GABA and Glutamate Synaptic Coadaptations to Chronic Ethanol in the Striatum

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Contents

Abstract

Alcohol (ethanol) is a widely used and abused drug with approximately 90% of adults over the age of 18 consuming alcohol at some point in their lifetime. Alcohol exerts its actions through multiple neurotransmitter systems within the

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brain, most notably the GABAergic and glutamatergic systems. Alcohol's actions on GABAergic and glutamatergic neurotransmission have been suggested to underlie the acute behavioral effects of ethanol. The striatum is the primary input nucleus of the basal ganglia that plays a role in motor and reward systems. The effect of ethanol on GABAergic and glutamatergic neurotransmission within striatal circuitry has been thought to underlie ethanol taking, seeking, withdrawal and relapse. This chapter reviews the effects of ethanol on GABAergic and glutamatergic transmission, highlighting the dynamic changes in striatal circuitry from acute to chronic exposure and withdrawal.

Keywords
Action control · Addiction · Alcohol · Cortico-striatal loop · Neurotransmitter · Synaptic transmission

1 Introduction

Alcoholism is a progressive and chronic relapsing disorder that ultimately leads to detrimental health outcomes. Studies have revealed adaptations to cortico-basal ganglia circuits that mediate the stages of the addiction cycle. This includes initial drug use to habitual and continued use despite negative outcomes. The transition to addiction involves neuroplasticity in these brain regions that begin in the mesolimbic dopamine region and transition to the dorsal striatum (Ito et al. 2002; Everitt and Robbins 2013, 2016). Although great progress has been made in ethanol pharmacology demonstrating that acute ethanol has only a few known primary targets (Vengeliene et al. 2008), it has long been proposed that the acute behavioral effects of ethanol are mediated principally by potentiation of γ-aminobutyric acid A ($GABA_A$) receptors and/or inhibition *N*-methyl-D-aspartate (NMDA) receptors. This presumption is due to the similarities in behavioral effects between ethanol and benzodiazepines that act on $GABA_A$ receptors, as well as NMDA antagonists such as ketamine (Krystal et al. 2003). An imbalance in the striatum of GABAergic and glutamatergic transmission is thought to play a role in alcohol use and abuse. Understanding how ethanol alters GABAergic and glutamatergic systems through the progression to alcohol addiction within specific brain regions/circuits will provide valuable insights for developing finely targeted therapeutics.

2 GABAergic Synapses

GABA is the major inhibitory neurotransmitter in the brain. GABA is derived from glutamate by the enzyme glutamic acid decarboxylase (GAD). There are two GAD isoforms, GAD65 and GAD67, named for their molecular weights. Since GAD is required for the synthesis of GABA, it is commonly used as a marker for GABAergic neurons. Once synthesized, GABA is packaged into vesicles by the vesicular GABA

transporter. The release of GABA is regulated by calcium concentration within the axon terminal, with increased concentration leading to vesicular release until basal calcium concentrations are restored.

GABA exerts its actions on transmission by $GABA_A$ ionotropic receptors and $GABA_B$ metabotropic receptors. $GABA_A$ receptors are heteropentomeric complexes that form a ligand-gated anion-selective channel that is permeable to chloride and bicarbonate. The $GABA_A$ receptor can be found both pre- and postsynaptically (Lovinger 2017). In mature neurons, the concentration of chloride is lower intracellularly leading to a net flow of anions into the neuron upon channel opening. Therefore, activation of $GABA_A$ receptors results in membrane hyperpolarization that decreases the excitability of a cell as chloride ions flow into the cell (Olsen and Sieghart 2008). In mammals, there are 19 different $GABA_A$ receptor subunits identified: α (1–6), β (1–3), γ (1–3), δ, ε, ρ (1–3), θ, and π (Olsen and Sieghart 2008, 2009). In addition to the 19 subunits, there are also subunit splice variants and phosphorylation states that can modify the activation of specific subunits. Most mammalian receptors consist of 2 α, 2 β, and 1 γ subunit. The subunits composing a $GABA_A$ receptor dictate their biophysical and pharmacological properties and location within the brain, as well as cellular distribution. Sensitivity to GABA is determined primarily by the α subunit expressed. $GABA_A$ receptors can possess a variety of allosteric modulatory sites also dependent on the subunits expressed, that allow modulators such as benzodiapines, neurosteroids, and barbiturates to alter their function. Most receptors containing the γ2 subunit are targeted to the synapse via their interaction with the scaffolding protein gephyrin (Farrant and Nusser 2005; Fritschy et al. 2012). The exception to this rule is α5βxγ2 receptors, which are targeted to the extrasynapse by the interaction of the α5 subunit and radixin (Loebrich et al. 2006). Receptors containing the δ subunit are localized exclusively in the extrasynapse (Walker and Semyanov 2008; Belelli et al. 2009; Herd et al. 2013). Posttranslational modifications of $GABA_A$ receptors regulate trafficking and stability. For example, Protein Kinase-A (PKA) phosphorylation of the β3 subunit leads to internalization of the receptor complex, whereas Protein Kinase C (PKC) phosphorylation of multiple subunits leads to membrane insertion (Kittler et al. 2005; Mele et al. 2014). Within the striatum, $GABA_A$ receptor subunits (α1–5, β1–3, γ1–3, and δ) are expressed to varying degrees, with the α2 and β3 subunits having the highest degree of immunoreactivity. The α2βxγ1/2 isoform is the most highly expressed isoform in the striatum and is located within the synaptic and extrasynaptic cellular compartments of striatal medium-sized GABAergic projection neurons (MSNs) (Schwarzer et al. 2001; Maguire et al. 2014). The α4βxδ isoform of the $GABA_A$ receptors is found exclusively extrasynaptically in MSNs and interneurons (Schwarzer et al. 2001; Maguire et al. 2014).

The $GABA_B$ receptors are Gi-protein-coupled receptors. When activated, they mediate inhibition by activating potassium channels and decreasing calcium conductance. There are two subtypes of the $GABA_B$ receptor, $GABA_BR1$ and $GABA_BR2$, that form homo- and heterodimers in the membrane. $GABA_B$ receptors can be located either pre- and postsynaptically. Presynaptic $GABA_B$ receptors serve as autoreceptors, regulating the release of GABA. Postsynaptically located $GABA_B$ receptors are primarily coupled to the activation of potassium channels (Misgeld et al. 2007), whose activation serves to hyperpolarize the cell, albeit at a slower time scale than $GABA_A$ receptors.

GABA transmission is terminated when GABA is cleared from the synapse. Reuptake of GABA is mediated by GABA transporters located on the plasma membrane of both neurons and glia. Following uptake by both cell types, GABA is degraded by the enzyme GABA transaminase into glutamate.

3 Glutamatergic Synapse

Glutamate is the major excitatory neurotransmitter in the brain. Glutamate is synthesized by two different mechanisms: the first is synthesis from glucose through the Krebs cycle by transamination of α-ketoglutarate. Alternatively, glutamate is formed directly from glutamine by the glutaminase enzyme. Glutamate is packaged into synaptic vesicles by vesicular glutamate transporters.

The postsynaptic actions of glutamate are mediated by ionotropic and metabotropic glutamate receptors. The ionotropic glutamate receptors, *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainic acid (KA) receptors, are glutamate-gated cation channels.

NMDA receptors are voltage-sensitive ionotropic glutamate receptors that when open allow for the flow of calcium and/or sodium ions, albeit at slower kinetics than AMPA and KA receptors. NMDA receptors are regulated by presynaptic glutamate release and postsynaptic mechanisms such as phosphorylation states, subunit expression, and membrane potential that all contribute to its roles in neuronal plasticity, stabilizing neuronal activity, and coincidence detection (Malenka and Nicoll 1999; Wang 1999; Yuste et al. 1999). The voltage sensitivity aspect of NMDA receptors is due to the blockade at resting membrane potentials by magnesium, which is removed by membrane depolarization. NMDA receptors are tetramers that consist of an obligatory NR1 subunit and regulatory NR2 (A–D) and/or NR3 (A–B) subunits. The regulatory subunits control the biophysical (conductance and open probability) and pharmacological properties of NMDA receptors (Wenzel et al. 1997; Traynelis et al. 2010). NMDA receptors are unique in that they require the binding of two different ligands, glutamate and glycine/d-serine, for activation. NR1 subunits bind glycine or d-serine, while the NR2 subunits bind glutamate (Gonda 2012). NMDA receptors play a role in synaptic plasticity mainly in the form of long-term potentiation that is associated with increases in membrane insertion of AMPA receptors, protein synthesis, spine formation, and the enlargement of existing spines (Malinow and Malenka 2002; Matsuzaki et al. 2004; Kasai et al. 2010). Phosphorylation state of NMDA receptors plays a role in their localization, activation state, and physiological properties (Traynelis et al. 2010).

The AMPA and KA glutamate receptors are also heterotetrameric protein complexes that form ligand-gated ion channels. AMPA receptors consist of GluR1–4 (also known as GluRA-D), GluRδ1, and GluRδ2 (Dingledine et al. 1999). Each GluR subunit contains a binding site for glutamate. Although AMPA receptors are capable of allowing the flow of calcium, sodium, and potassium, the majority of AMPA receptors contain the GluR2 subunit which renders the ion channel impermeable to calcium. AMPA receptors mediate most of the excitatory transmission in the brain due to its vast brain expression as well as lack of voltage sensitivity (as in the case of NMDA receptors). AMPA receptors have been well studied and shown to play a role in synaptic plasticity. KA receptor subunits

include GluR5–7, KA1, and KA2 (Dingledine et al. 1999) and their activation leads to the flow of sodium and potassium ions, and consequently membrane depolarization.

Metabotropic glutamate receptors (mGluRs) are G-protein-coupled receptors. mGluRs are divided into three familial groups. Group I mGluRs (mGluR1 and mGluR5) are Gq-coupled receptors whose binding of glutamate leads to activation of the enzyme phospholipase C (PLC) that ultimately induces the release of calcium from intracellular stores and increases PKC activity (Kenny and Markou 2004). Group1 mGluRs are mainly located on the postsynaptic membrane. mGluR 1 has moderate expression in the dorsal striatum and low expression in the NAc, whereas mGluR5 is highly expressed in the entire striatum (Olive 2009; Pomierny-Chamiolo et al. 2014). Group II mGlurRs (mGluR2 and mGluR3) are Gi/o-coupled receptors whose activation decreases the activity of adenylyl cyclase, ultimately decreasing the intracellular concentration of cyclic adenosine monophosphate (cAMP) (Kenny and Markou 2004). They are present both pre- and postsynaptically. Lastly, Group III mGlurRs (mGluR4, GluR6, GluR7, and GluR8) are similar to Group II mGluRs in that they are Gi/o-coupled receptors (Kenny and Markou 2004). These receptors are primarily located presynaptically and play a role in regulating neurotransmitter release. Of the Group III mGluRs, mGluR4, mGluR7, and mGluR8 are expressed in the striatum (Corti et al. 2002; Messenger et al. 2002; Bragina et al. 2015).

Similar to GABA, glutamate transmission is terminated when glutamate is cleared from the synapse. Glutamate is predominately taken up through plasma membrane transporters that are located on glia, mainly astrocytes, and to a lesser extent, on neurons. Once transported intracellularly, glutamate is metabolized to glutamine.

Corticostriatal GABAergic synapses can undergo synaptic plasticity by both long-term potentiation (LTP) and long-term depression (LTD). Corticostriatal LTP requires the activation of NMDA and D1Rs (Calabresi et al. 2000; Kerr and Wickens 2001), while LTD requires activation of postsynaptic mGluRs and presynaptic CB1 receptors (Calabresi et al. 2000).

4 The Striatum and Action Control

Cortico-basal ganglia loops play a role in the learning and selection of appropriate action sequences, as well as detecting deviations within the sequence and changes in the outcome. Cognitive control is required to guide the selection of appropriate actions based on an individual's current goals and situation, and at the same time inhibiting unwanted actions. The striatum, the main input of the basal ganglia, is innervated from all regions of the cortex. The striatum is divided into the dorsomedial striatum (DMS, roughly equivalent to the caudate nucleus in primates), dorsolateral striatum (DLS, roughly equivalent to the putamen nucleus in primates), and ventral striatum. The ventral striatum can be divided into the nucleus accumbens (NAc) and the olfactory tubercle (Heimer and Wilson 1975). Although, the striatum receives input from all regions of the cortex, specific cortical regions send inputs to distinct striatal regions. The striatum then sends converging projections to the output nuclei, the internal globus pallidus (GPi) and substantia nigra pars reticulata (SNpr). The output nuclei project to the thalamus that

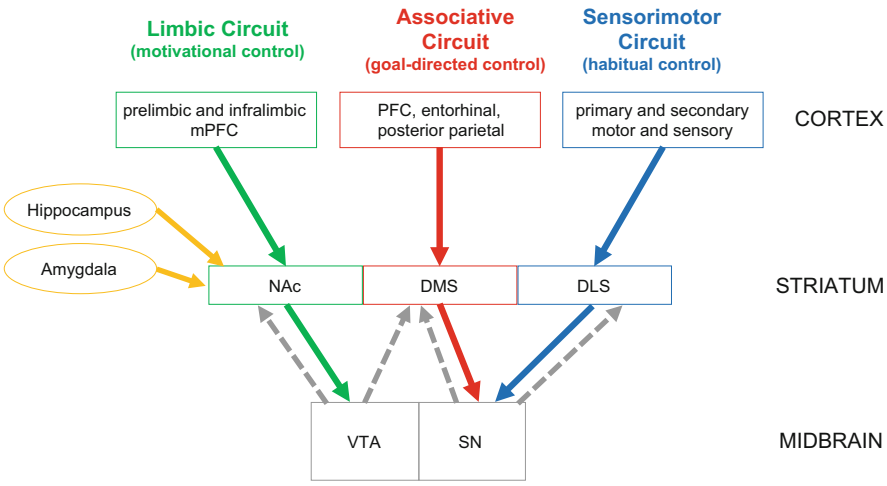

Fig. 1 Model of cortico-striatal circuitry focusing on the limbic (green), associative (red), and sensorimotor (blue) circuits. The nucleus accumbens (NAc) receives glutamatergic input from the limbic cortices, hippocampus (yellow) and amygdala (yellow), and dopaminergic projections (gray dashed lines) from the ventral tegmental area (VTA). It then projects to the VTA. The dorsomedial striatum (DMS), or the caudate nucleus in primates, receives glutamatergic input from the associative cortices and dopaminergic input from the VTA and substantia nigra (SN). It then projects to the SN. The dorsolateral striatum (DLS), or the putamen nucleus in primates, receives glutamatergic input from the sensory and motor cortices and dopaminergic input from the SN. It then projects to the SN. The VTA projects back to the NAc and the DMS, while the SN sends projections back to the DMS as well as the DLS

sends projections back to the cortical input regions, completing the loop (Alexander et al. 1986). Cortico-basal ganglia circuits can be divided based on their cortical inputs and their roles in learning, control, and performance of actions (Haber et al. 2000). These parallel circuits compete for the control of behavior and are suggested to be connected in a spiraling manner whereby MSNs in one striatal region project to the ventral tegmental area (VTA)/SN that send projections to MSNs of another striatal region, starting from the NAc medial shell then to the NAc core/DMS and ultimately to the DLS (Fig. 1). Dopaminergic innervation of the DLS is thus under the influence of the NAc.

Most alcohol users are casual consumers in which alcohol is consumed for its rewarding properties. In these individuals, alcohol consumption is thought to be a goal-directed action, in which alcohol use is dependent on the value of the outcome. Therefore, if alcohol consumption is devalued, for example it has become associated with unwanted intoxication/illness, alcohol use will cease. However with repeated, chronic use, alcohol drinking may transition to a habit in which an associated cue triggers voluntary alcohol consumption despite negative repercussions. This is highlighted by continued alcohol abuse by habitual alcoholics despite its negative outcomes (personal, social or financial). Drugs of abuse, including alcohol, are

thought to induce abnormally strong consolidation of instrumental learning mechanisms, enhancing drug seeking behavior in response to cues or contexts that are associated with the drug. This may occur by drug-induced cortico-basal ganglia circuit plasticity that reinforces the connectivity within the "spiral," leading to the recruitment of dorsal striatum circuitry proposed to underlie this transition from casual to habitual alcohol use and seeking (Koob and Volkow 2010).

4.1 Nucleus Accumbens: Motivation and Reinforcement

The limbic cortico-basal ganglia circuit is commonly referred to as the brain reward circuit (Haber 2011), with the nucleus accumbens (NAc) as its main basal ganglia input (Fig. 1 green pathway). The NAc can be divided into two subregions, the core and shell, based on MSN morphology, neurochemistry, projection patterns, and functions (Heimer et al. 1991; Zahm and Brog 1992; Meredith 1999).

The NAc core receives most of its input from glutamatergic projections from prelimbic medial prefrontal cortex (mPFC), hippocampus and amygdala (Groenewegen et al. 1999). It is also thought to be continuous with the DMS and therefore is implicated in conditioned responding, sensory motor integration, and emotional cues (Carlezon et al. 1995; Rodd-Henricks et al. 2002; Sellings and Clarke 2003; Ikemoto 2007; Guo et al. 2009; Suto et al. 2010). The NAc core sends GABAergic projections to the dorsolateral ventral pallidum and the substantia nigra (Zahm and Heimer 1990; Heimer et al. 1991; Zhou et al. 2003).

The NAc shell receives dopaminergic input from the VTA and glutamatergic projections from infralimbic mPFC, the basolateral amygdala, and ventral hippocampus (Britt et al. 2012; Papp et al. 2012). The NAc shell in conjunction with the bed nucleus of the stria terminalis and central amygdala have collectively been referred to as the extended amygdala complex, due to similarities in morphology and circuitry (Hopkins and Holstege 1978; Heimer and Alheid 1991). The extended amygdala complex has been implicated in the emotional processing of stimuli and drug addiction (Koob 2013). MSNs of the NAc shell project to the ventromedial ventral pallidum and the ventral tegmental area (Zahm and Heimer 1990; Heimer et al. 1991; Zhou et al. 2003). The NAc shell is implicated in reward processing, the control of motivation, behaviors by primary rewards, and behavioral inhibition such as aversion learning (Kravitz et al. 2012; Hikida et al. 2013).

With regards to alcohol use, ethanol increases the release of dopamine in the NAc. This increase in dopamine is believed to mediate the positive reinforcing effects of ethanol (Imperato and DiChiara 1986). The ventral striatum is also suggested to play a role in drug-induced increase in locomotion and cue-induced alcohol use.

4.2 DMS: Goal-Directed Behaviors

The DMS in the rodent, roughly equivalent to the primate caudate nucleus, is one of the subdivisions of the dorsal striatum that lines the lateral ventricle. It is part of the

associative circuit that includes the prefrontal, entorhinal, and posterior parietal cortical projections to the medial striatum (Fig. 1, red pathway). The DMS also receives dopaminergic inputs from the substantia nigra and the VTA and glutamatergic inputs from the basolateral amygdala and thalamus (Haber et al. 2000; Ikemoto 2007; Pan et al. 2010; Corbit et al. 2013; Kupferschmidt et al. 2015). MSNs of the DMS project to the substantia nigra pars reticulate, subthalamic nucleus, and globus pallidus.

As part of the associative circuit, the DMS is thought to influence goal-directed actions based on the expected consequences or value of the actions, also referred to as action-outcome (Yin et al. 2005a, b; Gunaydin and Kreitzer 2016). Goal-directed actions are flexible in that their performance is sensitive to changes in value or motivation for the outcome as well as changes in the contingency between the action and outcome.

Studies using an outcome devaluation test that examines whether a goal-directed or habitual strategy is used to perform an instrumental action (i.e. nose poke or lever press) suggest that early alcohol use is a goal-directed action (Corbit et al. 2012, 2014). In this task, rodents are trained to perform an instrumental action for alcohol. During the outcome devaluation test, the value of the alcohol reward is changed by either pairing it with an aversive stimuli, satiation to alcohol, or changing the contingency between the action and alcohol reward. With extended exposure to the action-alcohol pair, self-administration shifts from a goal-directed action sensitive to the change in the value of the alcohol reward to a value-insensitive habitual action that occurs regardless of a change in the value of the alcohol reward. (Corbit et al. 2012; Lopez et al. 2014). Pharmacological inactivation of the DMS, but not the DLS, led to a loss in the sensitivity to alcohol devaluation in mice suggesting that the DMS is important for goal-directed alcohol self-administration (Corbit et al. 2012).

4.3 DLS: Habit Formation

The sensorimotor circuit includes primary and secondary sensory and motor cortices that project to the DLS (equivalent to the primate putamen nucleus), a subdivision of the dorsal striatum (Fig. 1, blue pathway). The DLS also receives convergent dopaminergic input from the substantia nigra. The proposed role of the sensorimotor circuit is the maintenance and execution of well-learned actions that rely on external and internal cues and less on the changes in the consequences of the action often referred to in conditioning terms as stimulus-response control over behavior (Webster 1961; McGeorge and Faull 1989; Yin et al. 2006). DLS MSNs, in turn, send GABAergic projections to the substantia nigra, globus pallidus, and subthalamic nucleus.

As part of the sensorimotor cortico-striatal loop, the DLS is involved in habit formation or stimulus-response learning. A habitual behavior is an overlearned action associated with a specific cue or context. When triggered by that cue or context the habit will be performed automatically regardless of the outcome. Habitual actions require less executive control than goal-directed actions (Dalley et al.

2004; Muller et al. 2007), and therefore allows the habit system to react quickly yet it also makes it inflexible.

The habit system is thought to be strengthened under alcohol conditions in which executive control over drug taking is decreased. The DLS is also implicated in the drug-induced stereotypies as well as habitual and compulsive alcohol seeking (Everitt et al. 2008; Corbit et al. 2012, 2014). Relapse is also thought to involve the DLS (Fuchs et al. 2006). During chronic alcohol use DLS output is potentiated while the circuits involved in associative learning, such as the DMS, are altered (Belin-Rauscent et al. 2012; Hogarth et al. 2013).

4.4 Subtypes of Striatal Neurons

The striatum contains medium-sized GABAergic spiny projection neurons (MSNs), GABAergic interneurons, and cholinergic interneurons. MSNs are the principal cells of the striatum, constituting 90% of the neuronal population in rodents and 70% in primates (Kemp and Powell 1971; Kita and Kitai 1988). As the sole output neurons of the striatum, MSNs process and integrate information from cortex, thalamus, limbic structures, VTA/SN, and neighboring striatal neurons.

MSNs can be further divided into two classes based on their axonal projections, dopamine receptor expression, peptide expression, and electrophysiological properties. MSNs that express the dopamine D1 receptor, co-express dynorphin, substance P, and M4 cholinergic receptors, and directly project to the substantia nigra, are referred to as direct pathway MSNs (dMSNs) (Augood et al. 1997; Gerfen and Surmeier 2011). MSNs that express the dopamine D2 receptor, co-express enkephalin and neurotensin, and indirectly projects to striatal output regions are referred to as indirect pathway MSNs (iMSNs) (Le Moine and Bloch 1995; Surmeier et al. 1996; Augood et al. 1997; Aubert et al. 2000; Gerfen and Surmeier 2011). A small proportion of MSNs co-express D1 and D2 receptors in rodents and primates (Le Moine and Bloch 1995; Aubert et al. 2000). Direct pathway MSNs promote actions by disinhibiting the thalamus and cortex, whereas iMSNs "stop" actions by indirectly disinhibiting the SN (Kravitz et al. 2010). The balance between dMSN and iMSN activity is required for normal reward-related behaviors (Fig. 2 top). The basal electrophysiological properties of dMSN and iMSN neurons differ in the striatum, such that iMSNs are more excitable than dMSNs (Kreitzer and Malenka 2008; Grueter et al. 2010; Planert et al. 2013). Similarly, there is an increase in glutamate release onto iMSNs as compared with dMSNs (Kreitzer and Malenka 2008; Grueter et al. 2010). Although both MSN subtypes can undergo LTD including those that are NMDA-dependent, endocannabinoid-mediated, and transient receptor potential cation channel (TRPV) 1-dependent, LTD is more robust in iMSNs (Kreitzer and Malenka 2007; Grueter et al. 2010). Dopamine also leads to differential actions on dMSNs and iMSNs. When dopamine is released in the striatum, D1 receptor activation on dMSNs results in long-term potentiation (LTP) of synaptic efficacy. At the same time, D2 receptor activation prevents LTP on these synapses (Reynolds and Wickens 2002).

Although a majority of dMSNs and iMSNs are distinguished by expression and output regions, it should be noted that they are not entirely segregated. In the NAc,

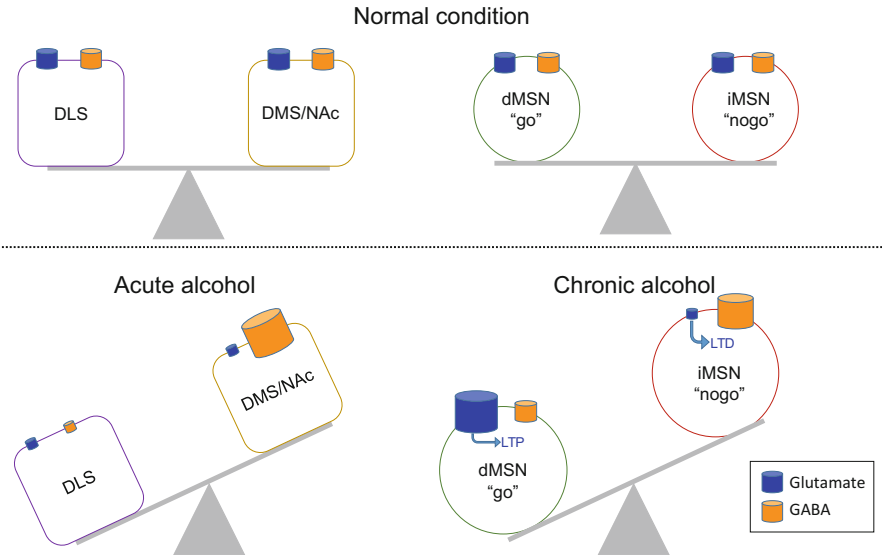

Fig. 2 Hypothetical model of the effects of acute and chronic alcohol on glutamatergic and GABAergic transmission onto the striatal subregions (left) and direct and indirect pathway MSNs of the striatum (right). Under normal conditions, glutamatergic (blue) and GABAergic transmission (orange) are balanced. This balance in output from the DLS and DMS/NAc as well as between dMSNs and iMSNs leads to normal action selection. Under acute alcohol exposure, data suggests that there is an overall hypoglutamatergic state in the striatum. However, there is a differential alcohol-induced effect on GABAergic transmission between striatal subregions: the acute ethanol-induced decrease in GABAergic transmission in the DLS and increase in GABAergic transmission in the DMS/NAc may lead to an imbalance in control of action selection between the striatal subregions. Under chronic alcohol exposure, there is a hyperglutamatergic state in dMSNs that is thought to lead to LTP of glutamatergic input onto dMSNs. In iMSNs, a decrease in NMDA receptors may lead to a decrease in glutamatergic transmission or LTD, concomitant with an increase in GABAergic transmission. Ultimately this is thought to bias towards activation of dMSNs and abnormal control over alcohol consumption

dMSNs and iMSNs are not as clearly segregated as in the dorsal striatum, with a larger proportion of MSNs co-expressing D1 and D2 receptors (Bertran-Gonzalez et al. 2008; Kupchik et al. 2015). dMSNs have been shown to send axon collaterals to the globus pallidus external and the ventral pallidum (Lu et al. 1998; Zhou et al. 2003; Fujiyama et al. 2011; Kupchik et al. 2015).

In addition to MSNs, approximately 4% of rodent striatal neurons are locally projecting GABAergic interneurons. Striatal GABAergic interneurons are medium sized, aspiny neurons and can be divided into three subtypes based on their electrophysiological properties and protein expression. Fast-spiking interneurons express the calcium binding protein parvalbumin and exhibit rapid and sustained firing (Cowan et al. 1990; Kawaguchi et al. 1995; Tepper and Bolam 2004). They provide the strongest input onto MSNs with approximately 100 connections targeting the soma and proximal dendrites of neighboring MSNs (Koós and Tepper 1999). Due to

their high degree of synchronization, vast number of connections, and proximity of synapses close to or on the soma, fast-spiking interneurons can greatly control action potential firing in MSNs (Kita 1993; Bennett and Bolam 1994; Koós and Tepper 1999; Kubota and Kawaguchi 2000; Tunstall et al. 2002; Mallet et al. 2005). Low threshold-spiking interneurons co-express a combination of neuropeptide Y, somatostatin, and nitric oxide synthase (Smith and Parent 1986). They have lower action potential firing rates than fast-spiking interneurons and exhibit plateau potentials. Synapses formed between low threshold-spiking interneurons and MSNs tend to be more apical on MSN dendrites than is true of fast-spiking interneurons. The last subpopulation of striatal GABAergic interneurons express calretinin and are considered to be low-threshold spiking interneurons (Tepper and Bolam 2004). This group of interneurons are less understood due to their limited numbers and the overlapping expression of calretinin on a subset of MSNs. MSNs receive both feed forward and lateral inhibition from GABAergic interneurons and recurrent collaterals from neighboring MSNs, respectively.

The remaining striatal neurons are large cell bodied (20–50 μm) and aspiny interneurons that release the neurotransmitter acetylcholine (Bolam et al. 1984; Smith and Bolam 1990; Wilson et al. 1990). These interneurons are tonically active and have a relatively depolarized resting membrane potential (Wilson et al. 1990; Kawaguchi et al. 1995). Due to their large size and vast dendritic and axonal fields, they are suggested to integrate and modulate synaptic connections (Kawaguchi et al. 1995). Although cholinergic interneurons and cholinergic transmission play a large role in striatal circuitry and alcohol addiction (Clarke and Adermark 2015; Gonzales and Smith 2015), the effects of ethanol on cholinergic transmission are not discussed in this chapter.

5 Ethanol Actions on GABAergic Transmission

Ethanol has long been thought to exert its effects through potentiating the GABAergic system. This is due to similarities in the behavioral effects between ethanol and benzodiazepines, such as sedation, decreases in anxiety, and ataxia. The activity of both ionotropic and metabotropic GABA receptors have been shown to be important for ethanol reinforcement and relapse to ethanol seeking (Augier et al. 2017).

5.1 Acute Actions

There has been mixed data regarding the acute effects of ethanol on $GABA_A$ receptor function. Alcohol is considered to be an allosteric modulator of $GABA_A$ receptors that enhances $GABA_A$ receptor activity by increasing the probability of channel opening or increasing agonist affinity (Nestoros 1980; Suzdak et al. 1986; Tonner and Miller 1995; Zhou et al. 1998; Welsh et al. 2009; Soyka et al. 2016). Other studies, however, found a lack of ethanol effect on $GABA_A$ receptor properties (Gage and Robertson 1985; Siggins et al. 1987; White et al. 1990). The discrepancy between studies has

been suggested to occur because of discrepant subunit composition, brain location, or phosphorylation state. In regards to subunit composition, it has been proposed that there is a specific ethanol binding site on the $GABA_A$ receptor located between the α and β3 subunit interface, or between the transmembrane region between TM2 and TM3. If this is the case, then it is safe to assume that $GABA_A$ receptors expressing a specific subunit composition profile will be sensitive to ethanol. Low concentrations of ethanol have been shown to act directly on extrasynaptic $GABA_A$ receptors containing α4/6β3δ (Wallner et al. 2006; Olsen et al. 2007), but this observation was contradicted elsewhere (Borghese et al. 2006; Botta et al. 2007). Several studies have demonstrated an involvement of PKC and its phosphorylation of subunits on the sensitivity of $GABA_A$ receptors to ethanol (Aguayo and Pancetti 1994; Weiner et al. 1994, 1997; Qi et al. 2007).

Failure to find a consistently observed direct ethanol effect on $GABA_A$ receptors suggests that the effect of ethanol on GABAergic transmission is perhaps at least partially via a presynaptic mechanism. Several studies have demonstrated an ethanol-induced increase in GABA release in various brain regions including the hippocampus, VTA, amygdala, spinal cord, cerebellum, and striatum (Crowder et al. 2002; Melis et al. 2002; Roberto et al. 2003; Ziskind-Conhaim et al. 2003; Ariwodola and Weiner 2004; Carta et al. 2004; Nie et al. 2004; Sanna et al. 2004; Siggins et al. 2005; Li et al. 2006; Ming et al. 2006; Zhu and Lovinger 2006; Criswell et al. 2008; Silberman et al. 2008; Theile et al. 2008; Wilcox et al. 2014). However not all studies have found an ethanol-induced alteration in GABA release (Proctor et al. 2006; Criswell et al. 2008). With regards to the striatum, the effects of GABAergic transmission appear to be subregion specific as it has been shown that acute ethanol increases the frequency of mIPSCs in the DMS and NAc but conversely decreases it in the DLS (Nie et al. 1997, 2000; Wilcox et al. 2014).

The regulation of GABA release by acute ethanol is thought to rely on activation of G-protein-coupled receptors including $GABA_B$ receptors (Peris et al. 1997; Nie et al. 2004; Wu et al. 2005; Silberman et al. 2009; Kelm et al. 2011). Acute ethanol has been shown to increase presynaptic $GABA_B$ receptor activity, suggesting its role in the ethanol-induced changes in GABA release. The presynaptic $GABA_B$ effect is thought to involve tonic inhibition of PKC. An ethanol-induced effect on postsynaptically located $GABA_B$ receptors has not been found (Ariwodola and Weiner 2004). The ethanol-induced alterations in presynaptic GABA release are further discussed in the chapter "Presynaptic Ethanol Actions: Potential Roles in Ethanol Seeking" found in this volume (Lovinger 2017).

5.2 Chronic Actions

Chronic ethanol exposure can result in tolerance to alcohol's behavioral effects. This may reflect neural adaptations that ultimately decrease GABAergic transmission (Fig. 2, bottom). Changes in $GABA_A$ receptor subunit expression have been found in several brain regions coincident with chronic alcohol exposure (e.g., Papadeas et al. 2001; Cagetti et al. 2003; Floyd et al. 2004; Hemby et al. 2006; Jin et al. 2014).

Specifically, in the NAc a decrease in the α4 subunit was found following 2 weeks of chronic ethanol drinking in rats compared to ethanol naïve rats (Papadeas et al. 2001). A different group demonstrated within the NAc a coordinated decrease in the protein and functional expression of the α1 and δ subunits, concomitant with an increase in α4, α5, and γ2 subunits, using a chronic intermittent ethanol exposure model followed by up to 40 days of withdrawal (Liang et al. 2014). This is suggestive of long-lasting adaptations in GABAergic transmission following chronic ethanol exposure. These differences may be due to length of exposure or withdrawal. In ethanol-dependent individuals engaged in prolonged withdrawal, lower $GABA_A$ receptor availability is found in the NAc of dependent individuals compared to controls (Lingford-Hughes et al. 2012). These adaptive changes in $GABA_A$ receptor subunit expression have also been found in other brain regions such as the hippocampus (Cagetti et al. 2003; Liang et al. 2004) and amygdala (Floyd et al. 2004; Roberto et al. 2004; Anderson et al. 2007). These alterations may induce changes in the functional properties of $GABA_A$ receptors leading to changes in affinity for GABA and allosteric modulators.

A few studies have reported that chronic ethanol exposure alters GABA release. An increase in GABA release was suggested to occur within the CeA and hippocampus of chronic ethanol treated rodents perhaps attributable to changes in the activity of $GABA_B$ autoreceptors (Tremwel et al. 1994; Peris et al. 1997; Roberto et al. 2004, 2008, 2010). Specifically, in the dorsal striatum a decrease in the frequency of mIPSCs was found in both the DLS of mice and in the putamen of monkeys (Cuzon Carlson et al. 2011, 2017; Wilcox et al. 2014). However, the role of $GABA_B$ receptors in modulating GABA release was not examined in these studies.

5.3 Pharmacotherapies for Alcohol Use Disorders That Target GABAergic Transmission

To date, there are only three medications approved by the US Food and Drug Administration (FDA) to treat alcohol use disorder: disulfiram, naltrexone, and acamprosate. Although these drugs have been shown to reduce alcohol consumption, their effects are modest and inconsistent. Therefore, there is a need to discover other pharmacological treatments need to be explored. The observed behavioral similarities between the effects of ethanol and benzodiazepines (Krystal et al. 2003) suggest that targeting the GABAergic system is a viable target for treating alcohol use disorder. There are three pharmacological agents that are thought to alter the GABAergic system that are currently being assessed for their ability to treat AUD: gabapentin, baclofen, and sodium oxybate. Gabapentin is structurally similar to the GABA, although it has no activity at GABA receptors. It is shown to have activity at voltage sensitive calcium channels and the ability to modulate GAD, increasing GABA synthesis (Taylor 1997). Gabapentin is currently FDA approved for the treatment of seizures, neuropathic pain, and restless leg syndrome. For alcohol use disorders, gabapentin has been shown to increase the rate of abstinence, decrease heavy drinking days, and decrease withdrawal symptoms (Voris et al. 2003; Mason et al. 2014). Baclofen is an agonist of the $GABA_B$ receptor and is currently FDA approved for muscle spasticity. Clinical studies have shown an increase in abstinence and a decrease in alcohol

consumption in AUD individuals using baclofen over placebo (Addolorato et al. 2007; Muller et al. 2015; Beraha et al. 2016; Reynaud et al. 2017). Sodium oxybate is the salt version of gamma-hydroxybutyrate (GHB), an endogenous neurotransmitter that has agonist activity at GABA receptors (Kamal et al. 2016). Sodium oxybate is FDA approved for the treatment of narcolepsy and is currently approved for alcohol relapse prevention in Italy and Austria. Clinical trials suggest that sodium oxybate increases abstinence rates (Gallimberti et al. 1992; Caputo et al. 2007) but may lead to craving and abuse of GHB (Caputo et al. 2007).

6 Ethanol Actions on Glutamatergic Transmission

The glutamatergic system has been implicated in the acute intoxicating effects of ethanol, ethanol dependence, and withdrawal, and recently has been suggested to be a potential target for treatment of alcoholism. These acute intoxicating effect correlates with a decrease in glutamatergic function. There is evidence that changes in brain circuitry occurring as a result of chronic alcohol exposure leads to a hyperglutamatergic state (Fig. 2). The glutamatergic system plays a role in alcohol-associated dependence, including chronic alcohol seeking and relapse (Dahchour et al. 1998; Rossetti et al. 1999; Bäckström and Hyytiä 2004; Krupitsky et al. 2007; Nagy 2008; Alasmari et al. 2015).

6.1 Acute Actions

Acute ethanol has been shown to elicit both pre- and postsynaptic effects that ultimately lead to decreased glutamatergic transmission. Presynaptically, acute low concentrations of ethanol elevate glutamate levels in the striatum (Moghaddam and Bolinao 1994; Selim and Bradberry 1996; Lominac et al. 2006; Szumlinski et al. 2007; Soyka et al. 2016; Goodwani et al. 2017; Hopf 2017) whereas at acute higher concentrations ethanol can decrease extracellular glutamate concentrations (Moghaddam and Bolinao 1994; Piepponen et al. 2002; Tiwari et al. 2014). However, other studies suggest no acute ethanol effect on glutamate levels (Dahchour et al. 1994, 1996; Quertemont et al. 2002). This discrepancy may be due to strain differences, differences in ethanol sensitivity, concentration of ethanol examined, or brain location. Nevertheless, it is proposed that ethanol can alter extracellular glutamate levels by exerting an effect on glutamate uptake by astrocytes (Smith 1997; Othman et al. 2002; Melendez et al. 2005) or by the effect of high concentrations of ethanol inhibiting the release of glutamate by its action on NMDA receptors (Martin and Swartzwelder 1992; Woodward 1994).

Postsynaptically, ethanol has been shown to alter the functioning of ionotropic and metabotropic glutamate receptors. NMDA receptor, an ionotropic glutamate receptor, is one of the major targets of ethanol (Lovinger et al. 1989, 1990; Holmes et al. 2013) and inhibition of NMDA receptors by alcohol is thought to contribute to the intoxicating effects of alcohol (Hodge and Cox 1998). Acute ethanol at concentrations that mimic intoxicating levels in humans (5–50 mM or ~23–230 mg/dL) has been shown to inhibit the function of NMDA receptors in a concentration-dependent

manner (Lovinger et al. 1989, 1990). This ethanol-induced inhibition of NMDA receptors is mediated by a decreased probability of channel opening and a decrease in mean open time (Lima-Landman and Albuquerque 1989; Weight et al. 1993).

The ethanol sensitivity of NMDA receptors is thought to be dependent on subunit composition, regional differences, phosphorylation state, and extracellular concentration of magnesium. NMDA receptors containing the NR2A or NR2B subunits are most potently affected by ethanol, with less potency for NMDA receptors containing the NR2C or NR3 subunits (Kuner et al. 1993; Yamakura et al. 1993; Masood et al. 1994; Chu et al. 1995; Mirshahi and Woodward 1995; Popp et al. 1998; Woodward 2000; Smothers and Woodward 2003). Fyn kinase, PKA, PKC, and DAARP-32 have been shown to phosphorylate NMDA receptors after ethanol administration (Moon et al. 1994; Snell et al. 1994; Miyakawa et al. 1997; Maldve et al. 2002; Li and Kendig 2003; Ferrani-Kile et al. 2003; Yaka et al. 2003) that may lead to the internalization of NR2 subunits (Suvarna et al. 2005). With regards to extracellular magnesium concentration, the inhibitory effect of ethanol on NMDA receptors correlates with the concentration of magnesium such that increasing concentrations of magnesium leads to an increase in ethanol-induced inhibition of NMDA receptors (Rabe and Tabakoff 1990; Martin et al. 1991; Morrisett et al. 1991; Calton et al. 1998). The ethanol sensitivity of NMDA receptors is also sensitive to glycine concentration, an allosteric modulator of the NMDA receptor. High concentrations of glycine (>10 μM) can decrease the ethanol-induced inhibition of NMDA receptors (Rabe and Tabakoff 1990). In the striatum, acute ethanol can inhibit the synaptic plasticity of excitatory postsynaptic currents in an ethanol concentration-dependent manner (Wang et al. 2007; Jeanes et al. 2011).

In addition to its effects on NMDA receptors, ethanol also inhibits the function of AMPA and kainate receptors (Moghaddam and Bolinao 1994; Costa et al. 2000; Crowder et al. 2002). AMPA and kainate ionotropic glutamate receptors are also sensitive to the acute effects of ethanol, albeit at concentrations exceeding those that block NMDA receptors (Lovinger et al. 1989; Dildy-Mayfield and Harris 1992; Costa et al. 2000; Moykkynen et al. 2003; Kalev-Zylinska and During 2007; Marty and Spigelman 2012; Santerre et al. 2014). A single 4-h two-bottle choice session in which mice had access to ethanol (20% v/v) and water leads to an increase in the protein level of the AMPA receptor subunit GluA1 (Beckley et al. 2016).

The role of Group I metabotropic glutamate receptors (mGluR1, mGluR5) in alcohol-related behaviors has been extensively studied. Gene variations in mGluR5 are associated with alcoholism risk (Schumann et al. 2008). Similarly, mGluR5 has been suggested to play a role in alcohol consumption and seeking as the blockade or deletion of mGluR5 specifically in the ventral striatum, attenuates these behaviors (Besheer et al. 2010; Cozzoli et al. 2012; Sinclair et al. 2012).

6.2 Chronic Actions

Chronic alcohol exposure leads to a hyperglutamatergic state in many brain regions, including the striatum (Ward et al. 2009; Ding et al. 2012, 2013; Das et al. 2015). In

response to chronic ethanol, there is a potentiation of glutamatergic transmission (Fig. 2, bottom), potentially as a compensation to chronic blockade of NMDA by acute ethanol.

In postmortem brains of human alcoholics, studies have found an increase in NMDA receptor ligand binding, density, and affinity (Michaelis et al. 1993; Freund and Anderson 1996, 1999). Similar findings were observed in rodent studies of chronic ethanol exposure in which binding to the NMDA receptor was increased concomitant with an increase in the expression of the NR1, NR2A, and NR2B subunits of the NMDA receptor (Trevisan et al. 1994; Kumari and Ticku 2000; Kash et al. 2009; Obara et al. 2009; Wang et al. 2010). In addition to up-regulation of NMDA subunit expression, chronic ethanol also increases NMDA receptor function (Kalluri et al. 1998; Carpenter-Hyland et al. 2004; Carpenter-Hyland and Chandler 2006; Kash et al. 2009; Wang et al. 2007, 2010) and conductance (Iorio et al. 1992; Sanna et al. 1993; Chen et al. 1999; Floyd et al. 2003; Nagy et al. 2003; Nelson et al. 2005). In chronic ethanol-exposed mice that were undergoing withdrawal, high frequency stimulation induced NMDA receptor-dependent LTP of glutamatergic transmission in the striatum. This was in stark contrast to the ethanol naïve condition in which the same high frequency stimulation paradigm induced NMDAR-dependent LTD of glutamatergic transmission (Yamamoto et al. 1999; Jeanes et al. 2011). The increase in LTP may be facilitated by an increase in the response of NR2B containing NMDA receptors (Wang et al. 2007). A decrease in LTD of glutamatergic transmission was also found in the striatum of chronic ethanol exposed rodents potentially through decreased endocannabinoid cannabinoid 1 receptor signaling (Xia et al. 2006; DePoy et al. 2013). These changes in NMDA receptor expression and function can lead to hyperexcitability that may underlie the increased seizure susceptibility associated with early withdrawal from ethanol (Tsai et al. 1995; Tsai and Coyle 1998). In prolonged withdrawal, a down-regulation of NMDA subunit express, function, and LTD induction have been observed in the NAc (Abrahao et al. 2013).

A chronic ethanol-induced increase in AMPA receptor expression has been found in a number of brain regions, including the striatum (Chandler et al. 1999; Neasta et al. 2010; Ary et al. 2012; Wang et al. 2012). Specifically within the striatum, an increase in the expression and synaptic trafficking of GluA1 and GluA2 subunits of the AMPA receptor was found following chronic ethanol (Neasta et al. 2010; Ary et al. 2012). An increase in AMPA receptor-mediated excitatory postsynaptic currents was observed in the DMS and amygdala following chronic ethanol (Läck et al. 2007; Ma et al. 2017). The chronic ethanol-induced facilitation of LTP observed in striatal MSNs has been suggested to involve an increase in the synaptic insertion of AMPA receptors (Wang et al. 2010, 2015).

In addition to changes in the postsynaptic ionotropic glutamate receptors, an increase in the postsynaptic release of glutamate and its concentration in brain tissue have also been observed following chronic ethanol exposure in rodents and humans (Rossetti and Carboni 1995; Bauer et al. 2013). Elevated glutamate concentrations were measured in rodents after chronic ethanol exposure in several brain regions, and the glutamate concentration measured in the NAc, in particular, correlated with

the severity of alcohol withdrawal (Fliegel et al. 2013). An increase in the spine density of MSNs as well as an increase in the frequency of excitatory postsynaptic currents were observed in the putamen of nonhuman primates (Cuzon Carlson et al. 2011). The observed chronic ethanol-induced increase in extracellular glutamate may be a result of alterations in vesicular glutamate transporters (Tsai and Coyle 1998; Fliegel et al. 2013). An increase in the expression and/or activity of mGluR1/5 may also increase glutamate release by way of activation of PLC (Obara et al. 2009; Meinhardt et al. 2013).

6.3 Pharmacotherapies of Alcohol Use Disorders That Target the Glutamatergic System

As stated above, there are currently only three FDA drugs for the treatment of AUD. Acamprosate was approved by the FDA in 2004 for the maintenance of abstinence in individuals with AUD (Maisel et al. 2013; Jonas et al. 2014; Donoghue et al. 2015). Although its exact mechanism of action is unknown, acamprosate is thought to reduce glutamate levels via antagonism of mGluR5 (Harris et al. 2003). Topiramate has shown potential as a potential AUD therapy drug. It is an antagonist of kainate and AMPA glutamate receptors (Gibbs et al. 2000) and is currently FDA approved to treat epilepsy. Topiramate has shown potential in reducing alcohol cravings and intake in human trials (Johnson et al. 2007; Blodgett et al. 2014; Martinotti et al. 2014). However, a number of adverse effects (including nausea, impaired cognitive function, and paraesthesia) has the potential to lead to noncompliance in some users as these adverse effects may outweigh the benefit of the drug (Kranzler et al. 2014).

7 Effects of Ethanol on Specific Neuronal Populations of the Striatum

Since it has been demonstrated that specific manipulation of either direct or indirect pathway MSNs leads to distinct downstream circuits mediating different behaviors (Kravitz et al. 2010; Carvalho Poyraz et al. 2016; Lambot et al. 2016), it is important to define these and other striatal cell types and highlight differences in alcohol-induced adaptations.

7.1 dMSN vs iMSNs

Evidence is mounting that GABAergic and glutamatergic transmissions within the striatum are modulated by ethanol in a cell-type specific manner. Repeated cycles of voluntary ethanol consumption and forced withdrawal selectively potentiate synaptic NMDA receptor activity in D1 receptor-expressing dMSNs but not in D2 receptor-expressing iMSNs of the DMS (Cheng et al. 2017). This imbalance in activity between dMSNs and iMSNs following chronic ethanol exposure occurs in

conjunction with a loss in the ability to elicit LTD selectively in dMSNs, while that ability was observed only in iMSNs (Fig. 2, bottom). Although this was recovered by 2 weeks of withdrawal (Jeanes et al. 2014), it is not known whether the occlusion of LTD in dMSNs following chronic ethanol was due to an ethanol-induced floor effect in LTD whereby it could not be further generated, or whether ethanol altered synaptic function in some manner rendering it resistant to change. Another study suggests that the bias towards activation of dMSNs is a result of chronic ethanol-induced facilitation of NMDA receptor currents and LTP while concomitantly inhibiting NMDA receptors and eliciting LTD in iMSNs (Fig. 2, bottom; Renteria et al. 2017). A further explanation is the increase in GluN2B-containing NMDA receptors specifically in dMSNs may facilitate AMPA receptor plasticity, LTP and an overall increase in activity of dMSNs (Wang et al. 2012, 2015).

Interestingly, this potentiation of glutamatergic transmission onto dMSNs with ethanol exposure was found to be concomitant with an increase in GABAergic transmission onto iMSNs (Fig. 2, bottom; Cheng et al. 2017). This increase in GABAergic transmission in the striatum may result from an ethanol-induced increase in GABAergic interneuron connectivity onto D2-MSNs (Gittis et al. 2011).

On the whole, the literature suggests a strong bias towards activation of dMSNs following chronic ethanol exposure that may be responsible for facilitating continued, compulsive, or excessive alcohol intake (Berglind et al. 2006; Luo et al. 2011). In agreement with an ethanol-induced increase in dMSN output, genetic knockout or blockade of glutamate receptors specifically in dMSNs that results in a decrease in output from dMSNs, reduces the alcohol deprivation effect in which there is a temporary increase in voluntary alcohol consumption over baseline when ethanol access is reinstated following a period of withdrawal (Sinclair and Senter 1967, 1968; Eisenhardt et al. 2015).

7.2 Interneurons

There are conflicting reports as to how ethanol affects fast-spiking parvalbumin expressing interneurons of the striatum. An acute ethanol-induced depression of GABAergic synapses in the DLS was found to specifically involve the GABAergic synapses of fast-spiking parvalbumin-expressing GABAergic interneurons onto MSNs through modulation of opioid transmission (Patton et al. 2016). Conversely, acute application of ethanol led to a reversible membrane depolarization in striatal fast-spiking GABAergic interneurons through a reduction in cholinergic transmission (Blomeley et al. 2011). This difference in results may have been due to species differences or differences in recording parameters. In low-threshold spiking interneurons, brief application of ethanol led to membrane hyperpolarization (Blomeley et al. 2011), an effect attributed to the ethanol's actions on potassium currents.

Acute ethanol also decreased the average action potential firing rate of cholinergic interneurons (Blomeley et al. 2011). Cholinergic interneurons have also been shown

to facilitate the acute ethanol effect on long-term synaptic plasticity in the striatum (Adermark et al. 2011).

8 Implications of the Effect of Ethanol on Striatal GABAergic and Glutamatergic Transmission in the Progression to Addiction

Repeated cycles of ethanol consumption and withdrawal are thought to reinforce ethanol consumption, in some instances leading to pathologically excessive use of ethanol. Gaining insights into the detailed mechanisms that underlie the control of ethanol consumption by excitatory and inhibitory neurotransmission onto striatal neuronal subpopulations is a required step in elucidating prospective synaptic and neuronal therapeutic targets for the development of new approaches for the treatment of alcoholism. A further goal would be uncovering differences in the cortico-basal ganglia circuits (limbic, associative, and somatosensory) to determine what sets the stage for ethanol consumption progressing to excessive, compulsive intake in some individuals while others are spared.

Acute ethanol leads to a reduction in excitatory drive by way of the inhibition of NMDA receptors. This coupled with the enhancement of inhibitory GABAergic transmission may account for the sedating and dose-dependent depressant effects of ethanol intoxication. In the striatum, the acute effects of ethanol on GABAergic transmission appeared to be subregion specific with increases in presumably the release of GABA in the DMS and NAc but a decrease in the DLS (Nie et al. 1997, 2000; Wilcox et al. 2014). This may lead to a disruption in the normal processing of reward-related behaviors mediated by the limbic circuit, or action control mediated by the dorsal striatum that may begin a bias towards the somatosensory circuit. It is posited that abnormal reward-related learning and action selection for the consumption of alcohol is brought about by ethanol-induced changes in striatal synaptic strength and plasticity. This could ultimately prime the activity of the same striatal circuits in response to future alcohol exposure. The alcohol-induced changes in neuronal signaling within the NAc could explain the erroneous cue-induced associations that are made by individuals during alcohol exposure. The activity of the DMS appears to be required during the developmental phase of excessive alcohol drinking in which the action of alcohol intake is still dependent on the outcome of that action (Corbit et al. 2012). In a related fashion, the DMS may play a role in the relapse to alcohol seeking.

One consequence of chronic ethanol exposure appears to be a disinhibition of striatal output that facilitates the recruitment of certain cortico-striatal circuits. In particular, the sensorimotor circuit may increase habit formation and alcohol seeking (Corbit et al. 2012; Dickinson et al. 2002). The resulting recruitment of the sensorimotor loop and the DLS is thought to underlie compulsive drug use. This may be further exacerbated by the alcohol-induced bias in activation of dMSNs via increased AMPAR activity. The activation or potentiation of dMSN circuitry concomitant with a decrease in iMSN circuitry could reduce the threshold of alcohol-related sensory stimulation and enhance multisensory integration surrounding alcohol use.

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