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Effects of galanin on monoaminergic systems and HPA axis: potential mechanisms underlying the effects of galanin on addiction- and stress-related behaviors

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Abstract

Like a number of neuropeptides, galanin can alter neural activity in brain areas that are important for both stress-related behaviors and responses to drugs of abuse. Accordingly, drugs that target galanin receptors can alter behavioral responses to drugs of abuse and can modulate stress-related behaviors. Stress and drug-related behaviors are interrelated: stress can promote drug-seeking, and the behavioral signs of drug withdrawal result from increased activity in brain circuits involved in the stress response. We review here what is known about the ability of galanin and galanin receptors to alter neuronal activity, and we discuss potential mechanisms that may underlie the effects of galanin on behaviors involved in responses to stress and addictive drugs. Understanding the mechanisms underlying galanin's effects on neuronal function in brain regions related to stress and addiction may be useful in developing novel therapeutics for the treatment of stress- and addiction-related disorders.

Keywords

galanin; drug abuse; opiates; psychostimulants; addiction; stress; locus coeruleus; mesolimbic dopamine system; HPA axis; dorsal raphe; opiate withdrawal

1. Introduction

The neuropeptide galanin was initially discovered as a gut peptide (Tatemoto, et al., 1983). Subsequent studies found that galanin is also distributed throughout the mammalian brain and is involved in many critical functions including feeding behavior, pain modulation, seizure, learning and memory (for a recent series of reviews see: (Bauer, et al., 2008, Counts, et al., 2008, Crawley, 2008, Hobson, et al., 2008, Hokfelt and Tatemoto, 2008, Kuteeva, et al., 2008, Lerner, et al., 2008, Mechenthaler, 2008, Mitsukawa, et al., 2008, Xu, et al., 2008).

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Galanin acts through three receptor subtypes: GalR1, GalR2 and GalR3, which are encoded by different genes (Burgevin, et al., 1995, Kolakowski, et al., 1998, Wang, et al., 1997). All three galanin receptor subtypes are G protein-coupled and can activate Gi and Go proteins (Lang, et al., 2007). Consistent with the ability of all three galanin receptor subtypes to decrease cyclic AMP levels (Nishibori, et al., 1988) and activate the GIRK family of potassium channels (Smith, et al., 1998), the effects of galanin on individual neuronal subtypes in several regions of the brain is largely inhibitory, as outlined below. The GalR1 and GalR3 subtypes appear to be very similar in their signaling through Gi and Go proteins, while GalR2 also activates Gq proteins (Lang, et al., 2007, Wang, et al., 1998) and can increase calcium signaling and the activity of downstream effectors such as PKC (Hawes, et al., 2006a, Mahoney, et al., 2003). This suggests that stimulation of GalR2 would be expected to have somewhat different effects on neuronal firing than activation of GalR1 and GalR3. Systemic administration of non-selective galanin agonists and antagonists that act at all three galanin receptor subtypes will therefore result in complex changes in the balance of activity in neuronal ensembles expressing these different galanin receptor subtypes.

In addition to its role in feeding, increasing evidence suggests that galanin has multiple effects on stress-related and addiction-related behaviors (Holmes and Picciotto, 2006). It has been known for some time that peptides involved in the stress response can potently alter behavioral responses to drugs of abuse in animals and humans (Koob, 2008). Further, many brain areas involved in stress, anxiety and depression also play an important role in behavioral correlates of addiction. This is particularly clear for subcortical regions that mediate behavioral signs of drug withdrawal, since many of these behavioral signs are thought to reflect a stress response resulting in part from activation of the hypothalamic-pituitary-adrenal (HPA) axis (Koob, et al., 1992). Accordingly, hyperactivity of noradrenergic nuclei such as the locus coeruleus (LC) and alterations of neuronal activity in serotonergic neurons of the dorsal raphe may be involved in stress responses, as well as affective and somatic signs of drug withdrawal.

It is also clear that brain areas essential for the rewarding and locomotor effects of drugs of abuse can be involved in affective and stress-related behaviors. Neuronal activity in the ventral tegmental area (VTA) and nucleus accumbens (NAc) is necessary for both preference for and aversion to drugs of abuse (McBride, et al., 1999, Wise, 1989), whereas activity in the NAc can also promote depression-like behaviors (Carlezon and Thomas, 2009, Nestler and Carlezon, 2006). In general, increased stress also increases drug seeking in both animal models of addiction and in human addicts (Koob, 2009). It is therefore essential to understand how molecules such as galanin, that modulate neuronal activity in brain areas related to both stress and drugs of abuse, coordinate responses of different neurotransmitter systems and converge to alter behaviors related to addiction.

2. Galanin, drug reward and the dopaminergic system

2.1. Galanin modulates midbrain dopamine activity

The mesolimbic dopamine system is critical for the rewarding and motivational effects of drugs of abuse (Koob, 1992). Several neurochemical studies have shown that galanin can modulate midbrain dopamine activity (Table 1 and Fig. 1). Galanin decreases stimulation-evoked dopamine release in rat striatal slices through a mechanism that involves Gi proteins (Tsuda, et al., 1998). This is consistent with the ability of galanin to decrease glutamate, but not GABA release in striatal slices (Ellis and Davies, 1994). Moreover, intraventricular administration of galanin can increase DOPA accumulation in the striatum, NAc and olfactory turbercles and reduce locomotor activity in rats. Since the net effect on behavior is hypoactivity, the authors suggest that the increase in DOPA accumulation results from a decreased release of dopamine, relieving an autoreceptor-mediated tonic inhibition of dopamine synthesis. The effect of galanin on DOPA accumulation also occurs when galanin is microinjected into the VTA, but

not the NAc, suggesting that the VTA is a primary site of action for the effects of galanin on the mesolimbic system (Ericson and Ahlenius, 1999). Consistent with this hypothesis, galanin decreases locomotor activity in rats when injected either into the ventricle, the VTA or the hypothalamus (Weiss, et al., 2005). Taken together, these results suggest that galanin effects in the VTA can decrease the activity of the mesolimbic system.

To date, there is only indirect evidence indicating which galanin receptors are involved in the actions of galanin on dopaminergic activity. Galanin can modulate the expression of tyrosine hydroxylase (TH) in primary cultures of rat embryonic ventral mesencephalic cells (Counts, et al., 2002). Although galanin has no effect on the number of TH-immunoreactive neurons on its own, treatment with dibutyryl cAMP increases the number of TH-positive neurons, and this effect is decreased by galanin. These cultures express GalR1, GalR2, and, to a lesser extent, GalR3 receptor mRNA, but treatment with dibutyryl cAMP specifically increases GalR1 mRNA levels. Therefore, galanin may inhibit midbrain dopamine activity through a reduction of TH activity mediated through activation of GalR1 receptors. While GalR1 knockout mice and wild type mice do not differ in baseline locomotion (Holmes, et al., 2003), indirect evidence supporting a role for GalR1 in regulation of the dopamine system comes from central administration of galanin which dose-dependently reduces locomotor activity in wild type mice but not in knockout mice lacking GalR1 receptors (Mitsukawa, et al., 2009).

At least a subset of galanin-containing axons that innervate the substantia nigra and the VTA originate from pontine noradrenergic nuclei, mainly the LC (A6 region) (Jacobowitz, et al., 2004). Stimulation of LC neurons with single pulses can increase the firing of VTA neurons (Grenhoff, et al., 1993). This effect may result from norepinephrine release, since it can be decreased by the α_1-adrenoreceptor antagonist prazosin and is not present in rats pretreated with the norepinephrine depletion reagent reserpine. In contrast to single pulses, multiple stimulatory pulses that cause burst firing of LC neurons produce a long-lasting inhibition of VTA neurons (Grenhoff, et al., 1993). Galanin is thought to mediate these inhibitory effects because they are unaffected by prazosin or reserpine. This interpretation is supported by other studies showing that galanin is preferentially released when cells fire rapidly, as in burst firing (Bartfai, et al., 1988, Consolo, et al., 1994). The dependence of galanin release on burst firing is consistent with the necessity for higher levels of intracellular calcium to release the large, dense-core vesicles in which neuropeptides are packaged (Elhamdani, et al., 1999, Seward, et al., 1995, Thomas, et al., 1993). Moreover, it suggests that noradrenergic neurons from the LC that co-release galanin can either activate the VTA through norepinephrine release at low firing rates, or inhibit the VTA through galanin release at higher firing rates.

Effects of galanin on the cholinergic system could also alter activity in the dopaminergic system. In striatum, GalR1 mRNA is expressed in a pattern that suggests that it is localized in cholinergic interneurons (O'Donnell, et al., 1999, Zachariou, et al., 2000) but specific galanin binding sites are much more widespread (Hawes and Picciotto, 2004) suggesting that galanin receptors may be highly represented on neuronal terminals in the striatum and NAc. The galanin receptor subtype(s) expressed on these terminals remain undetermined, due to the lack of specificity of available antisera, which produce similar staining patterns in tissue samples from wild type mice and their respective GalR knockout mice (Hawes and Picciotto, 2005, Lu and Bartfai, 2009). Galanin injected directly into the paraventricular nucleus (PVN) of the hypothalamus can increase dopamine release in the NAc while decreasing acetylcholine release (Rada, et al., 1998). While the pathways underlying the effect of PVN galanin on NAc DA are not clear, this effect has been attributed to a pathway involving the VTA (see Fig. 1; Rada, et al., 1998). In support of this assumption, several studies demonstrate a neuroanatomical connection between the PVN and the VTA (Quinn, et al., 2003, Rodaros, et al., 2007). As observed after administration in the PVN, locally-infused galanin also decreases acetylcholine release in the striatum, as shown in microdialysis studies in awake rats (Antoniou, et al.,

1997). Conversely, it can increase acetylcholine release in striatum of anesthetized rats (Antoniou, et al., 1997, Ögren, et al., 1993), suggesting that this effect is modulated by arousal. Increased cholinergic tone is thought to contribute to depression in human subjects (Janowsky and Overstreet, 1990), and more recent studies have focused on the role of acetylcholine in drug addiction (Williams and Adinoff, 2007). Lack of acetylcholine in the NAc (as a result of ablation of cholinergic interneurons) results in increased sensitivity to the rewarding effects of cocaine, while increased acetylcholine levels (as a result of acetylcholinesterase inhibition) attenuate the rewarding effects of cocaine, as assessed in the conditioned place preference paradigm (Hikida, et al., 2003). Thus, effects of galanin on acetylcholine transmission could influence behavioral responses to drugs of abuse.

2.2. Galanin modulates addiction-related behaviors

In accord with the ability of galanin to modulate midbrain dopamine activity, a number of studies have shown that the galanin system modulates drug-related behaviors. For example, administration of galanin into the lateral ventricles attenuates the development of conditioned place preference for morphine in mice (Zachariou, et al., 1999). Consistent with this finding, knockout mice lacking the galanin peptide, unlike congenic wild type mice, are sensitive to the locomotor stimulant properties of morphine and show increased morphine conditioned place preference (Hawes, et al., 2008). Several other links between the galanin system and opioid addiction have been reported. Chronic, systemic injection of morphine in rats downregulates galanin expression in the extended amygdala in a mu-opioid receptor-dependent manner (Befort, et al., 2008), whereas GalR mRNA is increased in the LC during opiate withdrawal (Zachariou, et al., 2000). Moreover, single nucleotide polymorphisms in the human galanin gene are associated with heroin addiction (Levran, et al., 2008). Galanin has also been shown to modulate the behavioral response to psychostimulants. Mice lacking the galanin peptide are more sensitive to the rewarding effects of cocaine as measured by conditioned place preference (Narasimhaiah, et al., 2009). Consistent with this effect, transgenic mice that overexpress galanin are less sensitive to the stimulant effects of amphetamine, compared to wild type mice (Kuteeva, et al., 2005a, Kuteeva, et al., 2005b). Taken together, these data suggest that the overall effect of galanin in the brain is to decrease behavioral responses to morphine and psychostimulants (Tables 2 and 3).

Neurochemical studies have identified signaling pathways that may be involved in the ability of galanin to decrease the rewarding effects of drugs of abuse. Extracellular-regulated kinase (ERK) activity is increased in the VTA and NAc of knockout mice lacking the galanin peptide after challenge with either morphine or cocaine (Hawes, et al., 2008, Narasimhaiah, et al., 2009), implicating inhibition of the mesolimbic pathway as a potential mechanism underlying the ability of galanin to decrease the rewarding effects of these drugs.

In contrast to morphine and psychostimulants, galanin can increase alcohol consumption under several experimental conditions. Administration of galanin either into the third ventricle or into the PVN of the hypothalamus enhances voluntary alcohol intake in normal rats, an effect also observed in the presence of food and in rats selected for high alcohol intake (Lewis, et al., 2004, Rada, et al., 2004, Schneider, et al., 2007). In contrast, central administration of the non-selective galanin antagonist M40 decreases alcohol consumption and blocks the ability of galanin to facilitate alcohol intake (Lewis, et al., 2004, Rada, et al., 2004). Administration of alcohol can, in turn, alter galanin expression. Both rats chronically injected with alcohol and those allowed voluntary alcohol consumption show increased galanin expression (both at the mRNA and protein levels) in several hypothalamic nuclei including the PVN, dorsomedial nucleus and perifornical nucleus of the lateral hypothalamus (Leibowitz, et al., 2003). The increase in galanin mRNA in response to alcohol in the dorsomedial and perifornical areas (but not the PVN) is attenuated when alcohol withdrawal is induced by acute naloxone

administration (Leibowitz, et al., 2003). These results indicate that alcohol administration may increase galanin levels, potentially initiating a positive feedback loop that leads to further alcohol consumption.

Paradoxically, activation of the galanin system increases the response to alcohol while decreasing the response to other drugs of abuse including morphine, cocaine and amphetamine. A major difference between alcohol and other abused drugs is that alcohol has a caloric component. The ability of galanin to increase food intake may preferentially involve circuits in the hypothalamus (Kyrkouli, et al., 1986) that also regulate alcohol intake (Leibowitz, et al., 2003). Galanin injected directly into the PVN can increase dopamine release in the NAc (Rada, et al., 1998), and this direction of modulation of the reward circuitry would be consistent with galanin's ability to increase the rewarding effects of alcohol. It is also possible that galanin could modulate alcohol reward in the same direction demonstrated for other drugs in a behavioral paradigm that is not influenced by the caloric value of alcohol. For example, it would be interesting to determine if knockout mice lacking the galanin peptide are more or less sensitive to the rewarding effects of alcohol as measured by conditioned place preference.

To date, two human genetic studies have linked polymorphisms in the galanin gene, or the genes encoding its receptors, to alcoholism. Polymorphisms in both the genes encoding galanin and the GalR3 receptor, but not GalR1 or GalR2, have been associated with alcoholism (Belfer, et al., 2007, Belfer, et al., 2006). These data provide evidence that natural genetic variation in the galanin system may modulate alcohol consumption and suggest that the GalR3 receptor could be involved in alcoholism.

3. Actions of galanin on brain regions related to drug withdrawal, depression and stress

3.1. Locus Coeruleus

Norepinephrine release is a primary response to stress (Morilak, et al., 2005), and drugs that alter noradrenergic neurotransmission are used to treat anxiety and depression in humans. Hyperactivity of a number of noradrenergic nuclei has also been observed during opiate withdrawal, whereas ablation of noradrenergic nuclei can attenuate opiate withdrawal signs (Aghajanian, 1978, Aston-Jones, et al., 1999, Maldonado and Koob, 1993, Rasmussen, et al., 1990). Moreover, noradrenergic signaling has also been implicated in opiate reward as measured by place preference (Olson, et al., 2006), suggesting that decreases in norepinephrine might also be protective against opiate addiction.

Galanin is expressed in more than 80% of the noradrenergic neurons of the LC (Melander, et al., 1986, Xu, et al., 1998a), and mRNA encoding all three galanin receptors has been detected in this region (Kolakowski, et al., 1998, O'Donnell, et al., 1999, Parker, et al., 1995) (Fig. 1). Consistent with an inhibitory effect of galanin on neuronal firing, application of the full-length galanin peptide to an acute LC slice preparation reliably decreases spontaneous firing of norepinephrine neurons (Pieribone, et al., 1995, Seutin, et al., 1989). The GalR1/2 agonist AR-M961 inhibits spontaneous firing, whereas the GalR2 specific agonist AR-M1896 produces only slight inhibition at a ten-fold higher concentration, indicating that GalR1 may be responsible for the inhibitory effect of galanin on these neurons (Ma, et al., 2001).

Mechanistically, galanin decreases LC neuron firing rate by increasing membrane conductance, resulting in hyperpolarization (Pieribone, et al., 1995). Galanin can still hyperpolarize LC norepinephrine neurons when synaptic activity is suppressed (Ma, et al., 2001, Pieribone, et al., 1995), suggesting that the galanin receptors mediating this effect are postsynaptic. Lines of evidence converge to suggest that a potassium current is responsible for the hyperpolarization that results from galanin receptor activation. First, chloride influx is

minimal, and second, preincubation with a potassium channel blocker attenuates the inhibition caused by galanin (Ma, et al., 2001, Pieribone, et al., 1995). While galanin can activate ATP-sensitive K^+ channels in the pancreas (Ahren, et al., 1989), blocking these channels with glibenclamide does not eliminate the galanin effect on LC neurons (Ma, et al., 2001, Pieribone, et al., 1995). These experiments show that galanin likely hyperpolarizes LC norepinephrine neurons by a GalR1-mediated increase in membrane permeability to potassium ions, potentially by opening GIRK family potassium channels (Smith, et al., 1998). Paradoxically, very low doses of galanin prolong a norepinephrine-induced outward current (Xu, et al., 2001). Consistent with this effect on norepinephrine signaling, swim stress results in a greater increase in norepinephrine and serotonin in mice overexpressing galanin as measured by microdialysis (Kehr, et al., 2001, Yoshitake, et al., 2004), suggesting either that increased galanin expression disinhibits norepinephrine and serotonin release in response to stress, or that adaptation to chronic expression of the galanin transgene alters the responsivity of these systems. One possibility is that these high-affinity effects of galanin result from activation of noradrenergic neurons by GalR2, whereas hyperpolarization occurs at higher doses of galanin through activation of GalR1. It should be noted, however, that *in vitro*, the binding affinity of the different receptor subtypes for galanin is quite similar (Burgevin, et al., 1995, Wang, et al., 1997), although it is not known whether there might be differential effects of galanin at different GalRs *in vivo*.

The ability of galanin to decrease behavioral signs of opiate withdrawal appears to result from activity of galanin in the noradrenergic system, since transgenic mice with selective overexpression of galanin in noradrenergic neurons exhibit decreased withdrawal signs (Zachariou, et al., 2003). In addition, the galanin receptor agonist galnon can decrease the activity of TH in the LC during opiate withdrawal (Zachariou, et al., 2003). Neurobiological changes in the galanin system during opiate withdrawal also suggest that this system is activated during withdrawal. Galanin receptor binding and mRNA levels of GalR1 are increased in the LC during opiate withdrawal (Zachariou, et al., 2001, Zachariou, et al., 2000), and a similar upregulation is seen in the LC of galanin knockout mice (Hawes, et al., 2005). These neuroadaptations seem to be due to the ability of cAMP to enhance activity of the GalR1 promoter, leading to regulation of this receptor subtype in response to alterations in cAMP signaling (Hawes, et al., 2006b, Zachariou, et al., 2001). The ability of galanin to suppress spontaneous firing in the LC is potentiated by μ-opioid antagonists (Sevcik, et al., 1993), supporting the idea that interactions between opiate and galanin signaling in the LC may account for the ability of galanin to suppress opiate withdrawal signs (Zachariou, et al., 2003). Overall, the ability of galanin agonists to decrease neuronal activity in the LC (Pieribone, et al., 1995) would be expected to decrease the stress response, counteract the behavioral signs of opiate withdrawal and decrease rewarding effects of drugs of abuse.

3.2. Dorsal Raphe

Serotonergic drugs are widely prescribed for both depression and anxiety, both of which are stress-related disorders. In addition, modulation of serotonergic function alters stress- and anxiety-like behaviors in rodent models (File, et al., 2000). Serotonin can also modulate the release of dopamine in the mesolimbic system, which may be the mechanism underlying the ability of serotonergic agents to modulate behaviors related to drug abuse (Di Matteo, et al., 2008). Consistent with a broad effect of galanin on stress systems in the brain, voltage-clamp recordings from serotonergic neurons of the dorsal raphe in rat reveal a mechanism of galanin action very similar to that seen in the LC (Fig. 1). Galanin hyperpolarizes the majority of patched dorsal raphe neurons through a postsynaptic effect that likely involves activation of GIRK-family potassium channels (Xu, et al., 1998b). A recent study suggests that galanin modulates raphe neuron firing largely by modulation of $GABA_A$-mediated inhibitory postsynaptic potentials (IPSPs) (Sharkey, et al., 2007). Both the full-length galanin peptide

and the GalR2/3 selective agonist gal2-11 cause a decrease in IPSP amplitude (Sharkey, et al., 2007), suggesting involvement of all three galanin receptor subtypes. In contrast, while galanin increases the paired-pulse ratio of the IPSPs, gal2-11 does not. This suggests that galanin can inhibit GABAergic transmission in the dorsal raphe both presynaptically via GalR1, and postsynaptically via GalR2/3.

Low dose galanin can also increase the sensitivity of dorsal raphe neurons to 5-HT_{1A}-receptor stimulation. This suggests an effect of galanin signaling on 5-HT_{1A} autoreceptors (Xu, et al., 1998b), which indicates that there could be receptor-receptor interactions between galanin and 5-HT receptors, as has been shown for different classes of G protein-coupled receptors (Fuxe, et al., 2008). Interestingly, 5-HT_{1A} autoreceptor dysfunction has been implicated in depression, suggesting that the ability of galanin to modulate their activity could contribute to its effects on depression-like behaviors. Consistent with this idea, increased galanin binding sites in the dorsal raphe have been demonstrated in the Flinders Sensitive line of rats, a rodent model of depression (Bellido, et al., 2002). More recent studies have begun to examine the roles of individual galanin receptors in the dorsal raphe. For example, the GalR3 antagonist SNAP 398299 has been shown to attenuate galanin-induced hyperpolarization and galanin-induced suppression of dorsal raphe cell firing (Swanson, et al., 2005). This compound, the related GalR3 antagonist SNAP 378899, and a novel GalR3 antagonist can also attenuate depressive-like behaviors (Barr, et al., 2006, Swanson, et al., 2005), suggesting that a shift from GalR3- to GalR1/2-mediated galanin signaling may be antidepressant-like (for recent reviews of galanin effects on anxiety and depression-related behaviors, see (Holmes and Picciotto, 2006, Karlsson and Holmes, 2006, Kuteeva, et al., 2008).

At the systems level, the ability of galanin to inhibit serotonergic projections from the dorsal raphe could modulate dopaminergic and cholinergic transmission in the NAc, an effect that might alter the rewarding effects of drugs of abuse (Di Matteo, et al., 2008). The NAc receives serotonergic axonal projections from the dorsal raphe nucleus (Hensler, 2006, Van Bockstaele, et al., 1993, Van Bockstaele and Pickel, 1993) and it has been suggested that serotonin release in the striatum, from fibers originating in the raphe nucleus, excites striatal cholinergic interneurons (Bonsi, et al., 2007). Activity in the dorsal raphe also regulates dopamine release in the NAc, possibly through modulation of signaling in the VTA (Yoshimoto and McBride, 1992). In addition, corticotrophin releasing factor (CRF) in the dorsal raphe nucleus can modulate serotonin release in the NAc, providing evidence of the ability of neuropeptide release in the raphe to alter neuronal activity in the NAc (Lukkes, et al., 2008). Galanin effects on dopamine, serotonin and acetylcholine have been implicated in the modulation of instrumental learning and cognition, behaviors that contribute to self-administration of drugs of abuse (for review see (Ögren, et al., 1999, Robinson and Brewer, 2008)). While these interactions are undoubtedly complex, further understanding of the modulatory roles that neuropeptides such as galanin may have on the overall circuitry involved in disorders like depression and addiction may result in more effective, novel pharmacotherapies for the treatment of these disorders.

3.3. The HPA axis

Many psychiatric disorders are characterized by functional changes in peripheral and central components of the HPA axis, as well as in limbic brain regions. It is well established that the HPA axis, through numerous neurohormone and neuropeptide signaling pathways, plays a major role in physiological responses and adaptations to stressful events within the central nervous system (Smith and Vale, 2006). Recent evidence suggests that limbic monoaminergic systems, such as the LC and dorsal raphe, act in concert with the HPA axis to regulate affective state, and disruptions in the crosstalk between these systems has been implicated in the etiology of anxiety, depression and addiction (Koob, 2009, Kreek, et al., 2009, Stone, et al., 2008). Furthermore, naloxone precipitated morphine withdrawal enhances the activity of the HPA

axis and is accompanied by increases in corticosterone secretion (Nunez, et al., 2007a). Since central administration of galanin, acting through GalR1, can reduce stress-related responses involving the release of corticosterone (Mitsukawa, et al., 2009), it is possible that the ability of galanin to alleviate morphine withdrawal signs also involves GalR1 receptor-mediated regulation of HPA axis activity.

Galanin is abundantly expressed at several levels of the HPA axis. Galanin levels are high in the PVN where it is co-expressed with vasopressin and CRH. It is also expressed in the supraoptic nucleus of the hypothalamus, the anterior pituitary gland and adrenal medulla. While the adrenal cortex does not express the galanin peptide, it contains high levels of GalR1 and GalR2 receptors. As discussed for other brain areas involved in the stress response, magnocellular hypothalamic neurons show a standard response to galanin, involving a post-synaptic receptor-induced increase in membrane conductance of potassium (Papas and Bourque, 1997). Similarly, a subpopulation of cells in the arcuate nucleus of the hypothalamus also display an outward potassium current and hyperpolarization in response to galanin (Dong, et al., 2006, Poulain, et al., 2003). In addition to its ability to cause postsynaptic hyperpolarization, galanin also decreases pre-synaptic glutamate release onto neurons of the arcuate and supraoptic nucleus of the hypothalamus (Kinney, et al., 1998, Kozoriz, et al., 2006, Tyszkiewicz, et al., 2008). Interestingly, galanin requires intact $GABA_B$ activity to modulate glutamate release in this brain region (Tyszkiewicz, et al., 2008).

The parvocellular division of the PVN is the primary location of CRF-positive neurons and is a key site for the HPA axis response to stress that stimulates adrenocorticotropic hormone (ACTH) release in the anterior pituitary. ACTH activates the adrenal cortex, which then releases glucocorticoid hormones (Fig. 1) (Owens and Nemeroff, 1991). In the absence of stress, galanin can stimulate the HPA axis and increase release of CRH and ACTH, thereby increasing glucocorticoid secretion from the adrenal cortex (Tortorella, et al., 2007); however, following activation of the HPA axis by stress, galanin can decrease stress responses, such as those typically observed during morphine withdrawal. CRF and noradrenergic activity are increased during withdrawal from several addictive drugs, and it has been proposed that the interaction of CRF and noradrenergic activity may be an important factor that contributes to the development of addiction (Koob, 2008). Overall, naloxone precipitated morphine withdrawal increases HPA axis activity, increasing neuronal activity and stimulating CRH and vasopressin mRNA levels in the PVN, while enhancing corticosterone secretion (Nunez, et al., 2007b). Stress exposure can also increase body temperature rapidly, a phenomenon referred to as stress-induced hyperthermia, which is accompanied by the elevation of ACTH and corticosterone. Central administration of a high dose of galanin attenuates stress-induced hyperthermia, while a low dose of galanin enhances the hyperthermic response (Mitsukawa, et al., 2009). This is reminiscent of the ability of low dose galanin to increase activity of norepinephrine neurons (Xu, et al., 2001), whereas high doses hyperpolarize norepinephrine neurons (Pieribone, et al., 1995). Although there are many potential circuit level explanations for the opposite effects of low and high dose galanin, one other possibility could be the involvement of different galanin receptors. Consistent with this possibility, galanin also suppresses ACTH and corticosterone increases associated with stress-induced hyperthermia in wild type mice, but not in knockout mice lacking GalR1 receptors (Mitsukawa, et al., 2009). Similarly, galanin infused in the PVN does not alter ACTH plasma concentrations in freely moving rats (Hooi, et al., 1990). However, intra-PVN administration of galanin markedly reduces the mild stress related increase of ACTH concentration in rats stressed by ether inhalation. Finally, galanin-induced decreases in input resistance of PVN neurons are significantly greater following dehydration stress rats, suggesting that several of galanin's effects are state dependent (Kozoriz, et al., 2006). Taken together, these results suggest that galanin decreases activity of the HPA axis through GalR1 receptors in a state-dependent

manner under stressful conditions (Fig. 1), but the story is complicated by the ability of low dose galanin to increase HPA axis activity under non-stressful conditions.

4. Conclusions

Exacerbated stress responses likely play an important role in the etiology of many psychiatric diseases including anxiety, depression and addiction. Moreover, several aspects of addiction and stress share a similar neurobiological basis. In particular, the monoaminergic systems and HPA axis are involved in response to stress, stress-induced reinstatement of drug seeking behavior, and drug withdrawal. In the current review, we have summarized studies investigating the involvement of the galanin system in addiction, stress-related behaviors and the critical brain systems whose activity mediates the stress response.

How can we resolve the distinct behavioral effects of galanin agonism and antagonism on behavioral responses to drugs of abuse, alcohol and stress, and identify mechanisms that explain these behavioral effects? Although the galanin system likely modulates affective and drug related behaviors through several distinct neuronal mechanisms, evidence suggests that the effects of galanin on morphine withdrawal are likely to result from its ability to reduce stress-related responses through its actions on the HPA axis. It has been proposed that galanin decreases the severity of morphine withdrawal symptoms through the activation of GalR1 receptors located in the LC (Zachariou, et al., 2003). Furthermore, increased activity of LC neurons may be responsible for many of the symptoms observed after withdrawal from morphine, and naloxone precipitated morphine withdrawal enhances the activity of the HPA axis (Nunez, et al., 2007b). Noradrenergic LC neurons send projections to the PVN and SO. Moreover, these cells also release galanin into these hypothalamic nuclei (Levin, et al., 1987, Sawchenko and Swanson, 1981). Since central administration of galanin reduces stress-related responses through GalR1 receptors (Mitsukawa, et al., 2009), it is possible that the ability of galanin to alleviate morphine withdrawal signs is mediated, at least in part, through activation of GalR1 receptor, which in turn inhibits noradrenergic neurons in the LC that project to the PVN in the hypothalamus (Fig. 1). In agreement with this hypothesis, morphine withdrawal is accompanied by increased release of noradrenaline in the PVN from fibers that project from the LC (Fuertes, et al., 2000).

At the celluar level, it is clear from the studies reviewed above that many of the fundamental cell autonomous effects of galanin in the nervous system can be explained by the ability of galanin receptors to decrease cAMP levels and activate potassium channels, leading to hyperpolarization and decreased firing of neurons expressing these receptors (Seutin, et al., 1989). This decrease in neuronal activity can also lead to presynaptic decreases in neurotransmitter release (Kinney, et al., 1998, Kozoriz, et al., 2006, Tyszkiewicz, et al., 2008). It is worth noting that galanin can decrease synaptic plasticity in a number of hippocampal areas (Coumis and Davies, 2002, Fisone, et al., 1987), an effect that may generalize to other neuronal populations. For example, galanin reduces long-term potentiation in both basal and apical dendrites in the CA1 region of the hippocampus (Coumis and Davies, 2002, Sakurai, et al., 1996), an effect maintained in GalR1 knockout mice (Badie-Mahdavi, et al., 2005). Dentate gyrus long-term potentiation is also decreased in transgenic mice overexpressing galanin, while it is enhanced in galanin knockout mice (Mazarati, et al., 2000).

One complication in understanding the cellular effects of galanin is the variety of downstream signaling cascades that can couple to GalR2 (Hawes, et al., 2006a). While all three galanin receptor subtypes can activate Gi/o pathways, GalR2 has also been shown to stimulate Gq, thus activating PKC. For this reason, neurons expressing GalR1/3 and neurons expressing GalR2 are likely to have distinct responses to galanin. This may explain the ability of low- and

high-dose galanin to respectively increase and decrease neuronal activity (Mitsukawa, et al., 2009, Pieribone, et al., 1995, Xu, et al., 2001).

At the systems level, galanin receptors are on principal neurons in a number of brain areas involved in behavioral responses to stress and drugs of abuse. As reviewed above, galanin receptors can influence the firing of multiple types of monoaminergic neurons. This influence on neuronal activity can, in turn, regulate release of a number of neurotransmitters, including dopamine, the primary mediator of the rewarding effects of drugs of abuse. The control of dopamine release by galanin is particularly complex, suggesting that this modulation may result from different neuronal systems involving distinct galanin receptor subtypes. In addition, modulation of the dopamine system may be indirect, through release of other neurotransmitters. For example, the ability of galanin locally infused into the PVN to increase dopamine release in the NAc (Rada, et al., 1998) contrasts with its ability to decrease dopamine release in striatal slices (Tsuda, et al., 1998) and with the ability of centrally-administered galanin to decrease mesolimbic dopamine activity (Counts, et al., 2002). Therefore, when galanin is administered i.c.v., or when galanin agonists and antagonists are administered peripherally, the behavioral consequences will be the result of a number of changes in neurotransmitter release in different brain regions that will depend on which systems are more or less active at the time of treatment. This is clear with respect to acetylcholine release, since galanin can increase striatal acetylcholine release in anesthetized animals, and decrease striatal ACh release in awake animals (Antoniou, et al., 1997).

In terms of the endogenous effects of the galanin peptide, much more needs to be known about the conditions leading to release of galanin. For example, galanin can be released from pituitary cells in response to dopamine stimulation (Hyde and Keller, 1991), and it is thought that high frequency firing is necessary for galanin release (Consolo, et al., 1994, Havel, et al., 1992), suggesting that strong stimulation in particular brain areas in response to stress, drug administration or drug withdrawal will selectively recruit galanin receptors in affected brain regions.

It is clear that galanin can alter neuronal activity in many areas of the brain involved in both the stress response and behavioral responses to acute administration of drugs of abuse, as well as drug withdrawal. In terms of opiate withdrawal, galanin effects on the noradrenergic system and HPA axis are well described and may explain the ability of galanin to decrease these stress-related behaviors. The systems underlying galanin's effects on drug reward are less clear. The opposite effects of galanin on morphine, amphetamine and cocaine locomotion and reward compared to alcohol intake suggest that different brain areas mediate these two sets of responses. It is tempting to speculate that galanin effects on hypothalamic circuits involved in feeding are important for its effects on alcohol intake, whereas modulation of systems converging on the mesolimbic dopamine system may be critical for its effects on psychotimulant- and opiate-related behaviors. The ability of galanin to alter norepinephrine, serotonin, acetylcholine and glutamate release may indirectly alter the activity of dopamine neurons, leading to modulation of drug-related behaviors. Taken together, a large, convergent body of evidence suggests that endogenous galanin exerts a tonic inhibition on multiple neurotransmitter systems that may mediate drug self-administration and withdrawal symptoms. Future studies focusing on the ability of galanin to modulate the mesolimbic pathway *in vivo* and *in vitro* will be necessary to gain a better understanding of how pharmacological agents targeting the galanin system might be used to treat drug addiction in human subjects.

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Abbreviations

VTA	ventral tegmental area
SN	subtantia nigra
PVN	paraventricular nucleus
TH	tyrosine hydroxylase
ACh	acetylcholine
NE	norepinephrin
5-HT	serotonin
AVP	arginin vasopressin
CRF	corticotropin-releasing factor
ACTH	adrenocorticotropic hormone

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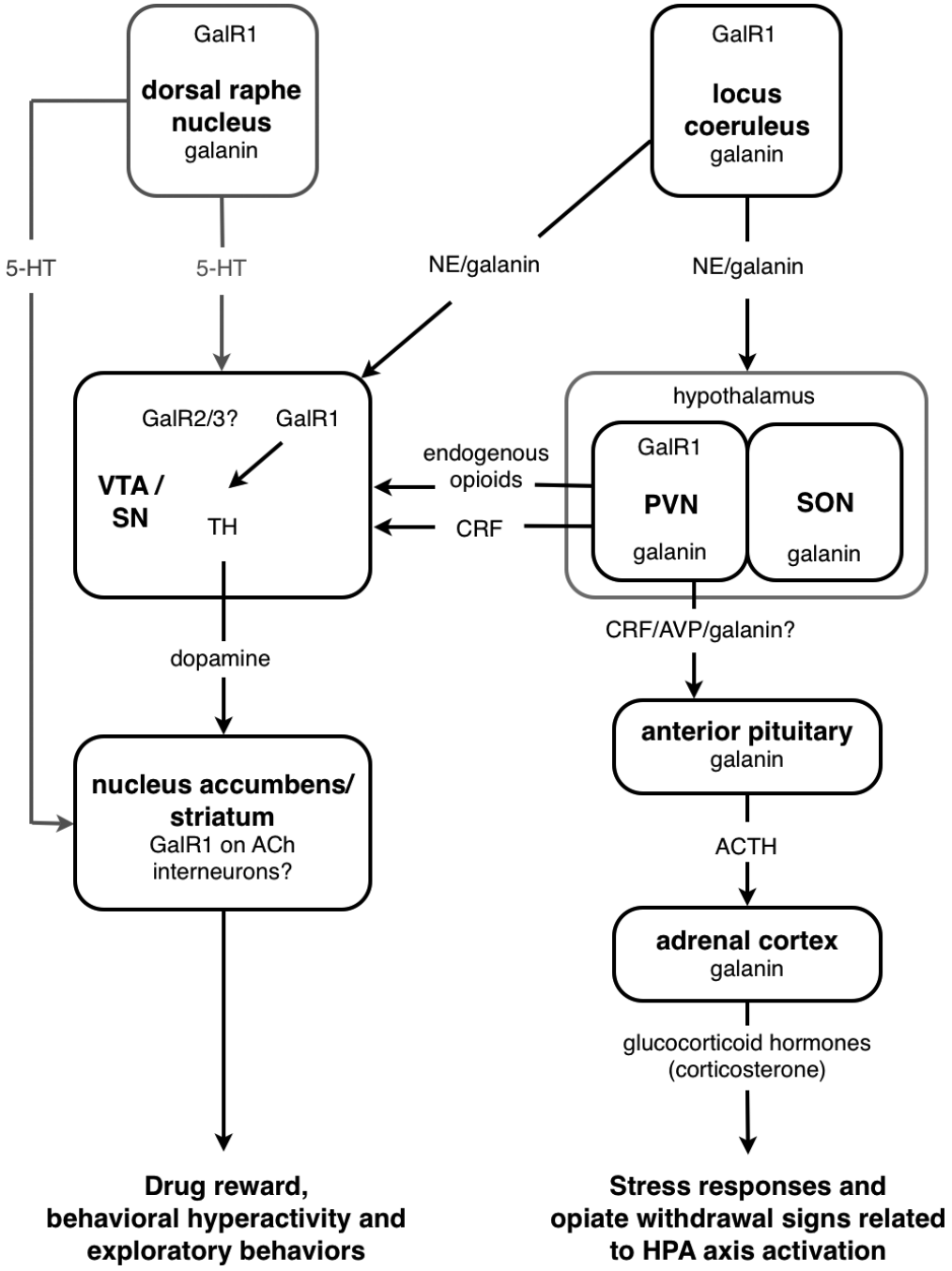

Figure 1. Schematic representation of potential pathways involved in the actions of galanin on brain regions involved in drug reward, behavioral responses to stress and opiate withdrawal

Noradrenergic neurons of the LC co-express galanin and send projections to the VTA, the PVN and the SON (Grenoff et al 1993; Levin et al., 1987). The PVN sends -opioid and CRF projections to the VTA (Quinn et al., 2003; Rodaros et al., 2007), which project dopaminergic fibers to the NAc. Numerous studies have shown that galanin can alter neuronal activity in the dopaminergic system, the LC and the HPA axis. Local infusions of galanin modulate striatal acetylcholine release (Ögren, et al., 1993; Antoniou, et al., 1997). Moreover, central administration of galanin decreases dopamine release in the striatum, likely through a GalR1-mediated mechanism (Tsuda et al., 1998; Ericson and Ahlenius, 1999; Counts et al., 2002). In

contrast, galanin injected into the PVN increases dopamine release in the NAc (Rada et al., 1998). The PVN is the primary location of CRF-positive neurons and is a key site for the HPA axis response to stress leading to increased adrenocorticotropic hormone (ACTH) release in the anterior pituitary. The action of galanin on the HPA axis under stressful conditions is inhibitory. Evidence suggests that GalR1 receptors in the LC inhibit noradrenaline release in the PVN, which in turn reduces exacerbated activity of the HPA axis. VTA, ventral tegmental area; SN, subtantia nigra; NAc, nucleus accumbens; PVN, paraventricular nucleus; TH, tyrosine hydroxylase; ACh, acetylcholine; NE, norepinephrin; 5-HT, serotonin; AVP, arginin vasopressin; CRF, corticotropin-releasing factor; ACTH, adrenocorticotropic hormone.

Table 1

Galanin effects on neurotransmission.

Brain area	State	Effect	Route of galanin administration	Mechanism	Subregion	References
Striatum		↓ DA release	Bath application to striatal slice	Gi	NAc	Tsuda et al. 1998
Striatum		↑ DA release	Intra- PVN	Gi	PVN ⌫NAc	Rada et al., 1998
Striatum		↑ DOPA accumulation	Intra-VTA, ICV		VTA, NAc and DS	Ehricson & Ahlenius, 1999
Striatum		↓ Glutatmate release	Bath application to striatal slice	ATP sensitive K^+ channels		Ellis & Davies, 1994
Striatum		↔ GABA release	Bath application to striatal slice			Ellis & Davies, 1994
Striatum		↓ACh	Intra-striatal			Antoniou et al., 1997
Striatum		↓ACh	Intra-PVN		PVN ⌫NAc	Rada et al., 1998
Striatum	Anesthetized	↑ACh	Intra-striatal			Antoniou et al., 1997
Olfactory tubercles		↑ DOPA accumulation	ICV			Ehricson & Ahlenius, 1999
LC		↓ Spontaneous firing, ↓ Membrane potential	Bath applied to slice	GalR1 activation of GIRK channels		Pieribone et al. 1995, Seutin et al., 1998, Ma et al., 2001
LC		↑ NE induced outward current	Bath applied to slice			Xu et al., 2001
VTA		↓ DA neuron activity	Endogenous, from LC			Grenhoff et al., 1993
Hippocampus	Stressed	↑ NE release ↑ 5-HT release	Transgenic overexpression		Ventral	Kehr et al., 2001
DR		↓ Membrane potential	Bath applied to slice	GalR3 component		Swanson et al., 2005
DR		↓ Membrane potential	Bath applied to slice	Non-ATP sensitive K^+ channel activation		Xu et al., 1998b
DR		↓$GABA_A$ mediated IPSPs	Bath applied to raphe slice	Presynaptic GalR1, postsynaptic GalR2/3		Sharkey et al, 2007
DR		↑5-HT_{1A} response	Bath applied to raphe slice			Xu et al., 1998b
Hypothalamus		↓ Membrane potential	Bath applied to hypothalamic slice	Outward K^+ current	Magnocellular neurons	Papas & Bourque, 1997
Hypothalamus		↓ Presynaptic glutamate release	Bath applied to hypothalamic slice	$GABA_B$ is required	Arcuate and Supraoptic nuclei	Kinney et al., 1998, Kozoriz et al., 2006, Tyszkiewicz et al., 2008
Hypothalamus		↓ Membrane potential	Bath applied to hypothalamic slice	Outward K^+ current	Arcuate nucleus	Dong et al., 2006, Poulain et al., 2003
Hypothalamus	Dehydrated	↓ Input resistance	Bath applied to hypothalamic slice		PVN	Kozoriz et al., 2006

Legend: DA = Dopamine; PVN = Paraventricular nucleus; NAc = Nucleus accumbens; DS = Dorsal striatum; ACh = Acetylcholine; LC = Locus coeruleus; NE = Norepinephrine; DR = Dorsal Raphe

Table 2

Pharmacological modulators of galanin signaling and effects on behaviors.

Drug	Route of Administration	Behavior	Mechanism	Reference
Galanin	ICV	↓ Locomotor activity		Ehricson & Ahlenius, 1999
Galanin	ICV	↓ Locomotor activity	GalR1	Mitsukawa et al., 2009
Galanin	Intra-VTA	↓ Locomotor activity		Weiss et al., 2005
Galanin	Intra-hypothalamus	↓ Locomotor activity		Weiss et al., 2005
M-35 (galanin antagonist)	ICV	↑ Locomotor activity		Ehricson & Ahlenius, 1999
Galanin	ICV	↔ Morphine locomotor stimulation		Zachariou et al., 1999
Galanin	ICV	↓ Morphine CPP		Zachariou et al., 1999
Galnon	IP	↓ Morphine withdrawal signs		Zachariou et al., 2003
Galanin	ICV	↑ Alcohol consumption		Lewis et al., 2004
Galanin	Intra-PVN	↑ Alcohol consumption		Schneider et al., 2007; Rada et al., 2004
Galanin	Intra-LH	↔ Alcohol consumption		Schneider et al., 2007
Galanin	Intra-NAc	↔ Alcohol consumption		Schneider et al., 2007
M40 (galanin antagonist)	ICV	↓ Alcohol consumption		Lewis et al., 2004
M40 (galanin antagonist)	Intra-PVN	↓ Alcohol consumption		Rada et al., 2004

Legend: VTA = Ventral tegmental area; PVN = Paraventricular nucleus; LH = Lateral hypothalamus; NAc = Nucleus accumbens

Table 3

Genetic manipulations of galanin signaling and effects on behaviors.

Gene	Genotype	Behavior	Reference
Galanin	TGOE (transgene expression under the control of the PDGF-B promoter - ubiquitous)	Locomotor activity TGOE=WT	Kuteeva et al., 2005a Kuteeva et al., 2005b
GalR1	GalR1KO	Locomotor activity KO=WT	Holmes et al., 2003
Galanin	Galanin KO	Morphine Stimulation KO>WT	Hawes et al., 2008
Galanin	Galanin KO	Morphine CPP KO>WT	Hawes et al., 2008
Galanin	Galanin KO	Morphine withdrawal sings KO>WT	Zachariou et al., 2003
Galanin	TGOE (transgene expression under the control of the DβH promoter - noradrenergic neurons)	Morphine withdrawal sings TGOE<WT	Zachariou et al., 2003
Galanin	Galanin KO	Cocaine CPP KO>WT	Narasimhaiah et al., 2009
Galanin	TGOE (transgene expression under the control of the PDGF-B promoter)	Amphetamine Stimulation TGOE<WT	Kuteeva et al., 2005a Kuteeva et al., 2005b

Legend: TGOE = Transgenic overexpression; WT = Wild type; KO = Knockout; CPP = Conditioned place preference