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Invited review

Alcohol and basal ganglia circuitry: Animal models

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ABSTRACT

Brain circuits that include the cortex and basal ganglia make up the bulk of the forebrain, and influence behaviors related to almost all aspects of affective, cognitive and sensorimotor functions. The learning of new actions as well as association of existing action repertoires with environmental events are key functions of this circuitry. Unfortunately, the cortico-basal ganglia circuitry is also the target for all drugs of abuse, including alcohol. This makes the circuitry susceptible to the actions of chronic alcohol exposure that impairs circuit function in ways that contribute to cognitive dysfunction and drug use disorders. In the present review, we describe the connectivity and functions of the associative, limbic and sensorimotor cortico-basal ganglia circuits. We then review the effects of acute and chronic alcohol exposure on circuit function. Finally, we review studies examining the roles of the different circuits and circuit elements in alcohol use and abuse. We attempt to synthesize information from a variety of studies in laboratory animals and humans to generate hypotheses about how the three circuits interact with each other and with the other brain circuits during exposure to alcohol and during the development of alcohol use disorders.

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1. Brief description of cortico-basal ganglia circuitry

Circuits that connect the cerebral cortex to the basal ganglia, and the connections back through thalamus to the cortex are a major feature of the mammalian forebrain. Each area of allo-, meso-or neocortex projects to a striatal or striatal-like subregion, which then communicates to downstream basal ganglia regions that ultimately connect to thalamo-cortical neurons (Gerfen, 1992; Haber and Calzavara, 2009). Within the basal ganglia, regions including the globus pallidus internal and external segments (GPi and GPe respectively), and the substantia nigra reticulata (SNr) process striatal output to provide feedback that ultimately influences cortical output. Monoaminergic transmission from midbrain and brainstem regions modulates circuit function mainly through actions in the striatal regions, but also at other subregions within the circuitry (Molliver, 1987; Berridge et al., 1997; Delfs et al., 1998; Beier et al., 2015; Lerner et al., 2015). These networks interface with the large thalamic network via thalamo-striatal projections. The overall loop of the cortico-basal ganglia-cortical (C-BG-C)

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system can be separated into numerous subcircuits based on anatomical and functional divisions (Alexander and Crutcher, 1990). The best known among these are circuits in which neocortical structures, mesocortical structures (e.g. cingulate and piriform cortices) and allocortical regions (e.g. hippocampus and amygdala) project to well-known dorsal and ventral striatal regions, with processing/feedback loop networks influencing those cortical regions. However, the C-BG-C loop type networks are also maintained within the olfactory system where olfactory bulb and cortical inputs converge in the olfactory tubercle. The extended amygdala also has a C-BG-like network, with the lateral and basolateral amygdala serving as the cortical substrates, and the CeA and other downstream structures having features in common with the striatum (Swanson and Petrovich, 1998). Cross-talk between the different C-BG-C networks also occurs at several levels throughout the cortex, BG and midbrain.

Other contributions to this volume will focus on the extended amygdala and prefrontal cortex, and thus, we will not cover these aspects of C-BG-C circuits except where needed to make key points about their role in the overall circuitry. Instead, our focus will be on the three predominant forebrain circuits known as the associative, limbic (aka cognitive) and sensorimotor (aka motor) C-BG-C circuits, and the interactions among these circuits (Haber, 2003).

The three C-BG-C circuits on which we will focus share a basic cellular and molecular connectivity (Dudman and Gerfen, 2015). Cortical regions send glutamatergic projections to striatum that innervate both GABAergic medium spiny projection neurons (MSNs) and striatal interneurons. Specific thalamic subregions also send glutamatergic inputs to the MSNs and striatal interneurons. The striatum also receives dense dopaminergic projections from the midbrain, and much sparser monoaminergic inputs from other hindbrain regions that vary in different striatal subregions (Molliver, 1987; Berridge et al., 1997; Delfs et al., 1998). The MSNs then send GABAergic projections to the GPe, GPi and SNr. Projections to GPi/SNr comprise the “direct” pathway that activates cortical output, while projections targeting the GPe via the “indirect” pathway inhibit cortical output. GABAergic projection neurons within the GPe project to the SNr and also form part of a reciprocal connection with the subthalamic nucleus (STN) in which the GPe contributes GABAergic innervation of STN, while STN sends glutamatergic afferents to GPe. The influence of these pathways on cortical function ultimately arises via GABAergic SNr projections to thalamus that gate thalamocortical glutamatergic inputs (Fig. 1).

The cortical components of the associative circuit consist of areas that process sensory, motor and cognitive information at a stage with greater integration than primary sensory or motor cortices (Yin and Knowlton, 2006). Examples include parts of the temporal and posterior parietal cortex, as well as prefrontal cortical regions. These cortical regions project predominantly to more medial areas of dorsal striatum (dorsomedial striatum, DMS) in the rodent brain (roughly equivalent to the primate caudate nucleus). Several anterior and medial and lateral thalamic regions project to DMS, and medial portions of the substantia nigra pars compacta (SNc) provide the bulk of dopaminergic innervation of this striatal subregion. The DMS MSNs project to the more medial parts of the GPe, GPi and SNr, and the GPe interacts with subregions of the STN. Ultimately, this circuit loop influences output from the same associative cortical areas that feed into the DMS (Balleine et al., 2007) (Belin et al., 2009), although there is potential for cross-talk between circuits at several levels, which will be discussed later in this review.

The cortical components of the limbic circuit consist of mesocortical and prefrontal areas, as well as the allocortical regions, such as the hippocampal formation and basolateral amygdala (BLA) (Gerfen, 1992; Yin and Knowlton, 2006). These cortical regions

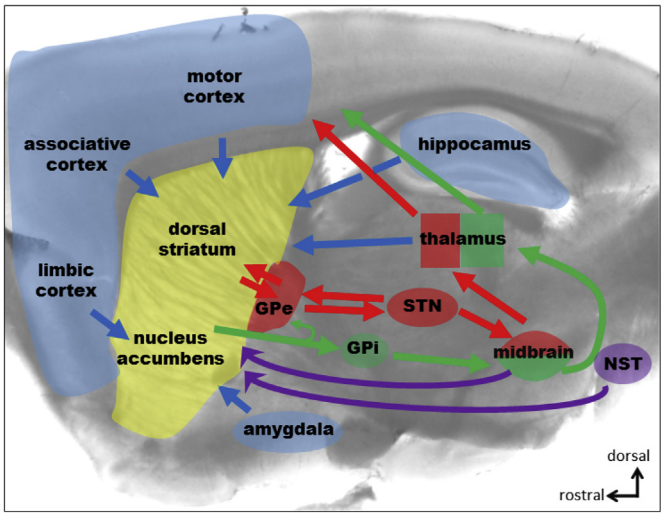

Fig. 1. Diagram of the cortex-basal ganglia-cortex loop showing the main projections that will be discussed in this review. Blue arrows represent all main glutamatergic inputs to the striatum and purple arrows the monoamine innervation from the midbrain dopamine neurons and the noradrenergic projection from the nucleus of the solitary tract (NST). Green and red arrows represent the two main output projections that form the direct- and indirect-pathway, respectively.

project predominantly to the nucleus accumbens (NAc) (although the BLA does give rise to an appreciable projection to the DMS). The NAc can be further subdivided into the “core” and “shell” subregions, and these have been implicated in different aspects of learning and responses to substances of abuse as will be discussed. Thalamic projections to the NAc from antero-medial subregions are also part of the limbic circuitry. The dopaminergic input to the NAc comes predominantly from the ventral tegmental area (VTA). The NAc shell subregion also receives a more robust noradrenergic input in comparison to DS and the NAc core, and this arises from the nucleus of the solitary tract (Berridge et al., 1997; Delfs et al., 1998). Some MSNs within the NAc send their projections to the ventral mesencephalon (VM), while others innervate the ventral pallidum (VP). While the VM and VP projections have a superficial resemblance to the direct and indirect pathways, respectively, recent studies indicate that there is considerable mixing of MSN projections to the VP (Kupchik et al., 2015). Thus, the limbic striatal inputs and outputs are different from the dorsal striatal counterparts. The output from the limbic BG affects many parts of the limbic system, but also has more indirect influence on the associative and sensorimotor circuits. It should also be noted that parts of the limbic C-BG-C circuitry loop also include the extended amygdala network that will be described in a separate article in this volume. Our focus when discussing limbic circuitry will be on actions that differ from the negative affect/negative reinforcement functions described in that review.

The final large C-BG-C circuit that we will discuss is the sensorimotor circuit. As the name implies, this circuit includes the primary sensory and motor neocortices, along with some secondary regions such as supplementary motor areas (e.g. mouse M2 cortex). These cortical regions project into the dorsolateral striatum (DLS) in rodents (roughly equivalent to the putamen nucleus in primates). Indeed, there are several subcircuits within the corticostriatal sensorimotor projections that roughly correspond to different body parts, forming a very diffuse “humuncular” representation. No attempt will be made to differentiate these subcircuits in the present review. The intralaminar nuclei of the thalamus project to DLS, including several regions extending across the anterior-posterior