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Intrinsic neuronal plasticity in the juxtacapsular nucleus of the bed nuclei of the stria terminalis (jcBNST)

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ABSTRACT

The juxtacapsular nucleus of the anterior division of the BNST (jcBNST) receives robust glutamatergic projections from the basolateral nucleus of the amygdala (BLA), the postpiriform transition area, and the insular cortex as well as dopamine (DA) 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. We recently described a form of long-term potentiation of the intrinsic excitability (LTP-IE) of neurons of the juxtacapsular nucleus of BNST (jcBNST) in response to high-frequency stimulation (HFS) of the stria terminalis that was impaired during protracted withdrawal from alcohol, cocaine, and heroin and in rats chronically treated with corticotropin-releasing factor (CRF) intracerebroventricularly. Here we show that DAergic neurotransmission is required for the induction of LTP-IE of jcBNST neurons through dopamine (DA) D1 receptors. Thus, activation of the central CRF stress system and altered DAergic 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 post-dependent individuals. These results provide a novel neurobiological target for vulnerability to alcohol and drug dependence.

1. Introduction

Neuroadaptive changes in the extended amygdala circuits are believed to be key in the motivation for excessive alcohol and drug intake (Koob et al., 1998). In particular, many motivational aspects of addiction have been localized to the central nucleus of the amygdala and the lateral subdivision of the bed nucleus of the stria terminalis (BNST) (Koob, 2003). The BNST is a collection of about a dozen nuclei that are well positioned to integrate somatomotor, autonomic and affective responses. Multiple reinforcing drugs including nicotine, morphine, ethanol, and cocaine were found to increase dialysate DA in the BNST (Carboni et al., 2000). Additionally, D1-class (D1/D5) DA receptors in the dorsolateral BNST have been implicated in the reinforcing properties of self-administered cocaine (Epping-Jordan et al., 1998) and alcohol (Eiler et al., 2003). The BNST has also been shown to be critical in mediating stress-induced reinstatement of cocaine self-administration in rodent models (Shaham et al., 2000). The BNST is also believed to play a central role in the regulation of stress response and in the long-term actions of drugs of abuse (Epping-Jordan et al., 1998; Aston-Jones et al., 1999; Delfs et al., 2000; Georges and Aston-Jones, 2001; Koob, 2003). Extracellular corticotropin-releasing factor (CRF) levels are increased in the BNST during ethanol withdrawal, and such an increase is reduced by subsequent ethanol intake (Olive et al., 2002).

The juxtacapsular nucleus of the BNST (jcBNST) is a small nucleus in the dorsal anterolateral BNST that is bounded laterally by the internal capsule and the caudoputamen complex, ventrally by the anterior commissure, and medially by the oval nucleus of the BNST (McDonald et al., 1999; Shammah-Lagnado and Santiago, 1999; Dong et al., 2001; Larriva-Sahd, 2004). The jcBNST contains gamma-aminobutyric acid (GABA)ergic neurons, lacks glutamatergic neurons (Larriva-Sahd, 2006; Francesconi et al., 2009) and has complex

Abbreviations: 4-AP, 4-aminopyridine; α-DTX, α-dendrotoxin; AMPA, α-hydroxy-5-methyl-4-isoazolepropionic acid; APir, amygdalopiriform transition area; jcBNST, juxtacapsular nucleus of the anterior division of the BNST; BLA, basolateral nucleus of the amygdala; BNST, bed nucleus of the stria terminalis; CEA, central nucleus of the amygdala; CEAm, central nucleus of the amygdala, medial division; CRF, corticotropin releasing factor; DA, dopamine; DAT, dopamine transporter; EPSP, excitatory post-synaptic potential; HFS, high-frequency stimulation; GABA, gamma-aminobutyrate; I_A, A-type K^+ current; I_{AHP}, Afterhyperpolarization current; I_D, D-type K^+ current; I_h, hyperpolarization activated current; I_M, M-type K^+ current; ICV, intracerebroventricular; LTP-IE, long-term potentiation of the intrinsic excitability; NA, noradrenergic; NMDA, *N*-methyl-D-aspartic acid; NPY, neuropeptide Y; PAG, periaqueductal grey; VTA, ventral tegmental area.

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interactions, which are likely to play important roles in the regulation of stress and reward. In particular, the jcBNST has direct projections to the medial part of the central nucleus of the amygdala (CEAm) and can indirectly also influence the CEA through its projections to the basolateral amygdala (BLA and other cell groups that in turn send projections to the CEA (Dong et al., 2000). The CEAm is the major output nucleus of the amygdala (Pitkanen et al., 1997). Thus, changes in the integration properties of jcBNST neurons may contribute to the overall amygdala output and to the persistent emotional dysregulation associated with protracted withdrawal.

Plastic changes of neuronal circuits are believed to underlie learning and memory as well as adaptive and maladaptive changes induced by the individual life experiences (Kandel, 2001; LaBar and Cabeza, 2006; Sigurdsson et al., 2007; Bonci and Borgland, 2009). A growing body of evidence supports that, in addition to synaptic forms of plasticity, plastic changes of the intrinsic membrane properties of neurons are possible and that these forms of plasticity have significant implications for the integrative properties of neurons. Plastic changes of synaptic efficacy and of the membrane properties of neurons can either coexist or occur independently of each other. Recent work from our group has described an activity-dependent modification of the threshold for action potential generation of jcBNST neurons, i.e. a long-term potentiation of their intrinsic excitability (LTP-IE), that was impaired during protracted withdrawal in rats with histories of alcohol dependence, escalated cocaine or heroin self-administration and in rats chronically treated with CRF by intracerebroventricular (ICV) injections (Francesconi et al., 2009). Inhibition of CRF1 receptors restored capacity for LTP-IE in the jcBNST of animals with a history of alcohol dependence (Francesconi et al., 2009). In the present report we also provide evidence that DA D1 receptors contribute to the induction of this LTP-IE. The requirement for the activation of DA D1-class receptors for the induction of LTP-IE in the jcBNST suggests that altered DAergic neurotransmission may contribute to the disruption of this form of intrinsic neuronal plasticity in jcBNST neurons during protracted withdrawal from dependent drug use. The elucidation of the mechanisms behind the changes in the intrinsic neuronal plasticity that are induced by alcohol and drugs of abuse in the jcBNST is likely to have heuristic value for the understanding of the neurobiological bases of drugs of abuse.

1.1. The jcBNST at the interface between the stress and the reward systems

The extended amygdala is a neuroanatomical macrostructure stretching from the temporal lobe to the rostral forebrain that comprises several basal forebrain regions sharing similarities in morphology, neurochemistry and connectivity (Alheid and Heimer, 1988; Alheid et al., 1995). The brain regions that compose the extended amygdala include the central and medial nuclei of the amygdala, the BNST, and the cellular corridors that bridge the gap between these structures, dorsally along the path of stria terminalis, and ventrally, in the sublenticular region (Alheid and Heimer, 1988; Alheid et al., 1995). This anatomical system is composed of two major divisions: the medial and the central subdivision that are related to the medial and central amygdaloid nuclei, respectively (Alheid and Heimer, 1988; Alheid et al., 1995).

The medial subdivision of the extended amygdala is composed of the medial BNST, medial nucleus of the amygdala, medial sublenticular extended amygdala, and the medial supracapsular bed nucleus of the stria terminalis (Alheid and Heimer, 1988; Alheid et al., 1995). Afferents to the medial division include the accessory olfactory bulb, anterior olfactory nucleus, agranular insular cortex, and infralimbic cortex, ventral subiculum, and basomedial amygdala. Efferents from the medial division include the ventral striatum, olfactory amygdaloid nuclei and medial hypothalamic nuclei (Alheid and Heimer, 1988; Alheid et al., 1995; Canteras et al., 1995). Neural circuits involving the medial amygdala, which is the main output of the medial subdivision of the extended amygdala, are involved in sexual and maternal behavior and aggression, among other behaviors (Numan, 2007; Caldwell et al., 2008). The central division of the extended amygdala comprises the central nucleus of the amygdala, the lateral subdivision of bed nucleus of the stria terminalis, the lateral sublenticular extended amygdala and the lateral supracapsular bed nucleus of the stria terminalis (Alheid and Heimer, 1988; Alheid et al., 1995). These structures display an overall cytoarchitectural similarity to the central nucleus of the amygdala, are profusely interconnected among each other, and project to the lateral rather than the medial hypothalamus and are interconnected with the ventral tegmental area (VTA) (Alheid et al., 1995) The central subdivision of the extended amygdala receives afferents from insular and prefrontal cortices, the posterior basolateral amygdala, medial part of the ventral pallidum, subparafascicular thalamus, parabrachial area , while it projects to the lateral hypothalamus, VTA and substantia nigra compacta, tegmental pedunculopontine nucleus, and to the locus ceruleus and the nucleus of the solitary tract (Alheid and Heimer, 1988; Alheid et al., 1995; McDonald et al., 1999; Valentino and Van Bockstaele, 2008). The lateral subdivision of the extended amygdala is believed to be a substrate for the integration of the brain arousal and stress systems with hedonic processing systems (Koob et al., 1998; Koob, 2003, 2009).

The BNST has been shown to have an anterior subdivision—further divided into lateral and a medial—and a posterior subdivision that differ in their functional connectivities (Phelix et al., 1992, 1994; Dong et al., 2001; Kozicz, 2001). The lateral anterior subdivision of the BNST is considered to be a part of the central subdivision of the extended amygdala. The lateral BNST has high amounts of DA and noradrenergic (NA) terminals, CRF terminals, CRF cell bodies, NPY terminals, and galanin cell bodies, abundant GABA-ergic neurons, and receives afferents from the prefrontal cortex, insular cortex, central and basolateral nuclei of the amygdala (Allen et al., 1984; Gray and Magnuson, 1992; Phelix et al., 1992, 1994; Dong et al., 2001; Kozicz, 2001).

The jcBNST is unique in the lateral BNST as, unlike the other lateral BNST subregions, it does not receive inputs from the central nucleus of the amygdala (Dong et al., 2000; Larriva-Sahd, 2004), but receives dense gutamatergic projections from the posterior part of the BLA, the amygdalopiriform transition area (APir), and the gustatory and visceral sensory areas in the dysgranular insular region, as well as light projections form the infralimbic cortex (McDonald et al., 1999; Shammah-Lagnado and Santiago, 1999; Dong et al., 2001; Larriva-Sahd, 2004). In the BNST, dopamine transporter (DAT)-immunoreactive fibers are found in the highest concentrations in the jcBNST and in the dorsolateral BNST in general (Freedman and Cassell, 1994). Conversely, noradrenergic (NA) inputs from the A1 and A2 cell groups of the caudal medulla are mostly directed to the ventral BNST (Phelix et al., 1992; Freedman and Cassell, 1994; Dumont and Williams, 2004; Egli et al., 2005). Dopamine (DA) inputs to the lateral BNST are primarily from the A10dc DAergic neurons in the periaqueductal grey (PAG) and from the VTA (A10), and to a lesser extent from the A10dr group in the dorsal raphe and the retrorubral nucleus (A8) (Hasue and Shammah-Lagnado, 2002). The origin of the DAergic innervation of the lateral BNST is similar to that of the CeA and unlike the one of the shell of the nucleus accumbens in those projections to the latter are predominantly from the VTA (Hasue and Shammah-Lagnado, 2002).

The jcBNST projects strongly to the medial central amygdalar nucleus (CEAm) and the subcommissural zone and caudal anterolateral areas of the BNST, which are involved in visceromotor responses (Dong et al., 2000; Larriva-Sahd, 2006). It also sends dense projections to the sublenticular extended amygdala and the mesencephalic reticular nucleus and retrorubral area (Dong et al., 2000). The jcBNST also provides inputs to the ventromedial striatum and anterior basolateral amygdalar nucleus, which are believed to