100 mM (at least in non-tolerant humans and experimental animals). A number of proteins involved in synaptic transmission are altered by EtOH effects within this concentration range. The target proteins include, but are not limited to, ion channels, neurotransmitter receptors, and intracellular signaling proteins. The first section of this article will review the literature describing the most prominent acute EtOH effects on synaptic transmission in the CNS. This review is not meant to be comprehensive, but rather to cover those effects that have been observed most consistently and are thought to contribute to intoxication.

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1.1 Ligand-Gated Ion Channels and Postsynaptic Ethanol Effects

Ion channels are among the best characterized targets for acute EtOH actions (Lovinger 1997; Vengeliene et al. 2008). Ligand-gated ion channels (LGICs) are heteromeric proteins that bind extracellular neurotransmitters or intracellular messengers and transduce that binding energy into opening of an intrinsic ion pore (Collingridge et al. 2009). Among those channels activated by extracellular neurotransmitters there are three classes.

1.1.1 Cys-loop Ligand-Gated Ion Channels—The "cys-loop" LGICs are pentameric proteins characterized by an obligatory cysteine double bond in the N-terminal binding domain. Each subunit protein contains an extracellular ligand-binding domain, four membrane spanning domains, and one large intracellular loop domain that also serves as a "portal" for ion permeability. This receptor class includes proteins with cation-permeable pores, the nicotinic acetylcholine (nAChR) and serotonin$_3$ (5-HT$_3$) receptors, as well as those with anion-permeable pores, the γ-aminobutyric acid$_A$ (GABA$_A$), and strychnine-sensitive glycine (GlyR) receptors. This class of receptors is distributed throughout the peripheral and central nervous systems.

Generally, acute EtOH exposure enhances the function of cys-loop LGICs (Aguayo et al. 2002; Harris 1999; Lovinger 1997; Perkins et al. 2010), but instances of inhibition of the nAChRs and GABA$_A$Rs have been reported (Aguayo et al. 2002; Cardoso et al. 1999; Davis and De Fiebre 2006; Marszalec et al. 1994; Roberto et al. 2003). The most common EtOH action is to potentiate channel opening in the presence of a low concentration of agonist by increasing the probability of channel opening (Zhou et al. 1998), and/or increasing agonist affinity (Tonner and Miller 1995; Welsh et al. 2009). This potentiating effect can influence both synaptic and extrasynaptic receptors (Sebe et al. 2003; Ye et al. 2001; Eggers and Berger 2004; Ziskind-Conhaim et al. 2003) (Fig. 1). For example, EtOH has been shown to increase the amplitude and/or duration of GABA$_A$ and GlyR-mediated inhibitory postsynaptic currents (IPSCs) (Sebe et al. 2003; Ziskind-Conhaim et al. 2003).

EtOH potentiation of GABA$_A$ receptor function has been extensively studied. There are 19 subunit proteins that contribute to the formation of GABA$_A$ receptors (International Union of Basic and Clinical Pharmacology, IUPHAR, database http://www.iuphar-db.org/index.jsp). Many of these subunit combinations have been examined for function and pharmacology in heterologous expression systems. To briefly summarize a large body of data, there is evidence that EtOH potentiates the function of α/β/γ-subunit-containing receptors, as well as those containing α4 or α6 along with β and δ subunits (Olsen et al. 2007; Lobo and Harris 2008; Mihic and Harris 1995; McCool et al. 2003). However, none of these findings has been uniformly replicated in all laboratories that have examined EtOH effects in heterologous systems (reviewed in Lovinger and Homanics 2007; Aguayo et al. 2002). Using cultured and isolated neurons, several investigators have observed potentiation of GABA$_A$R function (Celentano et al. 1988; Reynolds and Prasad 1991; Aguayo 1990; Nishio and Narahashi 1990; Sapp and Yeh 1998), but this sort of effect has not been observed in every neuronal type examined (e.g. McCool et al. 2003; White et al. 1990; Yamashita et al. 2006). A tonic GABA$_A$-mediated current is observed in many CNS neurons, and is thought to reflect the function of extrasynaptic, high affinity GABA

receptors containing the δ receptor subunit (Hanchar et al. 2005). The Potentiation of this tonic current has been observed in recordings from cerebellum, hippocampus, and thalamus using the brain slice preparation (Hanchar et al. 2005; Wei et al. 2004; Glykys et al. 2007; Jia et al. 2008, although see Botta et al. 2007).

Recent studies suggest that EtOH potentiation of GABA$_A$ receptor function depends on protein phosphorylation. Messing and co-workers have shown that activity of the epsilon subunit of protein kinase C (PKC) is necessary for EtOH potentiation of γ2-subunit-containing GABA$_A$ receptors expressed heterologously in a mammalian cell line (Qi et al. 2007). This PKC action appears to involve phosphorylation of a specific serine residue on the γ2 subunit. This finding may explain data from previous studies indicating the involvement of PKC in EtOH potentiation of GABAergic transmission (Weiner et al. 1994). However, in this earlier study it was not clear if the EtOH effects on transmission involved pre or postsynaptic mechanisms. A parallel line of investigation indicates that PKCδ is necessary for EtOH potentiation of tonic current involving δ-subunit-containing GABA$_A$Rs (Choi et al. 2008). It is not yet clear whether acute EtOH exposure activates PKC phosphorylation of the GABA$_A$R or whether phosphorylation on key amino acid residues is permissive for EtOH potentiation of receptor function, and this will be an interesting topic for future research.

EtOH potentiation of glycine-activated chloride channels appears to be dependent on receptor subunit composition. Potentiation is consistently greater at receptors containing the α1 subunit (Davies et al. 2003; Mascia et al. 1996; Mihic et al. 1997), at least when expressed in xenopus laevis oocytes (Valenzuela et al. 1998b, although see McCool et al. 2003; Yevenes et al. 2008). Receptors containing the α2 subunit also exhibit EtOH potentiation (McCool et al. 2003), but may be less sensitive than those containing the α1 subunit (Mascia et al. 1996). Inclusion of the β subunit along with α2 eliminates potentiation (McCool et al. 2003). Potentiation has also been observed in neurons from the brain and spinal cord, particularly in regions where the α1 subunit is expressed (Aguayo et al. 1996; Ye et al. 2001). Potentiation of the function of GABA$_A$ and glycine receptors is thought to increase inhibition of neurons. The relative influence of effects on synaptic versus extrasynaptic channels in producing this inhibition remains to be determined.

Acute EtOH exposure potentiates the function of 5-HT$_3$ receptors that contain an intrinsic cation channel (Lovinger 1991; Machu and Harris 1994). It is yet to be determined whether this action alters pre or postsynaptic mechanisms activated by this receptor.

1.1.2 Ionotropic Glutamate Receptors—The ionotropic glutamate receptors (iGluRs) constitute the second class of neurotransmitter- activated LGICs. Three major classes of iGluRs exist, the AMPA receptors (AMPARs, gene name GRIA, made by GluRs1-4), the NMDA receptors (NMDARs1-3, gene name GRIN), and the kainate receptors (KARs, made by GluRs5-7 and KAs1-2, gene name GRIK). These receptors are now thought to be tetrameric and each subunit contains a large N-terminal domain and an extracellular loop domain that together participate in ligand binding via a "venus fly-trap" motif (Gouaux 2004). The subunits have three membrane-spanning domains and a re-entrant pore-loop that forms the ion conduction pathway, as well as intracellular loops and a large intracellular C-

terminal domain. The iGluRs are all cationpermeable, with varying ratios of Na^+, K^+ and Ca^{2+} selectivity. These receptors are present on all CNS neurons, where they mediate fast synaptic transmission and activation of intracellular signaling.

EtOH has consistent inhibitory actions on iGluRs (although see Lu and Yeh 1999) (Fig. 1c, d). Inhibition of NMDARs at EtOH concentrations associated with intoxication is the best characterized of these effects (Criswell et al. 2003; Dildy and Leslie 1989; Hoffman et al. 1989; Lima-Landman and Albuquerque 1989; Lovinger et al. 1989). The synaptic responses mediated by NMDARs are also reduced by EtOH (Lovinger et al. 1990; Morrisett and Swartzwelder 1993; Roberto et al. 2004b; Wang et al. 2007).

Functional NMDARs always contain an obligatory NR1 subunit in combination with at least one NR2 or NR3 subunit. While EtOH inhibits all NMDAR subtypes, differences in the sensitivity to inhibition have been observed for recombinant with receptors containing different subunit compositions. The most common observation is that EtOH is less potent at receptors containing the NR1/2C composition in comparison to those containing NR1/2A or NR1/2B (Masood et al. 1994; Chu et al. 1995, but see Kuner et al. 1993; Lovinger 1995). There are several splice variants of the NR1-subunit, and a recent comprehensive study by Woodward and co-workers showed that the NR1 splicing status, in combination with the identity of the co-assembled NR2 subunit, has small but reliable effects on EtOH sensitivity (Jin and Woodward 2006). This NR1 splice variant effect could account for the previous difference in reports of low EtOH sensitivity of NR2C-containing receptors. Receptors containing the NR3 subunit are relatively insensitive to inhibition by EtOH, but inclusion of the NR2B-subunit enhances the EtOH inhibitory action on NR3-containing receptors (Jin et al. 2008). In addition, Mg^{2+} enhances EtOH inhibition of several NR1/2 and N1/2/3 receptor combinations, especially when NR2B is present (Jin et al. 2008). This finding may account for the larger effect of EtOH on NR2B containing NMDARs seen in some neuronal preparations (e.g. Fink and Göthert 1996; Lovinger 1995).

EtOH also inhibits the function of AMPARs, and effects can be seen at concentrations as low as 10 mM (Akinshola 2001; Akinshola et al. 2003; Dildy-Mayfield and Harris 1992; Möykkynen et al. 2003; Nieber et al. 1998; Wirkner et al. 2000). In neurons from the brain, EtOH generally shows lower potency for inhibition of AMPARs in comparison to NMDARs (Frye and Fincher, 2000; Lovinger et al. 1989; Lovinger 1995). The EtOH sensitivity of recombinant AMPAR receptors is not greatly altered by changing the receptor subunit composition (Lovinger 1993), although the potency of EtOH is slightly higher for inhibition of GluR1-containing in contrast to GluR3-containing GluRs in *X. laevis* oocytes (Akinshola 2001). In addition, recombinant AMPA receptors containing GluRs 2 and 3 exhibit slightly decreased EtOH sensitivity in comparison to those containing GluRs1, 2, and 3 or 3 alone (Akinshola et al. 2003). Recent studies suggest that this EtOH action involves increased receptor desensitization (Möykkynen et al. 2003, 2009), and thus the drug has little impact on AMPAR-mediated synaptic responses at most synapses given that desensitization does not contribute to the amplitude or time course of excitatory postsynaptic currents (EPSCs) (Lovinger et al. 1990; Ariwodola et al. 2003, but see Nie et al. 1993, 1994; Roberto et al. 2004b; Mameli et al. 2005; Zhu et al. 2007).

Inhibition of KAR-mediated responses has been observed at quite low EtOH concentrations (Costa et al. 2000; Lack et al. 2008; Valenzuela et al. 1998a; Weiner et al. 1999). However, direct examination of KAR-mediated ion current has yielded mixed results, at least for the receptor constructs examined to date (Dildy-Mayfield and Harris 1992; Valenzuela et al. 1998a). Thus, it is not yet clear whether EtOH inhibition of KAR function involves a direct effect on protein function or a more indirect action. EtOH inhibition of iGluRs is generally thought to dampen neuronal excitability in many brain regions by reducing excitatory synaptic drive and inhibiting synaptic plasticity that requires iGluR activation.

1.1.3 Purinergic Ligand-Gated Ion Channels—The third major subtype of LGIC is the P2X purinergic receptor subclass. P2X receptors are trimeric (Mio et al. 2005) with each subunit containing an N-terminal ligand binding domain, two membrane-spanning domains linked by an extracellular ligand binding domain, and a C-terminal intracellular domain of moderate length. The second membrane-spanning domain appears to serve as the lining for the ion conduction pathway. EtOH inhibits the function of most P2X receptor subtypes, with some effects reported at concentrations associated with intoxication (Davies et al. 2002; Li et al. 1993). The P2X4 receptor appears to be the most sensitive to inhibition by EtOH, while P2X3 receptors exhibit EtOH-induced potentiation (Davies et al. 2002, 2005). At present, the physiologic consequences of P2X inhibition are unclear.

1.2 G protein-Coupled Receptors and Roles in Ethanol Effects

The majority of neurotransmitter receptors are members of the G protein-coupled receptor (GPCR) superfamily. These receptors are specialized for binding a neurotransmitter, and this binding stimulates rearrangement of the protein to favor activation of intracellular signaling proteins known to bind GTP and GDP. In the GTP-bound state, the G protein is activated. Several forms of intracellular signaling proteins are affected by activated G proteins, including proteins that generate small molecule second messengers, as well as protein kinases and ion channels. Thus, G protein activation can affect neurophysiology fairly directly by altering ion channel function, and can have a long-lasting influence on neuronal function by altering intracellular signaling and even gene expression.

Receptor-activated G proteins are heterotrimeric, consisting of α, β, and γ subunits. The β and γ subunits form a tight complex, but when the G protein is activated the α subunit affinity for the β/γ complex is reduced. The result is that two signaling elements arise from the G protein activation and can act on different intracellular targets. The GPCRs act predominantly on three G protein subclasses: Gi/o, Gq-like, and Gs-like (Wickman and Clapham 1995). The Gi/o G protein class has net inhibitory effects on neuronal function, through actions of both the α and β/γ protein subunits. For example, the α subunit inhibits the enzyme adenylyl cylase (AC) that normally generates the second messenger cAMP. The β/γ subunits activate potassium channels that inhibit neuronal activity (the so-called G protein-activated inward rectifier, GIRK, potassium channels). The β/γ subunits also inhibit the function of voltage-gated calcium channels, leading to inhibition of neurotransmitter release, and also appear to have more direct effects on vesicle fusion (Dolphin 2003; Elmslie 2003; Miller 1998; Wu and Saggau 1994). The Gq-like α subunits activate protein and lipid signaling pathways that activate ion channels that excite neurons, inhibit potassium

channels, and increase neurotransmitter release. Thus, activation of the Gq-subclass generally has a net excitatory effect on neuronal activity and synaptic transmission. The proximal effects of Gs-like G protein activation are not always clear. The α subunit of these G proteins stimulates AC/cAMP formation which can enhance synaptic transmission and inhibits some potassium channels. The effects on ion channel function of the different G proteins are outlined in detail in previous review articles (Dolphin 2003; Elmslie 2003; Wickman and Clapham 1995).

Direct effects of acute EtOH on the function of GPCRs and G proteins are generally weak. Furthermore, the physiologic impact of these actions is not always clear. However, there are mechanisms involving these molecules that are influenced by EtOH. Studies beginning in the 1980s showed that EtOH can stimulate cAMP formation (Luthin and Tabakoff 1984; Rabin and Molinoff 1981). This may be due to direct EtOH actions on AC, but other proteins that influence GPCRs and their signaling might play roles in the neural actions of EtOH (Bjork et al. 2008). The physiologic consequences of this AC activation have long been unclear. However, recent studies indicate that acute EtOH exposure can increase neurotransmitter release (described in greater detail later in this review, Fig. 1), and activation of AC is a strong candidate to mediate these effects (Kelm et al. 2008).

In heterologous expression systems, EtOH has been shown to inhibit responses to activation of GPCRs that couple to Gq-like G proteins. These findings mostly involve demonstrations that pharmacologically relevant concentrations of EtOH reduce the ability of the GPCRs to activate a calcium-dependent chloride current in the *Xenopus laevis* oocyte preparation (Minami et al. 1997a, b, 1998). Among the GPCRs that have been examined in this context are metabotropic glutamate receptors (mGluRs), muscarinic ACh receptors and serotonin type 2 receptors. The observation that these three receptor effects are all inhibited despite differences in the structures of the receptor molecules themselves, indicates that the EtOH target site is likely downstream of the receptor itself. Indeed there is some evidence for involvement of protein kinase C, at least in the inhibition of muscarinic AChR-induced responses (Minami et al. 1997b).

EtOH can also potentiate the function of GIRK-type potassium channels (Aryal et al. 2009; Kobayashi et al. 1999; Lewohl et al. 1999). This effect occurs at concentrations associated with intoxication. The net effect of GIRK activation is to inhibit neuronal activity. This action of EtOH was originally observed in cerebellar granule neurons (Lewohl et al. 1999), and subsequent studies have indicated similar actions in midbrain dopaminergic neurons (Federici et al. 2009). EtOH effects on this G protein target may contribute to intoxication. Studies by Blednov et al. (2001) indicate that loss of the GIRK2 channel subunit alters acute EtOH actions. There is certainly a need for additional studies of how GIRK activation might contribute to intoxication.

1.3 Presynaptic Effects of Ethanol

EtOH potentiation of GABAergic synaptic inhibition is now known to result from both pre and postsynaptic actions. As discussed in the section on LGICs, the postsynaptic effects result from potentiation of GABA$_A$/anion channels. Recent studies indicate that EtOH also acts to enhance GABA release from presynaptic terminals, and this action contributes to

enhanced synaptic inhibition (reviewed in Siggins et al. 2005) (Fig. 1). Increases in fast GABAergic synaptic transmission during EtOH treatment have been observed in cerebellum, hippocampus, ventral tegmental area (VTA), hypoglossal nucleus, and amygdala, both basolateral and central nuclei (Ariwodola and Weiner 2004; Ming et al. 2006; Kelm et al. 2007; Theile et al. 2008; Zhu and Lovinger 2006; Roberto et al. 2003; Sebe et al. 2003; Ziskind-Conhaim et al. 2003). These studies have been carried out mostly in brain slices and isolated brain neurons. Examination of spontaneous and miniature GABAergic IPSCs allows investigators to determine whether the frequency of synaptic events is altered (a likely presynaptic change), or whether the amplitude is affected (likely a postsynaptic change). Such analyses have consistently shown that sISPC and mIPSC frequencies are increased at EtOH concentrations associated with intoxication, at least in the amygdala, cerebellum, hippocampus and VTA (Ariwodola and Weiner 2004; Zhu and Lovinger 2006; Theile et al. 2008; Roberto et al. 2003; Kelm et al. 2007). These effects are rapid at onset and rapidly reversible following EtOH removal from tissue.

At present, little is known about the mechanisms underlying EtOH potentiation of GABA release. The increase in mIPSC frequency suggests that the site of EtOH action is downstream of action potential generation and calcium entry into the presynaptic terminal. Experiments in the cerebellum and VTA suggest that EtOH interacts with mechanisms involved in intracellular calcium release, perhaps increasing calcium concentrations in the presynaptic terminal (Kelm et al. 2007; Theile et al. 2009). It would be helpful to know whether EtOH increases calcium concentrations in the relevant population of GABAergic presynaptic terminals. However, this is difficult to determine given the small size (<1 μM diameter) of terminals, and the diversity of subtypes of terminals found on any given neuron.

The role of intracellular signaling pathways in this potentiating EtOH effect has also been examined. It is well established that activation of AC or PKC potentiates transmission at synapses throughout the nervous system (see Leenders and Sheng 2005; Nguyen and Woo 2003 for review). Thus, it is logical to speculate that these signaling molecules might play a role in the acute alcohol action. Potentiation of GABA release onto cerebellar Purkinje neurons is eliminated in the presence of AC and protein kinase A (PKA) inhibitors (Kelm et al. 2008), and is also affected by compounds targeting phospholipase C and PKC (Kelm et al. 2010). The potentiating effect of EtOH is impaired in central amygdala (CeA) in mice that lack PKCε (Bajo et al. 2008). Thus, PKC is implicated in both the pre and postsynaptic effects of EtOH at GABAergic synapses. It is notable that GABA release appears to be increased in the PKCε knockout mice prior to EtOH exposure, and thus the effect in this case may be more akin to occlusion rather than blockade of the drug action. It remains to be determined whether the effects of EtOH on these signaling molecules are direct or indirect.

In contrast to the effects on GABA release, the vast majority of studies indicate that acute EtOH either has no effect or inhibits release of glutamate (reviewed in Siggins et al. 2005, although see Xiao et al. 2009; Eggers and Berger 2004). These findings suggest a fundamental difference between GABAergic and glutamatergic terminals in most brain regions that may be useful in determining what factors contribute to EtOH sensitivity of release.

1.4 Monoamines and Neurotransmitter Transport

Acute EtOH effects on neurotransmitter transport have been investigated using brain tissue and heterologous expression systems. In vivo studies indicate that EtOH increases monoamine levels in brain (reviewed in Gonzales et al. 2004, LeMarquand et al. 1994; Thielen et al. 2001). However, most studies of neurotransmitter transporters show them to be relatively insensitive to EtOH. However, increased cell surface expression of the dopamine transporter (DAT) was observed when this protein was heterologously expressed (Mayfield et al. 2001; Maiya et al. 2002). This effect would most likely decrease striatal dopamine during acute in vivo EtOH exposure in rodents, and thus does not help to explain the findings from in vivo studies. However, there is some controversy as to whether EtOH has potent effects on dopamine uptake measured in brain tissue using voltammetric techniques (Jones et al. 2006; Mathews et al. 2006; Robinson et al. 2005; Yavich and Tiihonen 2000). The EtOH-induced increase in striatal DA levels is unperturbed in DAT knockout mice, suggesting that the drug action responsible for this effect does not involve the transporter (Mathews et al. 2006). Furthermore, studies using in vitro voltammetry and in vivo microdialysis to measure dopamine levels indicate that direct infusion of EtOH into striatum does not alter DA levels (Mathews et al. 2006; Yan 2003; Yim et al. 1998). Thus, the physiologic impact of alterations in DAT function is not yet clear.

Examination of EtOH effects on the brain serotonergic system has yielded interesting findings. In addition to potentiating 5-HT$_3$ receptor function, as mentioned in the previous section on ligand-gated ion channels, inhibition of 5-HT1c by EtOH has also been reported (Sanna et al. 1994) although it is not clear whether this inhibition results from a direct effect on the receptor or on downstream signaling mechanisms. Exposure to acute EtOH also increases extracellular 5-HT levels in brain (LeMarquand et al. 1994; Thielen et al. 2001), and a recent report indicates that reduced 5-HT uptake may contribute to this effect as well as to the acute intoxicating effects of EtOH (Daws et al. 2006). However, EtOH effects on serotonin and other monoamines require further examination.

1.5 Ethanol and Synaptic Plasticity

Long-lasting changes in the efficacy of synaptic transmission are thought to contribute to brain development, learning and memory, and addiction (Hyman et al. 2006; Kauer and Malenka 2007). The most commonly studied forms of long-lasting synaptic plasticity are long-term potentiation (LTP), a persistent increase in synaptic transmission, and long-term depression (LTD), a persistent decrease in transmission. These types of plasticity are usually brought about by repetitive patterned activation of afferent inputs to a given postsynaptic neuron.

Effects of EtOH on LTP have been studied in different brain regions, but the majority of information comes from studies of the Schaffer collateral inputs to the CA1 pyramidal neurons of the hippocampal formation (Blitzer et al. 1990; Morrisett and Swartzwelder 1993; Mulkeen et al. 1987; Sinclair and Lo 1986). Acute EtOH exposure generally suppresses the induction of LTP at this and other synapses (Yin et al. 2007; Blitzer et al. 1990; Givens and McMahon 1995; Morrisett and Swartzwelder 1993; Mulkeen et al. 1987; Sinclair and Lo 1986; Wayner et al. 1993; Weitlauf et al. 2004). Effects occur at EtOH

concentrations associated with intoxication, and in some studies at surprisingly low concentrations (Blitzer et al. 1990; Fujii et al. 2008). EtOH also inhibits LTP induced by kainate receptor activation in the basolateral amygdala (Lack et al. 2008).

There is not as much information regarding EtOH effects on LTD. Two prominent subtypes of LTD can be elicited in the hippocampal CA1 region. The most widely studied form of LTD is induced by repetitive low-frequency synaptic activation, and requires activation of NMDA receptors (Dudek and Bear 1992; Mulkey and Malenka 1992). In the hippocampal CA1 region LTD is enhanced by exposure to EtOH at a concentration associated with strong intoxication (Hendricson et al. 2002), although this observation has not been consistent (Izumi et al. 2005).

Other forms of LTD observed in hippocampus and elsewhere involve activation of mGluRs (reviewed in Lüscher and Huber 2010). One report indicates that EtOH, at concentrations associated with severe intoxication, prevents mGluR-LTD at hippocampal synapses (Overstreet et al. 1997). At glutamatergic synapses onto cerebellar Purkinje neurons mGluR-LTD involves decreased surface expression and function of AMPARs (Ito 2001). Acute EtOH exposure inhibits this cerebellar LTD (Belmeguenai et al. 2008; Su et al. 2010), most likely due to inhibition of voltage-gated calcium channels and mGluR function. This finding is intriguing given that acute EtOH is known to impair motor coordination, and cerebellar function has been implicated in these effects. In the dorsal striatum, LTD involving these receptors also requires endocannabinoid (EC) signaling from the post to the presynaptic neuron (retrograde EC signaling) and subsequent activation of CB1 cannabinoid receptors (Gerdeman et al. 2002). The expression of this form of LTD appears to be on the presynaptic side of the synapse. Acute EtOH increases the expression of this EC-dependent mGluR-LTD in dorsal striatum (Yin et al. 2007). It is presently not clear what mechanisms contribute to this effect of EtOH.

2 Chronic Ethanol Actions

2.1 Chronic Ethanol Effects on Glutamatergic Transmission and Glutamate Roles in Synaptic Plasticity

Chronic EtOH treatment in animals provides critical information relevant to central changes that take place during long-term alcohol abuse in humans. Persistent EtOH exposure produces both tolerance and dependence. Tolerance is manifested as a decreased behavioral response to EtOH that implies a decrease in the intoxicating effects and other responses to the drug. Therefore, higher amounts of EtOH are required to achieve the same intoxicating effects seen with acute drug administration. EtOH dependence is generally described by symptomology elicited during and following withdrawal from EtOH (Heilig et al. 2010). These effects include anxiety, dysphoria and increased seizure susceptibility, hyperalgesia and disruption of sleep states (Enoch 2008; Grobin et al. 1998; Kumar et al. 2009). Chronic EtOH treatment is known to induce many neuroadaptive changes in the CNS involving both glutamatergic and GABAergic synaptic transmission.

The majority of work on chronic EtOH effects on glutamatergic transmission has focused on changes in glutamate receptors, particularly in light of the sensitivity of these receptors to

acute EtOH actions (see previous discussion). Chronic EtOH exposure generally produces an increase in the function of NMDARs and in NMDAR-mediated glutamatergic synaptic transmission (Cebere et al. 1999; Grover et al. 1998; Gulya et al. 1991; Lack et al. 2007; Smothers et al. 1997) (Fig. 1d). Initial studies examined effects of receptor activation on neuronal calcium and nitric oxide signals either in preparations made from EtOH-exposed animals or in cultured neurons treated with EtOH in the medium (Grover et al. 1998; Gulya et al. 1991; Chandler et al. 1997; Iorio et al. 1992; Smothers et al. 1997). Exposure to EtOH for days to weeks increased NMDAR agonist-induced increases in intracellular calcium. These effects could be observed at EtOH concentrations that did not alter neuronal viability and did not affect baseline intracellular calcium levels. Furthermore, changes in responses to NMDAR activation were consistently larger than changes in the effects of activation of other ionotropic glutamate receptors (Chandler et al. 1997; Gulya et al. 1991; Smothers et al. 1997). Direct examination of ion current through the NMDAR pore has revealed effects consistent with a chronic EtOH-induced upregulation of NMDAR function (Floyd et al. 2003; Grover et al. 1998). An increase in the component of current mediated by NR2B-containing receptors has also been observed (Floyd et al. 2003; Kash et al. 2009; Roberto et al. 2004b, 2006). Interestingly, acute EtOH inhibition of NMDARs in most brain regions is still intact or even increased after chronic in vivo exposure (Floyd et al. 2003; Roberto et al. 2006; Roberto et al. 2004b), although a small decrease in inhibition was observed in medial septum/diagonal band neurons (Grover et al. 1998). Evidence of tolerance to EtOH inhibition during acute exposure has also been observed in hippocampal slices (Grover et al. 1994; Miyakawa et al. 1997). Overall, it appears that NMDAR function is still suppressed during intoxication even after prolonged EtOH exposure, and thus the increase in NMDAR function is likely to be dramatic after EtOH withdrawal following chronic exposure. One consequence of the increase in NMDAR-mediated calcium influx appears to be an increase in susceptibility to excitotoxic effects of NMDA (Chandler et al. 1993; Iorio et al. 1993), although enhanced NMDAR-mediated neuroprotection can also be observed in young cerebellar granule neurons (Pantazis et al. 1998). It has thus been postulated that excitotoxicity during EtOH withdrawal contributes to alcohol-related neuronal loss in the brain.

The mechanisms underlying the increase in NMDAR function are still under investigation, but several interesting facets of the story have already emerged. Analysis of receptor function and pharmacology, as well as examination of receptor subunit expression and location, indicate that receptors containing the NR2B subunit are the subtypes most strongly affected by chronic EtOH exposure (Carpenter-Hyland et al. 2004; Floyd et al. 2003; Kash et al. 2009; Roberto et al. 2004b) (Fig. 1d). The molecular basis of increased NR2B function is less clear. While some investigators have reported increases in NR2B mRNA expression following chronic alcohol exposure in vitro (Hu et al. 1996; Snell et al. 1996), and in vivo (Follesa and Ticku 1995; Kash et al. 2009; Roberto et al. 2006) such increases have not been observed in every brain region (Cebere et al. 1999; Floyd et al. 2003; Läck et al. 2005). Increases in NR2B, and to a lesser extent NR2A, protein expression have also been observed using immunologic techniques after both in vitro and in vivo EtOH exposure (Kash et al. 2005; Obara et al. 2009; Snell et al. 1996). However, other investigators did not observe increased expression of this protein. Increased expression of mRNA and protein for other

NR subunits and particular NR1 splice variants has been observed in some brain regions following chronic EtOH exposure (Raeder et al. 2008; Trevisan et al. 1994; Roberto et al. 2006; Winkler et al. 1999, but see Morrow et al. 1994), but there is less evidence for increased receptor function as a result of these increases. Thus, it is not clear whether increased subunit expression is the driving force behind increased receptor function, and if so, what mechanisms underlie the increase in expression or trafficking.

Changes in subcellular distribution of receptors may also contribute to altered NMDAR function following chronic EtOH exposure. In cultured hippocampal neurons, exposure to EtOH leads to increased NMDAR expression in dendritic spines, the location of glutamatergic synapses (Carpenter-Hyland et al. 2004). This increased trafficking to spines is accompanied by an increase in the contribution of NMDARs to glutamatergic transmission, but does not appear to involve increased NMDAR protein expression. The synaptic NMDARs observed following chronic EtOH exposure appear to contain the NR2B subunit. Increases in the contribution of NMDARs to glutamatergic synaptic transmission have also been observed following subacute (10 s of seconds or minutes) EtOH exposure, and NR2Bcontaining receptors also appear to contribute to these increases (Wang et al. 2007; Yaka et al. 2003). Tyrosine phosphorylation by a Fyn-like kinase has been implicated in these rapid increases in the function of NR2B-containing receptors (Wang et al. 2007), but it is yet to be determined whether this mechanism plays a role in chronic EtOH effects on the receptor.

Chronic EtOH effects on AMPA and kainate receptors have been examined, with variable results. Increases in AMPA receptor subunit mRNA have been observed in hippocampus following chronic EtOH exposure (Bruckner et al. 1997). Expression of AMPAR subunit proteins was also induced by chronic exposure in primary cortical cultures (Chandler et al. 1999), while increased AMPAR binding was observed in cortical membranes from EtOH exposed animals (Haugbol et al. 2005). Evidence of increased AMPAR function has also been reported following chronic EtOH exposure, as measured with intracellular calcium signals in cerebellar Purkinje neurons (Netzeband et al. 1999), and AMPA receptor-mediated synaptic responses are increased in basolateral amygdala (Lack et al. 2007). This latter effect was observed following during withdrawal but not just after the end of chronic EtOH exposure. However, other studies have reported that AMPAR expression and function are not altered following chronic EtOH exposure (e.g. Smothers et al. 1997). The factors that underlie this variability in findings may include the type of preparation examined, the duration and pattern of EtOH exposure, and whether assays were performed just after the end of drug exposure or after withdrawal had been allowed to proceed. With respect to kainate receptors, Chandler and collaborations (Chandler et al. 1999) observed no change in receptor expression in cultured cortical neurons following chronic EtOH exposure. In contrast, enhancement of both subunit protein and kainate receptor function was found in cultured hippocampal neurons (Carta et al. 2002), and chronic intermittent EtOH increased KAR-mediated synaptic transmission in basolateral amygdala (Lack et al. 2009).

Chronic EtOH intake has also been shown to enhance intracellular signaling associated with mGluRs, particularly mGluR5, in the nucleus accumbens (NAc) (Cozzoli et al. 2009). While chronic EtOH drinking can induce increases in mGluR1 and mGluR5 protein expression in

NAc and amygdala (Szumlinski et al. 2008; Obara et al. 2009), changes in mGluR5 signaling in NAc are not always associated with an increase in the protein itself (Szumlinski et al. 2008). In cultured cerebellar Purkinje neurons, exposure to EtOH for 11 days produced a decrease in mGluR-induced dendritic calcium signals (Netzeband et al. 2002). Clearly, more work is needed to determine how signaling by the many mGluR subtypes changes with long-term EtOH exposure and drinking.

Measurements of extracellular glutamate levels in brain have generally shown increases produced by chronic EtOH exposure, especially after withdrawal or repeated cycles of withdrawal (Dahchour and De Witte 1999, 2003; Rossetti and Carboni 1995; Roberto et al. 2004b). These findings have generally been derived from measurements using in vivo microdialysis in brain. However, microdialysis measures of this type must be interpreted carefully, as both synaptic and nonsynaptic sources of glutamate contribute to the extracellular pool of this amino acid. Indeed, there is mounting evidence that changes in the cystine/glutamate exchanger generate increases in extracellular glutamate produced by some drugs of abuse (Kalivas 2009). Evidence of increased synaptic glutamate release has been observed in amygdala following chronic EtOH treatment (Lack et al. 2007; Zhu et al. 2007; Roberto et al. 2004b). Decreases in glutamate uptake have also been noted following chronic EtOH exposure (Melendez et al. 2005). There may be multiple factors that contribute to increased extracellular glutamate levels and increased glutamatergic transmission following chronic EtOH exposure and withdrawal.

Despite the evidence that NMDAR function and extracellular glutamate levels are increased following chronic EtOH exposure, studies of hippocampal LTP indicate that this form of synaptic plasticity is decreased under the same conditions (Durand and Carlen 1984; Roberto et al. 2002, although see Fujii et al. 2008). Similar results have been obtained in the amygdala (Stephens et al. 2005). It is not yet clear what factors underlie the decrease in LTP, but it is most likely that the loss of plasticity involves mechanisms occurring downstream of NMDAR activation in the LTP induction process.

2.2 Chronic Ethanol and GABAergic Transmission: Postsynaptic Effects

Chronic EtOH treatment is known to induce many neuroadaptative changes in the CNS. Over the past 20 years, it has been widely demonstrated that GABAergic transmission is sensitive to EtOH in distinct brain regions and is clearly involved in EtOH tolerance and dependence (Eckardt et al. 1998; Grobin et al. 1998). Chronic EtOH exposure often results in the development of tolerance to many GABAergic effects of the drug including the anxiolytic, sedative, ataxic, and positive reinforcing effects (Kumar et al. 2004, 2009). Substantial evidence suggests that these behavioral and neural adaptations involve marked changes in the expression profile of specific $GABA_A$ receptor subunits (Grobin et al. 1998) and in the pharmacological properties of $GABA_A$ receptors (Kang et al. 1998b) (Fig. 1).

Chronic EtOH administration differentially altered the expression of distinct $GABA_A$ receptor subunit mRNAs and peptide levels in various brain regions. In the cerebral cortex, both mRNA and peptide levels for $GABA_A$ receptor $\alpha 1$, $\alpha 2$, and $\alpha 3$ subunits were decreased (Devaud et al. 1995, 1997). In contrast, both $\alpha 4$, $\beta 1$, $\beta 2$, $\beta 3$, $\gamma 1$ and $\gamma 2$ subunit mRNA and peptide levels were increased (Devaud et al. 1995, 1997). These alterations in

the subunit expression affect the GABA$_A$ receptor assemblage and consequently, also affect receptor function and binding. It has been reported that recombinant GABA$_A$ receptors with α4β2γ2 subunits are less sensitive to GABA and benzodiazepines compared to α1β2γ2 receptors (Whittemore et al. 1996). Therefore, these alterations may account for the decreased sensitivity to GABA in cerebral cortical synaptoneurosomes (Morrow et al. 1988) and benzodiazepines in cortical membrane vesicles (microsacs) (Buck and Harris 1990). Following chronic EtOH exposure, acute EtOH did not facilitate the GABA or muscimol-stimulated Cl- uptake in cortex (Morrow et al. 1988) and in cerebellum (Allan and Harris 1987). In the cerebellum, chronic EtOH exposure decreased GABA$_A$ receptor α1 subunit mRNA and increased α6 subunit mRNA (Mhatre and Ticku 1992; Morrow et al. 1992). Chronic EtOH administration also decreased the polypeptide levels of the δ subunit of GABA$_A$ receptors in the rat cerebellum and hippocampus, whereas there were no changes in the δ subunit polypeptide levels in the rat cerebral cortex (Marutha Ravindran et al. 2007). Furthermore, chronic EtOH administration caused a down-regulation of native δ subunit-containing GABA$_A$ receptor assemblies in the rat cerebellum as determined by [(3)H]muscimol binding to the immunoprecipitated receptor assemblies (Marutha Ravindran et al. 2007).

The alterations in GABA$_A$ receptor gene expression are regionally and temporally dependent. For example, chronic EtOH consumption produced a significant increase in the level of GABA$_A$ receptor α4 subunit peptide in the hippocampus following 40 days but not 14 days exposure (Matthews et al. 1998). The relative expression of hippocampal GABA$_A$ receptor α1, α2, α3, β(2/3), or γ2 subunits was not altered by either period of chronic EtOH exposure (Charlton et al. 1997; Matthews et al. 1998). Hippocampal α1 subunit immunoreactivity and mRNA content were also significantly reduced after 12 weeks of treatment, but not after 4 weeks of exposure. In contrast, α5 mRNA content was increased in this brain region. In marked contrast, chronic EtOH consumption for both 14 (Devaud et al. 1997) and 40 (Devaud et al. 1997; Matthews et al. 1998) days significantly increased the relative expression of cerebral cortical GABA$_A$ receptor α4 subunits and significantly decreased the relative expression of α1 subunits (Devaud et al. 1997; Matthews et al. 1998). These findings indicate that chronic EtOH consumption alters GABA$_A$ receptor gene expression in the hippocampus but in a different manner from that in either the cerebral cortex or the cerebellum. In addition, these alterations are dependent on the duration of EtOH exposure (Grobin et al. 1998).

The Olsen and Spigelman groups have developed a chronic intermittent EtOH treatment paradigm in which rats are given a 5–6 g/kg dose of EtOH on alternate days for 60 treatments (120 days). This chronic administration of EtOH to rats on an intermittent regimen, for 60 repeated intoxicating doses and repeated withdrawal episodes, increases levels of α4 subunit mRNA in hippocampus with no significant change in the mRNAs for the α5 subunit (Mahmoudi et al. 1997). Similarly, rats that were exposed to intermittent episodes of intoxicating EtOH and withdrawal showed increased hippocampal α4 subunit peptide expression (Cagetti et al. 2003) and alteration in the pharmacological responses of GABA$_A$ receptors to benzodiazepine agonists and inverse agonists (Cagetti et al. 2003). The mRNA levels for the γ2S and γ1 subunits were also elevated. In CA1 pyramidal slices from chronic intermittent EtOH exposed rats, the baseline decay time of GABA$_A$R-mediated

mIPSCs was decreased, and the positive GABA receptor modulation of mIPSCs was also reduced compared with control rats. However, mIPSC potentiation by the α-preferring benzodiazepine ligand bretazenil was maintained, and mIPSC potentiation by Ro15-4513 was increased (Cagetti et al. 2003; Liang et al. 2009).

In the VTA, levels of α1 subunit immunoreactivity were significantly decreased after 12 weeks but not 1–4 weeks of treatment (Charlton et al. 1997). Papadeas et al. (2001) found that in the amygdala, α1 and α4 subunit expression was significantly decreased after two weeks of chronic EtOH consumption. In the nucleus accumbens (NAC), α4 subunit expression was decreased, but α1 subunit expression was not altered. In the VTA, there were no changes in α1 and α4 subunit expressions. Muscimol-stimulated Cl⁻ uptake was enhanced in the extended amygdala, but not the NAC of EtOH-dependent rats. These results suggest that chronic EtOH exposure alters GABA$_A$ receptor expression in the amygdala and NAC and that decreased expression of α4 subunits is associated with increases in GABA$_A$ receptor function in the amygdala but not the NAC (Papadeas et al. 2001).

Alterations in subunit assembly could induce alterations in the functional properties of GABA$_A$ receptors without alterations in the total number of receptors (Devaud et al. 1995; Kumar et al. 2009; Morrow et al. 1992). The expression of GABA$_A$ receptors involves a highly regulated process of synthesis, assembly, endocytosis, and recycling or degradation. Changes in the expression and composition of various GABA$_A$ receptors could result from selective endocytosis, recycling, and/or trafficking of newly synthesized receptors to the cell surface. GABA$_A$ receptor trafficking on the cell surface following EtOH consumption is thought to contribute to the development of EtOH-dependence (Kumar et al. 2004). It has been reported by Kumar et al. (2003) that chronic EtOH exposure selectively increases the internalization of α1 GABA$_A$ receptors with no change in the internalization of α4 GABA$_A$ receptors into clathrin coated vesicles of the cerebral cortex. There is also a decrease in α1 GABA$_A$ receptors and a significant increase in α4 subunit peptide in the synaptic fraction following chronic EtOH exposure. These results suggest that the regulation of intracellular trafficking following chronic EtOH administration may alter the subtypes of GABA$_A$ receptors on the cell surface and may account for changes in the pharmacological properties of GABA$_A$ receptors (Kumar et al. 2004) (Fig. 1).

Clathrin and the adaptor complex (AP) play a crucial role in the internalization of GABA$_A$ receptors following chronic EtOH administration. Notably, in the intracellular fraction, the clathrin-α1-GABA$_A$ receptor complex is increased following chronic EtOH administration (Kumar et al. 2004). Specific GABA$_A$ receptor subunits (β2 and/or γ2) are required for recognition of the receptor by the AP-2 that precedes clathrin-dependent endocytosis (Herring et al. 2003; Kittler et al. 2008). Chronic EtOH exposure induces an increase in the expression of α4-, β2-, and β3- GABA$_A$ receptor subunits in the cerebral cortex and all of these subunits contain consensus phosphorylation sites for PKC. In contrast, α1, α2, and α3 GABA$_A$ receptor subunits are decreased in the cortex and these subunits do not contain consensus phosphorylation sites for PKC. Hence, it has been hypothesized that PKC may phosphorylate the GABA$_A$ receptor subunits and/or AP-2 following chronic EtOH administration, altering the recognition and endocytosis of GABA$_A$ receptors by blocking AP-2 binding (Macdonald 1995; Mohler et al. 1996). A single dose of EtOH also increases

the internalization of GABA$_A$ receptor α4 and δ subunits (Liang et al. 2007). In rat hippocampus, chronic EtOH exposure induces a decrease in the tyrosine kinase phosphorylation of α1 subunits, an increase of β2 subunits and no alteration in γ2 subunits (Marutha Ravindran et al. 2007).

GABA$_A$ receptor trafficking is regulated by many protein kinases, including PKC, PKA, and fyn. However, to date, the role of these protein kinases has not yet been studied in the trafficking of GABA$_A$ receptors, especially following EtOH exposure. Chronic EtOH consumption decreases association of PKCγ with α1 GABA$_A$ receptors and increases association of PKCγ with α4 GABA$_A$ receptors, accompanied by a decreased expression of the α1 subunit and an increased expression of α4 at the cell surface in cerebral cortex (Kumar et al. 2002). However, there were no alterations in the association of PKCγ with GABA$_A$ receptors in the α1 subunit expression following chronic EtOH administration in the hippocampus (Kumar et al. 2004). The increased association of PKCγ with α4 GABA$_A$ receptors may phosphorylate GABA$_A$ receptor subunits and prevent recognition of the receptor by AP-2, thus preventing its internalization. Indeed, phosphorylation of GABA$_A$ receptor subunits reduced the binding of receptors with AP-2 and subsequent internalization (Kittler et al. 2008). Moreover, reduced PKC-dependent GABA$_A$ receptor phosphorylation increases receptor binding to the AP-2 and promotes receptor endocytosis (Terunuma et al. 2008). Chronic activation of PKA in cerebellar granule cells increases cell surface expression of GABA$_A$ receptor α1 subunit (Ives et al. 2002). EtOH exposure alters expression and translocation of PKA (Diamond and Gordon 1994; Newton and Messing 2006) suggesting that PKA is likely also involved in the trafficking of GABA$_A$ receptors following EtOH exposure. Future studies will determine the specific role of various protein kinases in GABA$_A$ receptor trafficking following chronic EtOH administration.

Post-translational modifications such as phosphorylation and glycosylation of GABA$_A$ receptors may play a role in the development of EtOH-dependence. In particular, phosphorylation of GABA$_A$ receptors has been demonstrated to modulate receptor function. In *Xenopus* oocytes and isolated mouse brain membrane vesicles (microsacs), PKC and PKA phosphorylation of GABA$_A$ receptors decreases receptor activation (Kellenberger et al. 1992; Krishek et al. 1994; Leidenheimer et al. 1992). Phosphorylation by CAM kinase II or tyrosine kinase enhances GABA$_A$ receptor function (Churn et al. 2002; Valenzuela et al. 1995). As discussed previously, acute EtOH induces changes in GABA$_A$ receptor function that may be dependent on phosphorylation of particular proteins. Chronic EtOH exposure might be expected to result in long-term changes in second messenger systems, including kinase activity. However, the heterogeneity of GABA$_A$ receptors expressed in vivo has precluded definitively answering this question and none of these studies have directly demonstrated that phosphorylation is involved in EtOH modulation of GABA$_A$ receptor function. The exact mechanisms involved in the alteration of GABA$_A$ receptor function following chronic EtOH exposure still remain to be determined.

From the preceding review, it is clear that the majority of the early studies characterizing chronic effects of EtOH on GABAergic transmission focused mainly on postsynaptic properties and the subunit composition of the GABA$_A$ receptors themselves. Some of the disparity in the findings across laboratories on postsynaptic sites of EtOH action may reflect

the differences in the chronic EtOH treatment duration and protocol, brain region examined, and methods of assessing receptor function. Most of these studies were generally in agreement that chronic EtOH exposure and withdrawal did not result in dramatic decreases in the number of GABA$_A$ receptors in most brain regions. However, many of these studies reported marked alterations in the expression of specific GABA$_A$ receptor subunits and hypothesized that those changes in the subunit composition of the GABA$_A$ receptors may account for the physiologic and pharmacologic alterations in GABAergic signaling associated with chronic EtOH administration (Grobin et al. 1998).

Of particular clinical importance is the development of tolerance and dependence to EtOH, and it is likely that adaptive changes in synaptic function in response to ethanol's actions on GABA$_A$ receptors play a role in this process. Indeed, it is well known that chronic EtOH treatment can lead to tolerance and physical dependence (Chandler et al. 1998) and withdrawal following long-term EtOH consumption is associated with increased neuronal excitability (Kliethermes 2005; Weiner and Valenzuela 2006). These alterations have been hypothesized to represent, in part, a compensatory adaptation to the in vitro acute facilitatory effects of EtOH on GABAergic synapses (Siggins et al. 2005; Weiner and Valenzuela 2006). Few studies have reported the effects of long-term EtOH exposure on GABAergic synaptic transmission looking at both postsynaptic and presynaptic mechanisms using in vitro brain slice methods.

As described above, the adaptive changes in GABA$_A$ receptor expression are thought to lead to a pronounced hypofunction of GABAergic neurotransmission and possibly the development of tolerance to the in vitro acute effects of EtOH on these synapses. In the hippocampus, there is a decrease in the threshold for seizure induction by the GABA$_A$ receptor antagonist pentylenetetrazole (Kokka et al. 1993) and a decrease in GABA$_A$ receptor activity in hippocampal slices that also lasts for at least 40 days after the last EtOH dose (Cagetti et al. 2003; Kang et al. 1996; Liang et al. 2004, 2009). Using analysis of tetrodotoxin (TTX)-resistant mIPSCs recorded from CA1 pyramidal neurons of chronic EtOH exposed and control rats, this group demonstrated a significant decrease in the amplitude and decay of these responses (Cagetti et al. 2003) possibly reflecting the observed alteration in the expression of α1 and α4 subunits. The mIPSC frequency is also slightly decreased, suggesting that chronic EtOH exposure may also be associated with a presynaptic decrease in GABA release at these synapses (see later section). Importantly, the pharmacological alterations in the properties of GABAergic synapses were consistent with the observed changes in subunit expression. For example, diazepam and the neurosteroid alphaxalone did not have any effect on mIPSCs in slices from chronic EtOH exposed rats (Cagetti et al. 2003), possibly reflecting the loss of α1 and γ-subunits, respectively.

On the other hand, drugs with some selectivity for α4-subunits (e.g., RO 15-4513 and DMCM) showed an increased modulation of mIPSCs possibly reflecting the increase in α4 subunit expression (Kang et al. 1996, 1998a, b). Interestingly, the evoked IPSCs were still sensitive to alphaxalone (Kang et al. 1998b) suggesting differences in the populations of GABA$_A$ receptors that underlie evoked and mIPSCs. In addition, the acute effect of EtOH on evoked IPSCs was significantly increased in slices from chronic EtOH-exposed rats (Kang et al. 1998a, b). Liang et al. (2004) have also compared the effects of chronic EtOH

exposure on synaptic and extra-synaptic receptor functions in CA1 neurons. These investigators found similar alterations in the synaptic mIPSCs and the tonic extrasynaptic GABA$_A$ receptor-mediated conductance associated with chronic EtOH exposure. Both mIPSCs and the tonic current show profound tolerance to α1-containing GABA$_A$ receptor selective doses of diazepam and zolpidem (Cagetti et al. 2003). As previously demonstrated (Grobin et al. 2000), chronic EtOH exposure results in a decrease in BZP-sensitive α1-subunits and an increase in BZP-insensitive α4-subunits at synaptic receptors. Thus, THIP (a high affinity and efficacy agonist of the α4-containing GABA$_A$ receptors and a partial agonist at most other GABA$_A$ receptor assemblies) activated the tonic GABA current in slices from control-untreated rats and had little effect in slices from chronic EtOH exposed rats (Liang et al. 2004). However, THIP depressed mIPSCs in control-untreated rats but strongly increased mIPSCs in chronic EtOH-treated rats. In addition, the chronic EtOH-treated rats show a modest tolerance to the soporific effects of THIP and no change in its anxiolytic effects (Liang et al. 2004).

In the previous decade, non-human primates (*Cynomolgus macaques*) have been a powerful model to study the effects of long-term EtOH consumption (Vivian et al. 2001). Ongoing research in the Weiner lab has provided the first evidence of neuroadaptations in the GABAergic synapses in monkey hippocampus (Weiner et al. 2005). In this paradigm of EtOH self-administration, cynomolgus macaques are trained to self administer a 4% EtOH solution on an operant panel and then given 22 h daily access to the EtOH solution. Control subjects were age-and sex-matched animals that had free access to food and water but were not exposed to the operant panels. The preliminary in vitro electrophysiologic findings revealed a significant increase in paired-pulse facilitation (PPF) of GABA$_A$ IPSCs in dentate granule cells in slices prepared immediately following the last day of 18 months of daily EtOH drinking. Their finding is consistent with a decrease in release probability (see later section) and is in agreement with the decrease in mIPSC frequency observed in rats following chronic intermittent EtOH exposure (Cagetti et al. 2003). Interestingly, there was lack of tolerance for both the acute facilitatory effect of EtOH and flunitrazepam on evoked GABA$_A$ IPSCs (Weiner et al. 2005). Using the same paradigm of EtOH self-administration, whole-cell patch clamp recordings on acutely dissociated amygdala neurons from EtOH-exposed cynomolgus macaques showed a decrease in the effect of flunitrazepam on the currents gated by exogenous GABA application compared with amygdala neurons from control animals (Anderson et al. 2007; Floyd et al. 2004). However, the modest inhibition of GABA-gated currents induced by acute EtOH was not affected by the chronic EtOH consumption. In addition, mRNA expression levels for the β, γ, and δ subunits in total amygdala RNA isolated from control and EtOH-drinking animals were measured. Chronic EtOH significantly reduced amygdala β1 and γ2 subunit expression. Overall, these findings demonstrate that chronic EtOH self-administration reduces the benzodiazepine sensitivity of amygdala GABA$_A$ receptors and this reduced sensitivity may reflect decreased expression of the γ subunit.

Roberto et al. (2004a) recently assessed whether GABAergic synaptic changes occur with EtOH-dependence in rat central amygdala (CeA) slices. To obtain dependent rats, these investigators used an EtOH vapor inhalation method (Rogers et al. 1979). In this study, male

Sprague–Dawley rats were exposed to a continuous EtOH vapor for 2–3 weeks with a targeted blood alcohol level of 150–200 mg/dL. Control rats were maintained in similar chambers without EtOH vapor. On experiment days, the chronic EtOH-treated rats were maintained in the EtOH vapor chamber until preparation of the CeA slices, and recordings of GABAergic transmission were made in EtOH-free solution 2–8 h after cutting the slices (Roberto et al. 2004a). The evoked IPSCs in CeA neurons from EtOH-dependent rats were significantly larger than in naïve rats. In EtOH-dependent rats, the mean baseline amplitude of mIPSCs was also significantly increased compared to naïve rats, suggesting a post synaptic effect of chronic EtOH (Roberto et al. 2004a). However, possible changes in the expression of GABA$_A$ receptor subunits were not characterized. It was also found that the baseline PPF ratio of IPSCs was significantly decreased and the mIPSC frequency was higher in neurons of EtOH-dependent rats compared to naïve rats, suggesting that GABA release was augmented in chronic EtOH treated rats (Roberto et al. 2004a) (see later section on presynaptic change).

In addition, acute EtOH (44 mM) increased IPSCs, decreased the PPF ratio of IPSCs and increased the mIPSCs frequency to the same extent in EtOH-dependent rats and naïve rats, suggesting a lack of tolerance for the acute EtOH effects (Roberto et al. 2004a). One of the most consistent findings from these recent studies is the lack of tolerance for the acute potentiating effect of EtOH on GABAergic synapses. These studies suggest that GABAergic mechanisms may not be associated with the tolerance that is known to develop with some of the behavioral effects of EtOH (e.g. ataxia, sedation). Additional studies will be needed to more carefully determine the molecular mechanisms responsible for these adaptive changes in different brain regions and length/duration of EtOH exposure required to induce such neuroadaptations in GABAergic synapse. Moreover, these data also suggest that, as with the acute effects of EtOH, long-term exposure to EtOH results in both pre and postsynaptic alterations and these changes may differ between brain regions (Siggins et al. 2005; Weiner and Valenzuela 2006).

2.3 Chronic Ethanol and GABAergic Transmission: Presynaptic Effects

There are only a few studies reporting that chronic EtOH exposure can alter GABAergic transmission by effects on GABA release. Short in vitro chronic EtOH exposure (one day) induced a transient decrease in mIPSC duration in cultured cortical neurons. Chronic EtOH exposure did not change mIPSC frequency nor did it produce a substantial cross-tolerance to a benzodiazepine in cortical neurons (Fleming et al. 2009). The results suggest that EtOH exposure in vitro has limited effects on synaptic GABA$_A$R function and action potential-independent GABA release in cultured neurons. This group also investigated the effect of chronic EtOH exposure on GABA release in cultured hippocampal neurons (Fleming et al. 2009). These investigators found that chronic EtOH exposure did not alter mIPSC kinetics and frequencies in hippocampal neurons (Fleming et al. 2009). These results suggest that EtOH exposure in cultured cortical and hippocampal neurons may not reproduce all the effects that occur in vivo and in acute brain slices.

In fact, more results generated using in vitro brain slices show a stronger effect of EtOH on GABA release, as discussed earlier in this review (Fig. 1). In vitro brain slice preparations

provide a number of highly sensitive experimental strategies that can be employed to detect presynaptic changes in transmitter release (for reviews of these approaches, see Siggins et al. 2005; Weiner and Valenzuela 2006).

Studies in the hippocampus show that chronic EtOH exposure decreased long-term potentiation (LTP) by increasing the electrically stimulated (but not basal) release of tritiated GABA pre-loaded in CA1 hippocampal slices (Tremwel et al. 1994). The GABA uptake or GABA$_A$R function was not altered, and this effect may be due to alterations in the muscarinic receptor regulation of GABA release at presynaptic terminals (Hu et al. 1999). In addition, studies using the GABA$_B$ receptor agonist baclofen to reduce release of tritiated GABA suggest that a change in GABA$_B$ auto-receptors on GABAergic terminals may also contribute to this effect of chronic EtOH exposure on LTP (Peris et al. 1997) (see later GABA$_B$ paragraph). For a general review of brain region specific EtOH actions on the GABA system see (Criswell and Breese 2005; Siggins et al. 2005; Weiner and Valenzuela 2006). More recent studies also reported that chronic EtOH consumption induces tolerance to the impairing effects of acute EtOH treatment on induction of LTP in rat CA1 slices (Fujii et al. 2008). In CA1 slices from control rats, stable LTP was induced by tetanic stimulation, and LTP induction was blocked if the tetanus was delivered in the presence of 8.6 mM EtOH or muscimol. A decrease in the stimulation threshold for inducing LTP was found in hippocampal slices from chronic EtOH-treated rats. In addition, application of EtOH or muscimol did not affect LTP induction in these cells, suggesting that the effects of chronic EtOH exposure on LTP induction are mediated by a reduction in GABAergic inhibition in hippocampal CA1 neurons (Fujii et al. 2008).

Weiner et al. (2004) found that voluntary EtOH drinking is associated with a significant increase in paired-pulse plasticity at GABAergic synapses in dentate gyrus neurons from the hippocampal formation of monkeys (cynomolgus macaques), consistent with a reduction in GABA release probability. In addition, a lack of tolerance to the facilitating effects of both acute EtOH and flunitrazepam on the GABA$_A$ IPSCs was reported.

In contrast, Melis et al. (2002) reported that a single EtOH exposure in vivo induces a long-lasting facilitation of GABA transmission in the VTA of EtOH-preferring C57BL/6 mice. These investigators observed that evoked GABA$_A$ IPSCs in dopaminergic neurons of EtOH-treated animals exhibited paired-pulse depression (PPD) compared with saline-treated animals, which exhibited PPF (Melis et al. 2002). An increase in frequency of mIPSCs was also observed in the EtOH-treated animals. Moreover, the GABA$_B$ receptor antagonist, CGP35348, shifted PPD to PPF, indicating that presynaptic GABA$_B$ receptor activation, likely attributable to GABA spillover, might play a role in mediating PPD in the EtOH-treated mice (see later GABA$_B$ paragraph). In a more recent study, the same group (Wanat et al. 2009) demonstrated that EtOH exposure also increased GABA release onto VTA dopamine neurons in EtOH non-preferring DBA/2 mice. However, a single EtOH exposure reduced glutamatergic transmission and LTP in VTA dopamine neurons from the EtOH non-preferring DBA strain but not EtOH-preferring C57BL/6 mice (Wanat et al. 2009).

Additional data from Roberto et al. (2004a, 2010) further suggest that chronic EtOH exposure can affect CeA GABA release, perhaps via an action on GABAergic terminals.

Baseline GABA$_A$ IPSCs were significantly higher, and baseline PPF of GABA$_A$ IPSCs was significantly smaller in CeA neurons from EtOH-dependent rats compared to non-dependent rats, suggesting that evoked GABA release was augmented after chronic EtOH exposure. These investigators also reported an increase in the baseline frequency of mIPSCs in CeA neurons from EtOH-dependent rats compared to that of naïve controls. Acute superfusion of EtOH significantly enhanced GABA$_A$ IPSCs, decreased the PPF ratio of IPSCs, and increased the mIPSC frequency to the same extent in CeA slices from EtOH-dependent rats and naïve rats, suggesting a lack of tolerance to the presynaptic acute EtOH effects (Roberto et al. 2004a). In addition, these investigators estimated the interstitial GABA levels in CeA using microdialysis in freely moving rats. In agreement with the in vitro electrophysiologic results, the in vivo data showed a fourfold increase of baseline dialysate GABA concentrations in CeA of EtOH-dependent rats compared to naïve rats. Moreover, local administration of EtOH by dialysis increased the dialysate GABA levels in CET rats. These findings again indicate a lack of tolerance to presynaptic acute EtOH effects on GABA release in CeA of CET rats (Roberto et al. 2004a). These studies strengthen the possibility that chronic as well as acute EtOH may alter the function of the GABAergic synapses acting at both the postsynaptic site and presynaptic terminals. Altogether, these data suggest that long-term exposure to EtOH causes changes at GABAergic synapses that may differ between brain regions and with the duration of chronic exposure. Further studies will be needed to more carefully determine the specific exposure durations required to elicit these changes in GABAergic synapses, the molecular mechanisms responsible for these adaptive changes, as well as their behavioral consequences with respect to withdrawal and dependence.

Another area in which action of EtOH on GABA function has been implicated is withdrawal from chronic EtOH. Withdrawal results in an increased sensitivity to induction of seizures (Allan and Harris 1987; Frye et al. 1983). Several functional and behavioral studies on benzodiazepines and other drugs with GABA mimetic action reduced such withdrawal-related hyper-excitability (Breese et al. 2006; McCown et al. 1985; Roberto et al. 2008; Ticku and Burch 1980). Collectively, these results offer strong support for the hypothesis that at least a part of the action of EtOH was mediated by effects on neural functions associated with GABA transmission and that these effects play an important role in the maintenance of addictive drinking behavior.

2.4 γ-Aminobutyric Acid$_B$ Receptors and Chronic Ethanol Actions

Several studies demonstrated GABA$_B$ receptor involvement in the effects of EtOH. For instance, GABA$_B$ receptor antagonists enhance the ability of acute EtOH to facilitate GABA transmission in the hippocampus (Ariwodola and Weiner 2004; Wan et al. 1996; Wu and Saggau 1994) and NAc (Nie et al. 2000). Ariwodola and Weiner (2004) suggested that the effect of EtOH to facilitate GABA transmission is limited because of GABA feedback on presynaptic GABA$_B$ receptors (Fig. 1). The presence of GABA$_B$ receptors accounted for the difference in sensitivity to EtOH influences on GABA transmission in specific subfields of the hippocampus (Weiner et al. 1997). On the other hand, GABA$_B$ receptors did not influence GABA release from neurons in the CeA (Roberto et al. 2003). Thus, the involvement of GABA$_B$ receptors on GABA release in various brain regions may not be

universal, suggesting that the presence or absence of presynaptic GABA$_B$ receptors may be an important determinant for the regional specificity of EtOH to affect GABA transmission (Ariwodola and Weiner 2004).

As mentioned above, Peris et al. (1997) showed that chronic EtOH treatment, sufficient for decreasing LTP in rats, also increased 3H-GABA release from hippocampal slices in these same animals. These investigators characterized presynaptic auto-receptor modulation of 3H-GABA release in hippocampal slices from control and EtOH-dependent rats. Effects of a GABA$_B$ receptor agonist (baclofen) and antagonist [2-hydroxy (OH)-saclofen] on electrically stimulated 3H-GABA release from superfused hippocampal slices were examined. Baclofen decreased stimulated release in a dose-dependent manner and the antagonist 2-OH-saclofen increased release consistent with the presence of presynaptic GABA$_B$ auto-receptors in hippocampus. The GABA$_A$ antagonist bicuculline did not significantly modulate basal or stimulated release. Presynaptic modulation of release by baclofen and 2-OH-saclofen was decreased in animals 48 h after withdrawal from EtOH. Using quantitative autoradiographic techniques, the density of 3H-baclofen binding sites in the hippocampus was not affected by chronic EtOH exposure, whereas the density of 3H-bicuculline binding sites was increased by 28% in EtOH-treated rats. These data may explain how chronic EtOH treatment increases presynaptic regulation of GABA release from hippocampus that may contribute to the decrease in LTP seen in rats after chronic EtOH exposure (Peris et al. 1997).

Another study assessed the impact of EtOH on postsynaptic GABA$_B$ receptors via baclofen-induced hyperpolarization of hippocampal CA1 and CA3 pyramidal neurons. These receptors activate outward K$^+$ currents via a pertussis toxin-sensitive G protein cascade to reduce membrane potential during the slow inhibitory postsynaptic potential and may play a role in EtOH intoxication and withdrawal excitability. In both types of pyramidal neurons, baclofen applied consecutively in increasing concentrations caused concentration-dependent hyperpolarization. There were no significant differences in resting membrane potential, input resistance, maximum baclofen-induced hyperpolarization, or EC$_{50}$ between CA1 and CA3 neurons, although slope values were significantly smaller in the former neurons. These parameters were not significantly changed in the presence of EtOH 10–100 mM. Chronic EtOH treatment (12 days) did not shift sensitivity or maximum response to baclofen in CA1 neurons. These results suggest that GABA$_B$ receptors in this model were essentially insensitive to EtOH (Frye and Fincher 1996).

Melis et al. (2002) linked the long-lasting potentiation of GABAergic synapses on dopaminergic neurons in the VTA by systemic EtOH to an effect on presynaptic GABA$_B$ receptors. Moreover, the frequency (but not the amplitude) of mIPSCs was also significantly higher in VTA neurons of EtOH-treated animals compared to controls, further supporting an increased probability of presynaptic GABA release independent of neuronal discharge in VTA neurons treated with EtOH. Interestingly, the GABA$_B$ receptor antagonist, CGP 35348, shifted PPD to PPF in EtOH-treated animals by increasing the amplitude of the second evoked GABA$_A$ IPSC and without affecting GABA$_A$ IPSC in the saline-treated animals. In addition, both the frequency and the amplitude of mIPSCs were unaffected by CGP 35348 in both groups of mice. Thus, the PPD observed in the EtOH-treated mice could

result from an increased probability of GABA release, which might in turn lead to activation of presynaptic $GABA_B$ receptors and decrease the second IPSC. These results further support the hypothesis that GABA levels are increased after EtOH exposure, leading to spillover onto presynaptic $GABA_B$ receptors, whose activation leads to inhibition of release (Hausser and Yung 1994; Melis et al. 2002).

In a recent study, Roberto et al. (2008) reported neuroadaptations in $GABA_B$ receptors in CeA after chronic EtOH exposure. The sensitivity of GABA IPSCs to the $GABA_B$ receptor antagonist CGP 55845A and agonist baclofen was decreased after chronic EtOH, suggesting downregulation of this system. Specifically, the $GABA_B$ receptor antagonist, CGP 55845A significantly increased the mean amplitude of evoked IPSCs (by $12 \pm 5\%$) in CeA from naïve rats. This increase in the IPSC amplitude was associated with a significant decrease in PPF, suggesting a tonic activation of presynaptic $GABA_B$ receptors in naïve rats. In contrast, in CeA from EtOH-dependent rats, CGP 55845A did not alter the mean evoked IPSCs ($98 \pm 4\%$) and did not affect mean PPF. Baclofen ($10\ \mu M$) markedly depressed evoked GABA-IPSC amplitudes in neurons of naïve rats (to 38% of control), with recovery during washout. The baclofen-induced inhibition of GABA IPSCs was significantly reduced (to 86% of control) in neurons of EtOH-dependent rats. In addition, in CeA neurons from EtOH-dependent rats, baclofen-induced depression was associated with a smaller increase of the PPF ratio of GABA IPSCs compared to that in neurons of naïve rats. These data suggest that the downregulation of the $GABA_B$ system associated with EtOH-dependence may explain in part the increased GABAergic tone reported in dependent rats (Roberto et al. 2008).

3 Neuropeptide Roles in Acute and Chronic Alcohol Actions

Neuropeptides are potent neuromodulators in the CNS whose actions are mediated via GPCRs. In contrast to classical neurotransmitters, neuropeptides are released in a frequency-dependent fashion and often have a longer half-life of activity after release. These factors, among others, enable neuropeptides to produce long-lasting effects on cellular functions such as excitatory and inhibitory synaptic transmission, neuronal excitability, and gene transcription (Gallagher et al. 2008). Thus, a long-lasting dysregulation of neuropeptides could have significant effects on the activity of neurons and consequently, behavior.

3.1 Corticotropin-Releasing Factor

Corticotropin-releasing factor (CRF) is a 41-amino acid polypeptide that has a major role in coordinating the stress response of the body by mediating hormonal, autonomic, and behavioral responses to stressors. CRF (originally called corticotropin- releasing hormone, although the International Union of Pharmacology designation is CRF) was identified through classic techniques of peptide sequencing (Vale et al. 1981). Subsequently, genes encoding three paralogs of CRF—urocortins 1, 2, and 3 (*Ucn 1, Ucn 2, Ucn 3*), were identified by modern molecular biologic approaches. Ucn 2 and Ucn 3 are also referred to as stresscopin-related peptide and stresscopin, respectively. CRF and the urocortins have been implicated in the modulation of multiple neurobiologic systems, including those that regulate feeding, anxiety and depression, hypothalamic-pituitary-adrenal (HPA) axis signaling, and EtOH consumption (Hauger et al. 2006; Heilig and Koob 2007; Ryabinin and Weitemier 2006; Smith and Vale 2006). CRF and the Ucn peptides produce their effects by

binding to the G protein-coupled CRF type 1 (CRF1R) and CRF type 2 (CRF2R) receptors. CRF binds to both receptors, but has greater affinity for the CRF1R (Bale and Vale 2004; Fekete and Zorrilla 2007; Hauger et al. 2006; Pioszak et al. 2008).

CRF1R and CRF2R are GPCRs that are predominantly positively linked to the activation of AC (Fig. 1), and recent reports also implicate other second messenger systems such as inositol triphosphate and PKC (Blank et al. 2003; Grammatopoulos et al. 2001). Using corticotrophins, Antoni et al. (2003) demonstrated a coupling of CRF1R to AC9 and AC7. The switch in coupling from AC9 to AC7 results in a more robust cAMP signal when CRF binds to the CRF1R (Antoni 2000; Antoni et al. 2003). It should be emphasized that AC7 is localized both postsynaptically (striatum, hippocampus) and presynaptically (nucleus accumbens, amygdala) (Mons et al. 1998a, b), and is anatomically positioned to receive signals from GPCRs on both dendrites and axon terminals.

Pharmacological and transgenic studies show that brain and pituitary CRF1Rs mediate many of the functional stress-like effects of the CRF system (Heinrichs and Koob 2004). CRF and the Ucn peptides have a wide distribution throughout the brain, but there are particularly high concentrations of cell bodies in the paraventricular nucleus of the hypothalamus, the basal forebrain (notably the extended amygdala), and the brainstem (Swanson et al. 1983). Ucn1 binds with equal affinity to CRF1R and CRF2R, and Ucn2 and Ucn3 are CRF2R agonists (Hauger et al. 2006; Pioszak et al. 2008). CRF and the Ucn peptides exert their behavioral and neuroendocrine actions through central hypothalamic and extrahypothalamic pathways (Hauger et al. 2006; Heilig and Koob 2007; Heinrichs and Koob 2004; Koob and Le Moal 2008).

Increasing evidence implicates CRF and its receptors in the synaptic effects of EtOH. EtOH induces release of CRF from the hypothalamus that initiates the activation of the HPA axis (Ogilvie et al. 1998). EtOH also modulates the extraneuroendocrine CRF system involved in behavioral stress responses, particularly in the amygdala. EtOH withdrawal induces an increase in CRF levels in the amygdala (Merlo Pich et al. 1995) and in the BNST (Olive et al. 2002).

The central administration of a CRF antagonist attenuates both EtOH self-administration and the anxiety-like response to stress observed during alcohol abstinence (Valdez et al. 2002) and administration of a CRFR antagonist into the CeA reverses the anxiogenic-like effect of alcohol (Rassnick et al. 1993). Rats tested 3–5 weeks post alcohol withdrawal showed an anxiogenic-like response provoked by a mild restraint stress only in rats with a history of alcohol dependence. This stress-induced anxiogenic-like response was reversed by a competitive CRF1R antagonist (Valdez et al. 2003). The increased self-administration of alcohol observed during protracted abstinence also was blocked by a competitive CRF1R antagonist (Valdez et al. 2003). Gehlert et al. (2007) also described that a novel CRF1R antagonist, the 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (MTIP) has advantageous properties for both clinical development and in preclinical alcoholism models. MTIP dose-dependently reversed anxiogenic effects of EtOH withdrawal, and blocked excessive alcohol self-administration in Wistar rats with a history of dependence (Gehlert et al. 2007). CRF also contributes to increased alcohol

consumption in dependent animals, because increased EtOH self-administration is reduced by CRF1R antagonists in dependent animals but not in non-dependent animals (Funk et al. 2007; Overstreet et al. 2004) and by CRF1R deletion (Chu et al. 2007; Sillaber et al. 2002). More recently, it has been reported that chronic CRF1R antagonist treatment blocked withdrawal-induced increases in alcohol drinking by dependent rats, and tempered moderate increases in alcohol consumption (Roberto et al. 2010). These results have led to the hypothesis that negative emotional states (including anxiety-like states) contribute to the compulsive alcohol intake associated with dependence via negative reinforcement mechanisms (Koob 2008).

A recent review (Lowery and Thiele 2010) provides a comprehensive overview of preclinical evidence from rodent studies that suggest a promising role for CRFR antagonists in the treatment of alcohol abuse disorders. CRFR antagonists protect against excessive EtOH intake resulting from EtOH dependence without influencing EtOH intake in non-dependent animals. Similarly, CRFR antagonists block excessive binge-like EtOH drinking in non-dependent mice but do not alter EtOH intake in mice drinking moderate amounts of EtOH (Lowery and Thiele 2010). CRFR antagonists also protect against increased EtOH intake and relapse-like behaviors precipitated by exposure to a stressful event. Additionally, CRFR antagonists attenuate the negative emotional responses associated with EtOH withdrawal. The protective effects of CRFR antagonists are modulated by CRF1R. Finally, recent evidence has emerged suggesting that CRF2R agonists may also be useful for treating alcohol abuse disorders for review see (Lowery and Thiele 2010).

Low CRF concentrations can influence neuronal properties in the CNS (see (Aldenhoff et al. 1983; Siggins et al. 1985). CRF decreases the slow after hyperpolarizing potential in hippocampus (Aldenhoff et al. 1983) and CeA (Rainnie et al. 1992), and enhances R-type voltage-gated calcium channels in rat CeA neurons (Yu and Shinnick-Gallagher 1998). These and other data (Liu et al. 2004; Nie et al. 2004, 2009; Roberto et al. 2010; Ungless et al. 2003) also suggest that CRF plays an important role in regulating synaptic transmission in CNS. For example, in VTA dopamine neurons, CRF potentiates NMDA-mediated synaptic transmission via CRF_2 activation (Ungless et al. 2003), and we recently found that CRF augments GABAergic inhibitory transmission in mouse CeA neurons via CRF1 activation (Fig. 1).

3.1.1 Corticotropin-Releasing Factor Actions in the Ventral Tegmental Area—

The ventral tegmental area (VTA) receives CRF inputs from a number of sources including the limbic forebrain and the paraventricular nucleus of the hypothalamus (Rodaros et al. 2007). These CRF inputs form symmetric and asymmetric synapses, mostly onto dendrites that co-release either GABA or glutamate, respectively (Tagliaferro and Morales 2008). VTA dopamine neurons express both types of CRF receptors, CRF1R and CRF2R (Ungless et al. 2003), and approximately 25% of VTA dopamine neurons express the CRF binding protein (CRF-BP) (Wang et al. 2005; Wang and Morales 2008). CRF regulates dopamine neurons through a subtle interplay of effects at CRF1R, CRF2R, and CRF-BP. CRF increases the action potential firing rate in VTA dopamine neurons via CRF1R and involves a PKC-dependent enhancement of I_h (a hyperpolarization-activated inward current) (Wanat et al. 2008). CRF enhanced the amplitude and slowed the kinetics of IPSCs following

activation of D2-dopamine and GABA$_B$ receptors. This action is postsynaptic and dependent on the CRF1R. The enhancement induced by CRF was attenuated by repeated in vivo exposures to psychostimulants or restraint stress (Beckstead et al. 2009).

CRF can induce a slowly developing, but transient, potentiation of NMDAR-mediated synaptic transmission (Ungless et al. 2003). This effect involves the CRF2R and activation of the protein kinase C pathway and the requirement of CRF-BP. However, the effect of CRF is restricted to a subset of dopamine neurons expressing large I_h currents (Ungless et al. 2003).

In addition to fast, excitatory glutamate-mediated synaptic transmission, dopamine neurons also express metabotropic glutamate receptors (mGluRs) which mediate slower, inhibitory synaptic transmission (Fiorillo and Williams 1998). The rapid rise and brief duration of synaptically released glutamate in the extracellular space mediates a rapid excitation through activation of ionotropic receptors, followed by inhibition through the mGluR1 receptor (Fiorillo and Williams 1998). CRF can enhance these mGluRs via a CRF2R-PKA pathway that stimulates release of calcium from intracellular stores (Riegel and Williams 2008). The CRF modulation of VTA synaptic activity is very complex because CRF has diverse actions on dopamine neurons that are excitatory and inhibitory. In summary, the excitatory effects of CRF on dopamine neurons appear to affect fast events (e.g. action potential firing rate and NMDAR-mediated synaptic transmission), whereas the inhibitory effects involve slow forms of synaptic transmission. Another important aspect is that CRF1R-mediated effects do not involve interactions with the CRF-BP, whereas CRF2R-mediated effects do.

It is speculated that these effects on short-term plasticity phenomena may modulate longer lasting forms of plasticity. For example, NMDAR activation is required for the induction of long-term potentiation in VTA dopamine neurons (Bonci and Malenka 1999; Borgland et al. 2010).

3.1.2 Corticotropin-Releasing Factor Actions in the Central Amygdala—The central amygdala (CeA) contains CRF receptors and abundant CRF-containing fibers (De Souza et al. 1984) (Uryu et al. 1992; CRF itself is generally co-localized in CeA neurons together with GABA (Eliava et al. 2003) (Asan et al. 2005). Acute EtOH augments evoked GABA$_A$ receptor-mediated inhibitory postsynaptic currents (IPSCs) by increasing GABA release in both mouse (Bajo et al. 2008; Nie et al. 2004) and rat CeA neurons (Roberto et al. 2003, 2004).

CRF1Rs mediate the EtOH-induced augmentation of IPSCs in mouse CeA (Nie et al. 2004; Nie et al. 2009) via the PKCε signaling pathway (Bajo et al. 2008; Nie et al. 2004). Both CRF and EtOH augment evoked IPSCs in mice CeA neurons, and CRF1R (but not CRFR2) antagonists blocked both CRF and EtOH effects. In addition, CRF and EtOH augment IPSCs in wild-type and CRF2R knockout mice, but not in CRF1R knockout mice (Nie et al. 2004).

New electrophysiological data showed that CRF, like EtOH, also enhances GABAergic transmission in the rat CeA (Roberto et al. 2010). As in mice, CRF and EtOH actions

involve presynaptic CRF1R activation at the CeA GABAergic synapses. Interestingly, the interactions between the CRF and GABAergic systems in the CeA may play an important role in alcohol reward and dependence (Roberto et al. 2010). These results suggest that the presynaptic effect of EtOH on GABA release in rodent CeA involves CRF1R and perhaps release of CRF itself. Thus, superfusion of CRF has an effect on GABA IPSCs equivalent to that of EtOH: an increase in IPSC amplitude of about 30–50%. Furthermore, both CRF and EtOH decreased PPF of IPSCs in mouse and rat neurons, and the effects of both were selectively blocked by CRF1R antagonists. In addition, both EtOH and CRF increase the frequency of GABAR-mediated mIPSCs, and this effect is blocked by CRF1R antagonists (Nie et al. 2004; 2009; Roberto et al. 2010). Thus, EtOH probably enhances the release of GABA by activating CRF1R on GABAergic terminals (Nie et al. 2009; Roberto et al. 2010). Conversely, CRF1R antagonists directly increased PPF of IPSCs and decreased mIPSC frequencies, consistent with decreased GABA release, thus opposing EtOH effects. Because GABA and CRF are often co-localized in CeA neurons, the EtOH-elicited GABA release may involve release of the CRF peptide itself, perhaps even from the terminals synapsing on autoreceptors on the same cell bodies or on collaterals from other GABAergic interneurons. Thus, this example raises the possibility of involvement of other, secondary messengers in EtOH effects on GABAergic terminals.

Chronic EtOH exposure produces functional adaptation of the CRF system in CeA (Hansson et al. 2006, 2007; Sommer et al. 2008; Weiss et al. 2001). In the study by Roberto et al. electrophysiological experiments were performed 2–8 h after preparation of CeA slices from EtOH-dependent or naïve control rats. Interestingly, in CeA of dependent rats, the ability of maximal (200 nM) and a submaximal (100 nM) concentrations of CRF to augment evoked IPSCs was significantly enhanced compared to naïve CeA. A greater effect of CRF1R antagonists on basal IPSCs of dependent rats was also reported. The greater effect of CRF and CRF1R antagonists may reflect increased tonic release of endogenous CRF, constitutive CRF1R activation, increased receptor number, and/or sensitization of CRF1R in CeA of dependent rats. These combined findings suggest an important EtOH–CRF interaction on GABAergic transmission in the CeA that markedly increases during development of EtOH dependence (Roberto et al. 2010).

CRF-related peptides serve as hormones and neuromodulators of the stress response and play a role in affective disorders. It has been shown that excitatory glutamatergic transmission is modulated by two endogenous CRF-related peptide ligands, CRF rat/human (r/h) and Ucn I, within the CeA and the lateral septum mediolateral nucleus (LSMLN) (Liu et al. 2004). Activation of these receptors exerts diametrically opposing actions on glutamatergic transmission in these nuclei. In the CeA, CRF(r/h) depressed excitatory glutamatergic transmission through a CRF1R-mediated postsynaptic action, whereas Ucn I facilitated synaptic responses through pre and postsynaptic CRF2R-mediated mechanisms. Conversely, in the lateral septum mediolateral nucleus (LSMLN), CRF induced a CRF1R-mediated facilitation of glutamatergic transmission via postsynaptic mechanisms, whereas Ucn I depressed EPSCs by postsynaptic and presynaptic CRF2R-mediated actions. Furthermore, antagonists of these receptors also affected glutamatergic neurotransmission, indicating a tonic endogenous modulation at these synapses (Liu et al. 2004). These data show that CRF receptors in CeA and LSMLN synapses exert and maintain a significant

synaptic tone and thereby regulate excitatory glutamatergic transmission. The results also suggest that CRF receptors may provide novel targets in affective disorders and stress (Liu et al. 2004).

3.1.3 Corticotropin-Releasing Factor Actions in the Bed Nucleus of the Stria Terminalis—The bed nucleus of the stria terminalis (BNST), a brain region associated with anxiety, has enriched expression of CRF (Ju and Han 1989) and CRFRs (Van Pett et al. 2000). A component of the extended amygdala, the BNST is anatomically well-situated to integrate stress and reward-related processing in the CNS, regulating activation of the HPA axis and reward circuits. The BNST receives dense GABAergic and CRF input from the CeA (Sakanaka et al. 1986), suggesting that CRF regulation of function in the BNST is critical for shaping BNST output. Pharmacological studies suggest that CRF signaling in the BNST is involved in anxiety (Lee and Davis 1997) and stress-induced relapse to cocaine self-administration (Erb and Stewart 1999). Moreover, a stimulus that promotes anxiogenic responses, the withdrawal of rodents from chronic EtOH exposure, produces rises in extracellular levels of CRF in the BNST (Olive et al. 2002). Interactions between CRF and GABAergic transmission in BNST have been reported to play a role in regulating stress and anxiety (Kash and Winder 2006). In this study the actions of CRF on GABAergic transmission in the ventrolateral region of the BNST (vlBNST) were examined. This region projects to both the VTA (Georges and Aston-Jones 2002) and the PVN of the hypothalamus (Cullinan et al. 1993), thus providing a point of access to both reward and stress pathways. Using whole-cell recordings in a BNST slice preparation, Kash et al. found that CRF enhances GABAergic transmission. Their pharmacological and genetic experiments suggest that CRF and urocortin CRF enhance postsynaptic responses to GABA through activation of the CRF1R.

In the same laboratory, a recent study showed the action of dopamine on cellular and synaptic function in the BNST. Kash et al. (2008) directly assessed the ability of dopamine to modulate neuronal function in the BNST using an ex vivo slice preparation. These investigators demonstrated a rapid and robust dopamine-induced enhancement of excitatory transmission in the BNST. This enhancement is activity-dependent and requires the downstream action of CRF1R, suggesting that dopamine induces CRF release through a local network mechanism. Furthermore, it was found that both in vivo and ex vivo cocaine induced a dopamine receptor and CRF1R-dependent enhancement of a form of NMDA receptor-dependent short-term potentiation in the BNST. These data highlight a direct and rapid interaction between dopamine and CRF systems that regulate excitatory transmission and plasticity in a brain region key to reinforcement and reinstatement. Because a rise in extracellular dopamine levels in the BNST is a shared consequence of multiple classes of drugs of abuse, this suggests that the CRF1R-dependent enhancement of glutamatergic transmission in this region may be a common key action of substances of abuse (Kash et al. 2008).

Francesconi et al. (2009a, b) investigated the effects of protracted withdrawal from alcohol in the juxtacapsular nucleus of the anterior division of the BNST (jcBNST). The jcBNST receives robust glutamatergic projections from the Basolateral amygdal (BLA), the postpiriform transition area, and the insular cortex as well as dopamine inputs from the

midbrain. In turn, the jcBNST sends GABAergic projections to the medial division of the central nucleus of the amygdala (CeAm) as well as other brain regions. These investigators described a form of long-term potentiation of the intrinsic excitability (LTP-IE) of neurons of the jcBNST in response to high-frequency stimulation (HFS) of the stria terminalis that was impaired during protracted withdrawal from alcohol (Francesconi et al. 2009b). Administration of the selective CRF1R antagonist (R121919), but not of the CRF2R antagonist (astressin 2B), normalized jcBNST LTP-IE in animals with a history of alcohol dependence (Francesconi et al. 2009b). In addition, repeated, but not acute, administration of CRF itself produced a decreased jcBNST LTP-IE. These investigators also showed that dopaminergic neurotransmission is required for the induction of LTP-IE of jcBNST neurons through dopamine D1 receptors (Francesconi et al. 2009b). Thus, activation of the central CRF stress system and altered dopaminergic neurotransmission during protracted withdrawal from alcohol and drugs of abuse may contribute to the disruption of LTP-IE in the jcBNST. Impairment of this form of intrinsic neuronal plasticity in the jcBNST could result in inadequate neuronal integration and reduced inhibition of the CeA, contributing to the negative affective state that characterizes protracted abstinence in postdependent individuals (Francesconi et al. 2009a, b).

3.1.4 Corticotropin-Releasing Factor Actions in the Basolateral Amygdala—

Liu et al. (2004) demonstrated that CRF and its related family of peptides act differentially at CRF1 versus CRF2 synaptic receptors to facilitate or depress excitatory transmission in CeA and lateral septum mediolateral nucleus. Notably, the effects of CRF and its ligands occurred without any apparent direct action on membrane potential or membrane excitability, suggesting that the role of CRF at these limbic synapses is that of a 'neuroregulator'. The investigators suggested pre and postsynaptic loci for CRF1 and CRF2 receptors within the glutamatergic CeA and LSMN synapses. Although both synapses exhibit a comparable pre and postsynaptic location of CRF1 and CRF2 receptors, their functions (facilitation versus depression of glutamatergic transmission) are opposite within each synapse (Gallagher et al. 2008). Liu et al. (2004) also demonstrated that endogenous CRF ligands induce a tonic effect on excitatory glutamatergic transmission at synapses within both of these nuclei since application of competitive, selective CRF1 or CRF2 receptor antagonists resulted in an enhancement or depression of glutamatergic EPCS. A similar tonic endogenous action of CRF ligands was not observed under control conditions in the medial prefrontal cortex (Orozco-Cabal et al. 2006). This latter result further emphasizes that CRF effects are different depending upon the CNS synapse being investigated. Most of these studies in the Gallagher group aimed to investigate the action of CRF on glutamatergic synapses in relation to cocaine administration. There is very poor data on EtOH–CRF–glutamate interaction.

Taken together these data suggest that a dysregulation of the extrahypothalamic CRF function is a major determinant of vulnerability to high alcohol intake and maintenance of alcohol and drug dependence.

3.1.5 Neuropeptide Y—Neuropeptide Y (NPY) is an inhibitory peptide produced in abundance in the hypothalamus, and phylogenetically conserved across species (Allen et al.

1986). NPY is involved in regulation of food and water intake. It has recently been ascribed its prominent role in the aversive aspects of alcohol withdrawal and relapse via their actions in the CeA. Endogenous NPY reduces anxiety via actions in the amygdala (Heilig et al. 1993; Sajdyk et al. 2002) and suppresses alcohol drinking in rats (Gilpin et al. 2003) via its actions in CeA (Gilpin et al. 2008a, b; Thorsell 2008). More specifically, NPY microinjection into the CeA exhibits an enhanced ability to suppress alcohol drinking in certain subpopulations of drinkers, including rats that are made dependent on alcohol via vapor inhalation.

NPY is generally co-localized with GABA in inhibitory interneurons. NPY mediates its actions by interacting with a family of G protein-coupled receptors (GPCRs), at least five of which have been cloned and designated Y1, Y2, Y4, Y5, and Y6. These receptors are widely distributed throughout the brain. NPY has also been shown to be a regulator of neuronal excitability in hippocampus, where its cellular actions have been most extensively studied (Colmers et al. 1991). In the amygdala, NPY has anxiolytic effects that are mediated via activation of Y1 receptors (Heilig et al. 1993). NPY neurons in the amygdala project to the BNST (Allen et al. 1984), which also contains Y1 receptors and Y1 and Y2 receptor mRNA. Further, the CeA receives NPYergic input from the nucleus of the solitary tract, arcuate nucleus, and the lateral septum (see (Kask et al. 2002) for a review). Y1, Y2, and Y5 receptors, and receptor mRNA are found in the amygdala, and each of these receptor subtypes has been implicated in anxiety (Kask et al. 2002). Y2 receptors are thought to act presynaptically as auto-receptors providing negative feedback to NPYergic nerve terminals, whereas Y1 receptors appear to act postsynaptically (Kask et al. 2002; Wolak et al. 2003).

Many in vivo studies point to the involvement of NPY in mediating some of the behavioral effects of EtOH (Caberlotto et al. 2001; Cippitelli et al. 2010; Rimondini et al. 2005). NPY KO mice show increased EtOH preference but blunted behavioral responses to EtOH, while NPY overexpressors show a lower preference and increased sensitivity to EtOH (Thiele et al. 1998). Likewise, increased NPY expression in the CeA was noted in two independent strains of alcohol-preferring rats (Hwang et al. 1999). There were increased levels of NPY in the paraventricular nucleus of the hypothalamus (PVN) and arcuate nucleus of EtOH-preferring rats and decreased NPY levels in the CeA of EtOH-preferring rats, suggesting an inverse relationship between NPY levels in the CeA and EtOH consumption. Additionally, alcohol-preferring rats show significant decreases in both cAMP-responsive element-binding protein (CREB) and NPY levels in the CeA and medial amygdala, but not the basolateral amygdala (Pandey et al. 2005). Further, virally mediated alterations in NPY levels in the CeA differentially affect EtOH consumption in rats with low and high basal levels of anxiety (Primeaux et al. 2006). Also, recent genetic and pharmacological evidence indicates that C57BL/6 J mice have low NPY levels in CeA compared to DBA/2 mice, suggesting that NPY contributes to the high EtOH consumption characteristic of C57BL/6 J mice (Hayes et al. 2005).

Electrophysiologic findings suggest that NPY and EtOH have a similar profile of actions (Ehlers et al. 1998a, b, 1999). Increased sensitivity to NPY and CRF was observed in cortex and amygdala after chronic EtOH exposure, as measured by EEG activity and event-related potentials (Slawecki et al. 1999). Modulation of amygdala EEGs by NPY differs in naïve P

and NP rats, suggesting that NPY has different neuromodulatory effects in these two strains (Ehlers et al. 1998a). Furthermore, NPY antagonizes the effects of CRF in the amygdala. However, to date neither the cellular actions of NPY in neither the CeA nor its interactions with EtOH or CRF, have been fully characterized. Recent findings by Gilpin et al. (2009, 2011) show that NPY superfusion decreased baseline GABAergic transmission in CeA slices and blocked the alcohol-induced enhancement of inhibitory transmission in CeA via presynaptic Y2 receptors.

Recently, it has been shown that NPY and CRF have opposing effects on stress and anxiety as well as on synaptic activity in BNST (Heilig et al. 1994; Kash and Winder 2006). Kash and Winder found that NPY and CRF inhibit and enhance GABAergic transmission, respectively: NPY depresses GABAergic transmission through activation of the Y2 receptors, whereas CRF and urocortin enhance GABAergic transmission through activation of CRF1 receptors. Further, NPY appears to reduce GABA release, whereas CRF enhances postsynaptic responses to GABA, suggesting potential anatomic and cellular substrates for the robust behavioral interactions between NPY and CRF in the extended amygdala.

3.1.6 Orphanin FQ/nociceptin (OFQ/N)—Nociceptin (known also as orphanin FQ) is the most recently discovered member of the endogenous opioid peptide family, albeit nearly 15 years ago. Nociceptin mediates or influences many behavioral, psychological, and neurobiological processes, including memory, anxiety, stress, and reward (Economidou et al. 2008; Martin-Fardon et al. 2010; Murphy 2010). The hepta decapeptide nociceptin is the endogenous ligand of the nociceptin opioid receptor (NOR), previously referred to as opiate receptor-like1 (ORL1). NOR is a GPCR that belongs to the opioid receptor family (Mogil et al. 1996; Mogil and Pasternak 2001). In rodents, moderate to high levels of NOR mRNA are detected in cerebral cortex, nucleus accumbens, amygdala, dorsal raphe nucleus, and hippocampus (Harrison and Grandy 2000). Nociceptin has a high structural homology with opioid peptides, especially dynorphin A (Meunier et al. 1995; Reinscheid et al. 1995), but nociceptin does not bind to MOR, DOR or KOR (μ, δ and κ-opioid receptors) and opioid peptides do not bind NOR (Lachowicz et al. 1995; Reinscheid et al. 1995). Nociceptin inhibits forskolin-stimulated cAMP formation (see Harrison and Grandy 2000; Hawes et al. 2000), and protein kinase C (PKC), MAP kinases and phospholipase A2 have been linked to NOR (Fukuda et al. 1998; Hawes et al. 2000; Lou et al. 1998).

At the cellular level, nociceptin acts at NOR to augment K^+ conductances in amygdalar (Meis and Pape 1998, 2001), hippocampal (Amano et al. 2000; Ikeda et al. 1997; Madamba et al. 1999; Tallent et al. 2001; Yu and Xie 1998) and thalamic neurons (Meis 2003; Meis et al. 2002), thus depressing cell excitability. Nociceptin has also been shown to decrease Ca^{2+} currents (Abdulla and Smith 1997; Calo et al. 2000; Connor et al. 1999; Henderson and McKnight 1997; Larsson et al. 2000) and reduce the amplitude of both non-NMDA receptor-mediated excitatory postsynaptic currents (EPSCs) and IPSCs in rat lateral amygdala (Meis et al. 2002).

Roberto and Siggins (2006) found that nociceptin did not significantly alter the resting membrane potential, input resistance, or spike amplitude, in accord with the results reported by others in CeA (Meis and Pape 1998) and for other brain regions (Ikeda et al. 1997;

Madamba et al. 1999; Tallent et al. 2001). However, nociceptin dose-dependently reduced GABA$_A$ IPSCs. This inhibition of GABAergic transmission was reversible on washout (Roberto and Siggins 2006). Nociceptin also concomitantly increased the PPF of IPSCs, and decreased the frequency of mIPSCs, suggesting decreased GABA release. Thus, nociceptin decreases GABAergic transmission by reducing GABA release at CeA synapses (Roberto and Siggins 2006). Interestingly, nociceptin applied before EtOH completely prevented the EtOH-induced enhancement of GABAergic transmission in CeA. On the other hand, EtOH alone significantly increased both the evoked IPSCs and mIPSC frequencies, and decreased the PPF ratio; nociceptin in the presence of EtOH completely reversed these EtOH effects opposing the EtOH increase of GABA release (Roberto and Siggins 2006). These investigators also found that the nociceptin-induced decrease of GABAergic transmission was larger in EtOH-dependent rats and might reflect neuroadaptations associated with EtOH dependence.

The functional interactions of neuropeptides (CRF, NPY, nociceptin) with GABAergic and glutamatergic systems may play major roles in the acute effects of EtOH on GABAergic and glutamatergic transmission. Understanding the underlying mechanisms of these interactions may offer a possible avenue for restoring "normal" function following chronic drug exposure. The neuroadaptations induced by chronic EtOH on GABAergic and glutamatergic systems may represent homeostatic or compensatory mechanisms in response to the acute EtOH actions on these systems.

4 Conclusions

In this review we have focused on acute and chronic EtOH actions on synaptic transmission. It is not possible to cover all aspects of this topic, and thus we have focused on describing the best established EtOH actions. As the review attests, EtOH affects numerous aspects of synaptic transmission both directly and indirectly, to alter brain function and behavior. Acute exposure to EtOH generally increases the function of cys-loop ligand-gated ion channels, with prominent effects of GABA$_A$ and glycine receptors. These actions increase synaptic and extra-synaptic inhibition and are thought to contribute to sedation and other aspects of intoxication. Ionotropic glutamate and P2X receptors are generally inhibited by acute EtOH exposure, with some noted exceptions. The inhibitory effect on ionotropic glutamate receptors is most prominent at NMDARs and on NMDAR-mediated synaptic responses, and this inhibitory action is thought to contribute to cognitive impairment produced by EtOH. At present, the postsynaptic EtOH effects on neurotransmitter receptors appear to occur within the receptor molecules themselves, although more work is needed to elucidate the roles of post-translation modification. On the presynaptic side, acute EtOH generally potentiates GABA release, contributing to the enhanced neuronal inhibition produced by the drug. The molecular mechanisms involved in EtOH potentiation of GABA release remain to be fully explored. EtOH also alters other aspects of synaptic transmission involving amino acid transmitters and monoamines. The net result of the EtOH effects of transmission seems to be to dampen synaptic excitation in many brain regions and reduce most forms of synaptic plasticity (with noted exceptions).

Chronic exposure to EtOH, whether by forced administration or ingestion, generally enhances the function of NMDARs, most often those containing the NR2B subunit. Increases in glutamate release and responses to some other glutamate receptors are also observed following chronic exposure. The net effect of these increases in glutamatergic transmission appears to be a hyperexcitable CNS state during withdrawal that contributes to withdrawal symptoms and relapse. Excitotoxicity might be another result of this hyper-glutamatergic state. In general, acute EtOH effects on glutamate receptor function and glutamatergic transmission are intact even after subchronic or chronic EtOH exposure, suggesting that behavioral tolerance is not a simple function of loss of pharmacological effects at these synapses. At GABAergic synapses, chronic EtOH generally alters either the efficacy of inhibitory synaptic transmission or the types of receptors involved in transmission. Extrasynaptic GABA$_A$ receptor-mediated synaptic responses are also altered, leading to changes in tonic current in the postsynaptic neuron. The pattern of chronic EtOH effects on GABAergic transmission varies considerably across brain regions, making this subject a rich and important area for future investigation. The resultant alterations in patterns of GABAergic transmission in key brain regions may contribute to EtOH tolerance, dependence and drug intake. More work is needed to determine the exact pattern of changes in GABAergic inhibition across brain regions, and how these changes contribute to aspects of alcohol use disorders including tolerance, dependence, and escalating intake.

The modulatory effects of neuropeptides have become subjects of intense investigation in the alcohol research field. Neuropeptides implicated in stress responses, such as CRF, appear to contribute to stress–EtOH interactions as well as drinking and relapse. Acute EtOH exposure alters the release of some neuropeptides, while others alter synaptic transmission in ways that interfere with the actions of EtOH. Chronic EtOH exposure also appears to alter neuropeptide modulatory actions. In addition to providing tools for investigation of mechanisms involved in EtOH actions, the neuropeptides may also provide new avenues for pharmacotherapies that could be used in the treatment of alcohol use disorders. Researchers have just begun to explore the alcohol-related actions of a few of the many neuropeptides found in the brain. Thus, more work remains to fully define how peptides participate in the neural actions of alcohol.

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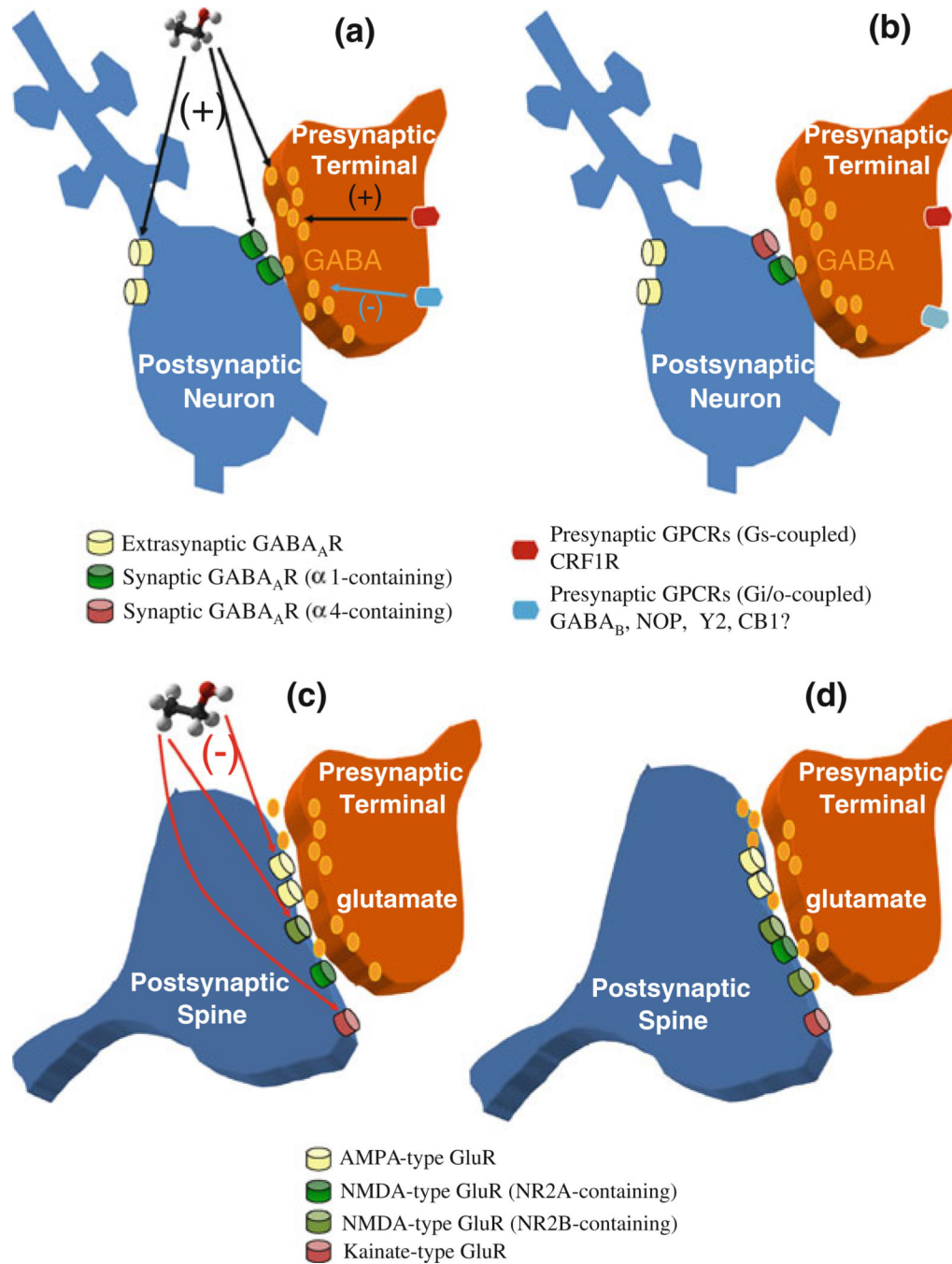
Fig. 1.

Acute and chronic EtOH effects on GABAergic and glutamatergic synaptic transmission. **a** Schematic diagram of a GABAergic synapse, including presynaptic GPCRs that modulate neurotransmitter release, and postsynaptic ionotropic receptors (located both at synapses and extrasynaptically) that mediate fast synaptic transmission. The predominant presynaptic effect of acute EtOH is potentiation of GABA release (most likely by increasing the probability of vesicle fusion). This presynaptic potentiation may involve neuromodulators such as CRF, and activation of presynaptic GPCRs and downstream signaling pathways.

Postsynaptically, EtOH potentiates ionotropic GABA$_A$ receptor function. Increases in synaptic GABA$_A$R function prolong synaptic responses, while potentiation of extrasynaptic receptors increases tonic current that affects neuronal excitability, **b** Changes in GABAergic synapses following chronic EtOH exposure. Presynaptically, the release of GABA is decreased. Alterations in levels of neuromodulators that act on GPCRs, as well as altered function of presynaptic GPCRs may contribute to these changes. Postsynaptically, the subunit composition of GABA$_A$Rs is altered, often including increased synaptic α4-containing receptors, and fewer α1-containing synaptic receptors. Synaptic α4-containing receptors may be less sensitive to acute EtOH, promoting tolerance to synaptic effect of the drug, **c** Schematic diagram of a glutamatergic synapse on a dendritic spine, including postsynaptic ionotropic receptors that mediate fast synaptic transmission. The predominant effect of acute EtOH is to inhibit ionotropic glutamate receptor function, and all subclasses of these receptors are sensitive to EtOH inhibition. The most potent effects have been observed at kainate and NMDA receptor subtypes, **d** Changes in glutamatergic synapses following chronic EtOH exposure. Presynaptically, the release of glutamate is enhanced. Postsynaptically, NMDAR function is increased, most likely due to increased receptor density at the synapse. There is also evidence for increased numbers of NR2B-containing NMDARs. There is also evidence of increased volume of the dendritic spine.