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Neurosci Biobehav Rev. Author manuscript; available in PMC 2009 October 1.

Published in final edited form as:
Neurosci Biobehav Rev. 2008 October ; 32(8): 1485–1493. doi:10.1016/j.neubiorev.2008.05.025.

Galanin: A Role in Mesolimbic Dopamine-Mediated Instrumental Behavior?

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Abstract

ROBINSON, J.K. and Brewer, A. Galanin: A Role in Mesolimbic-Dopamine Mediated Instrumental Behavior? NEUROSCI BIOBEHAV REV XX(X) XXX-XXX, 2008. The involvement of the neuropeptide galanin in the consumption of the primary "commodities" of food and water is well established. However, the present review describes anatomical and behavioral evidence that suggests that galanin may also modulate ascending mesolimbic dopamine function and thereby play an inhibitory role in the systems by which instrumental behavior is energized toward acquiring primary commodities. General anatomical frameworks for this interaction are presented and future studies that could evaluate it are discussed.

Keywords

drinking; galanin; feeding; progressive ratio; consumption; motivation

1. Introduction: Galanin as a multifunctional peptide

Galanin is a 29 amino acid (30 in humans) peptide that was isolated in 1983 (Tatemoto et al., 1983; Rökaeus et al., 1984). Though not as well known as many neuropeptides such as the opiates, it has been the focus of steady research attention for twenty-five years as evidenced by a recent symposium (Hökfelt, 2005) and over three thousand galanin-related publications in the literature. Galanin has been associated with a variety of important functions and dysfunctions, including learning and memory, anxiety, Alzheimer's disease, depression, pain sensation, and those described below (for reviews see Counts et al., 2003; Holmes, Mahony & Wynick, 2005; Lang, Gundlach & Kofler, 2007; Ögren et al, 2007; Robinson, 2004; Wiesenfeld-Hallin, Xu, Crawley & Hökfelt, 2005). However, new studies, as well as reassessment of older bodies of data, have prompted reevaluation of potential roles for galanin in psychological processes. The goal of this present theoretical review will be to consider one of these; in particular, a potential role for galanin in the modulation of mesolimbic dopamine

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systems underlying instrumental behavior. In doing so, we will first assess the distribution of galanin and known effects on the consumption of primary "commodities", food and water. We will then assess the anatomical evidence that puts galanin in the right place to modulate ascending dopamine function, and then review the physiological and behavioral evidence in favor of galanin-dopamine interactions. We will next discuss potential system-level models for this modulation and end by presenting a roadmap for future studies that could evaluate this assertion.

For the present discussion we will define *instrumental behavior* as behavior that reliably leads to an outcome, but not limit it to acquired operant responses or overt actions. In this way, the definition is broad and corresponds to "appetitive," in the sense used by of Craig (1917, 1918). This would allow it to include approach behaviors but also could include, for example, a reinforcer delivered contingently upon the instrumental response of remaining inactive for some set amount of time. The *outcome* is roughly analogous to Craig's consummatory act and Premack's (1962) and Timberlake & Allison's (1974) conception of a reinforcer as an opportunity to engage in a behavior that is contingent upon another.

2. Galanin: Anatomical Distribution

Galanin is expressed in many tissues throughout the body, though a major focus of work has been on its expression in the brain (Bartfai, Hökfelt, & Langel, 1993; Land, Gundlach & Kofler, 2007). Studies of the anatomical distribution of galanin, including immunohistochemical studies of galanin and galanin precursor protein mRNA and autoradiographic studies of binding to putative galanin receptors, showed expression in cortex, especially insular and cingulate cortices, hypothalamus, amygdala, central gray, dorsal raphe and locus coeruleus (Melander et al., 1988; Skofitsch & Jacobowitz, 1985; Skofitsch & Jacobowitz, 1986; Skofitsch, Sills, Jacobowitz, 1986; review by Merchenthaler, Lopez & Negro-Vilar, 1993). A vast majority of noradrenergic neurons express galanin and provide noradrenergic/galanergic input to the hypothalamus and ventral tegmentum (Holets et al., 1988; Xu, Shi, Hökfelt, 1998), though not the central amygdala (Barerra et al., 2006).

Studies in the late 1990s cloned three G-protein coupled receptor subtypes (GalR1, GalR2 and GalR3; reviewed in Branchek et al., 2000; Florén, Land, Langel, 2000) and mapped the distribution of mRNA for each in the rat. Of the three, GalR1 shows the broadest distribution patterns, with few areas of overlap with GalR2. The most prominent dissociations are that GalR1 is within discrete regions in hippocampus, amygdala, thalamus, and locus coeruleus, versus GalR2 predominance in dentate gyrus, substantia nigra/ventral tegmental area and dorsal raphe (O'Donnell et al., 1999). All three are found in low to moderate amounts in various hypothalamic nuclei, including arcuate, paraventricular, ventromedial and dorsomedial nuclei of the hypothalamus. GalR3 is also reported to have low levels of expression in motivation-related brain areas including the bed nucleus of the stria terminalis and medial nucleus of the extended amygdala, the periaqueductal gray, the lateral parabrachial nucleus, the medial medullary reticular formation and in the subfornical organ (Mennicken et al., 2002). Selective radioligands or antibodies for all three subtypes are not yet available to make specific confirmation of these distribution patterns, though indirect inferences are generally consistent with these patterns of mRNA (Lu et al., 2005; Hawes & Picciotto, 2005). Thus, it appears that galanin and galanin receptors are well situated for involvement in multiple aspects of motivation.

Numerous biochemical and physiological studies have characterized galanin as a hyperpolarizing peptide with both presynaptic and postsynaptic actions. However, excitatory effects may occur in some systems mediated by the GalR2 subtype or by indirect actions (see Lang, Gundlach & Kofler, 2007 for review). For example, galanin, administered

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intracerebroventricularly produces two particularly strong areas of metabolic activation of neurons in central amygdala and dorsomedial hypothalamus, as measured by cFos immunohistochemistry (Blackshear et al., 2007; Lawrence, Williams & Luckman, 2003; Parrado et al., 2007). Galanin may also exert broad tonic effects through a reduction in the firing rate of noradrenergic and serotonergic cells (Pieribone et al., 1995; Seutin et al., 1989; Sevcik, 1993; Xu, Zhang, Pieribone, Grillner & Hökfelt, 1998), and may have both inhibitory and excitatory influences on acetylcholine systems (Elvander et al., 2004; Elvander & Ögren, 2005; Jhamandas, et al., 2002).

3. Galanin and Feeding

Like many other CNS neuropeptides, galanin is implicated in diverse functions. However, a particular consistent and interesting role is in the regulation of feeding behavior. As detailed above, galanin mRNA expression is high in the rat hypothalamic nucleus, especially the supraoptic, paraventricular, arcuate, dorsomedial and ventromedial regions, all implicated in feeding regulation, as well as numerous other endocrine roles (Bonnefond et al., 1990). Galanin actions on circulating hormones related to appetite and body-weight is well documented, such as inhibition of insulin secretion and stimulation of growth hormone release (e.g. Dunning & Taborsky, 1988; Gundlach, Burazin, & Larm, 2001).

The most pronounced direct stimulatory effect on feeding is shown in the classic studies from Leibowitz and colleagues in which galanin microinjected into the paraventricular nucleus of the hypothalamus and central amygdala drastically increased food intake (Kyrkouli, Stanley, & Leibowitz, 1986; reviewed by Crawley, 1999). Subsequent experimental paradigms demonstrated this feeding stimulation effect in macronutrient diets that separate fat, protein and carbohydrates, as well as complex foods such as basic lab chow and cookie mash and showed that galanin preferentially increases the consumption of fat and carbohydrates (Tempel, Leibowitz & Leibowitz, 1988; Crawley et al., 1992; Corwin, Robinson & Crawley, 1993). Supporting this is a recent demonstration that galanin knockout mice consumed much less fat that wild-type controls under macronutrient choice conditions and when only fat was available (Adams, Clapham, Wynick & Speakman, 2008). It is important to note, however, that all of these feeding studies examined consumption in situations where food is made freely available to the animals.

Mounting evidence from several lines of research suggests galanin expression up-regulates rather than down-regulates in response to fat intake (Akabayashi, et al., 1994; Leibowitz, Akabayashi & Wang, 1998) and that galanin appears to be relatively insensitive to systemic signals of deprivation (Leibowitz, 2007). Thus, galanin seems to stimulate, in a non-homeostatic manner, the consumption of foods that would promote weight gain rather than meeting short-term metabolic needs (Leibowitz, 2005). This view suggests that galanin-induced feeding is more opportunistic (in response to availability) rather than drive-related (in response to deprivation conditions), and it follows from this that galanin induced consumption of foodstuffs may have the property of “elastic” rather than “inelastic” demand, where the increased “price” of the commodity results in its reduced consumption (Hursh, 1980).

4. Galanin in Fluid Intake Regulation

While the role for galanin in regulating food intake is well established, galanin regulation of consummatory behavior is not limited to feeding. Emerging evidence also shows that galanin regulates water intake and fluid balance. Brewer, Langel & Robinson (2005) demonstrated that relatively high doses galanin (10–20 μg i.c.v.) moderately reduced the intake of water in twenty-three hour water restricted rats. This effect was seen regardless of whether the water was made available in a cup in a tub cage or whether delivered response-independently in discrete droplets on a Fixed-Time (FT 20 sec) schedule in an operant chamber. However, a

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similar injection of galanin intracerebroventricularly into the nucleus accumbens or the lateral hypothalamus, produced no significant increase or decrease in low levels of water consumption in water-sated rats, though a slight trend toward increased consumption was apparent (Schneider et al., 2007). Kyrkouli et al. (1990) also reported that the proportion of time spent drinking relative to other activities, especially eating, did not increase from a low baseline level in response to galanin. Though the specific side-by-side experiment has not been performed, these studies together imply that fluid deprivation is a necessary precondition for a galanin-induced decrease in fluid consumption to be apparent.

This may be explained by exploring the likely underlying mechanism. First, it is known that galanin co-exists with vasopressin in the hypothalamus (Skofitsch, Jacobowitz, Amann & Lembeck, 1989), though the two peptides are somewhat compartmentalized (Landry, Vila-Porcile, Hökfelt & Calas, 2003). Several studies have shown that galanin inhibits the release of vasopressin under various conditions of osmotic challenge, when vasopressin release is maximal (Ciosek & Cisowska, 2003; Ciosek, Cisowska & Dabrowski, 2003; Kondo et al., 1991; Landry, Roche & Callas, 1995), but had no substantial effects when the animals were not challenged (Balment & al Barazanji, 1992). Further, experimental manipulations producing hyperosmosis and hypovolemia upregulated galanin and GalR1 mRNA in magnocellular paraventricular nucleus of the hypothamaus (Burazin, Larm, Gundlach, 2003; Koenig, et al., 1989; Landry, Aman & Hökfelt., 1998; Meister et al., 1990; Rökaeus, Young, Mezey, 1988; Villar et al., 1990; Yagita, Okamura & Ibata, 1994;). A recent study has elegantly demonstrated galanin inhibition of angiotensin II-sensitive neurons in the subfornical organ, a brain structure thought to be critical to integrating osmotic and hypovolemic thirst messages and then activating behavior directed toward water seeking (Kai et al., 2006). Taken together, these studies point to a role for galanin in modulating homeostatic fluid regulation processes under conditions of deprivation. However an examination of the effects of galanin on habitual and cue-occasioned fluid ingestion has not been performed.

5. Instrumental behavior: Anatomy and Conceptualization

While it is possible to talk about feeding and drinking as distinct behaviors, in reality they are closely related consummatory processes in mammals. This is illustrated by the phenomena of adaptive postprandial drinking (de Castro, 1989) and maladaptive schedule-induced polydipsia (Falk, 1961). But more importantly, the consummatory acts of feeding and drinking are both inextricably linked with the instrumental, species-typical, appetitive behavior in the wild of foraging which is traditionally reduced in the psychological laboratory to traversing the length of a maze or pressing a bar in an operant chamber (e.g. Krebs & Kacelnik, 1983; Mathis, Johnson & Collier, 1995). These instrumental acts are presumed to converge on and modulate the same neural systems, regardless of whether the consummatory behavior involves feeding, drinking or otherwise.

While it is certainly a gross oversimplification to reduce a complex construct like instrumental behavior to a single anatomical component, a critical, if controversial, neural system identified with instrumental behavior is the ascending dopamine systems commonly called the mesolimbic dopamine pathway (see Björkland & Dunnett, 2007 for a discussion of terminology). This pathway is clearly part of a complex system involving multiple brain structures and numerous neurotransmitter systems within them. The ventral tegmental area is a major source of dopaminergic input to frontal cingulate and entorhinal cortices, central amygdala, hippocampus, hypothalamus, basal forebrain, periacquaductal gray, raphe and parabrachial nuclei, locus coeruleus and the nucleus accumbens (Beckstead, Domesick & Nauta, 1979; Simon, LeMoal & Calas, 1979;). The ventral tegmental area receives diffuse descending input from a frontal cortex, hypothalamus, amygdala, and many ventral midline structures (Phillipson, 1979; Geisler & Zahm, 2005). While the exact nature of mesolimbic

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dopamine contributions to instrumental behavior remains controversial, there is good consensus that it is one critical component in the larger system that inputs information into executive and motor structures to direct or occasion behavior.

An influential theory by Wise (1982) suggested that mesolimbic dopamine underlies the subjective, pleasurable aspects of consumption (commonly called “the anhedonia hypothesis” to indicate that a blockade of dopamine would produce a loss of this pleasure from the act of consumption). However, a major focus of the current debate suggests that mesolimbic dopamine is maximally relevant to activating the behavior associated with the appetitive aspects rather than consuming (and the hedonic-perceptual) acts (e.g. Berridge, 2007; Berridge & Robinson, 2003; Baldo & Kelley, 2007; Barbano & Cador, 2006, 2007; Nicola, 2007; Phillips, Vacca & Ahn, in Press). To use the informal terms of Berridge & Robinson (1998), mesolimbic dopamine mediates the “wanting” rather than the “liking” of a commodity. One of the most clearly articulated theories is that of Salamone and colleagues (Salamone & Correa, 2002; Salamone et al., 2005) which suggests that mesolimbic dopamine “energizes” instrumental behavior, predicting that dopamine activity would be maximal during instrumental but not consummatory acts (“anhedonia” predicts the opposite), and that loss of dopamine though pharmacological blockade or lesioning would lessen or abolish this instrumental behavior.

To put this theoretical dissociation into practice, the clearest way to operationalize dopamine tone behaviorally would be in paradigms where some level of effort is applied to produce the **opportunity** to ingest, in the presence of a signal establishing the contingency between the effort and the consumption. This could be a Skinnerian three-term contingency, where a discriminative stimulus signals that responding on a reinforcement schedule will be reinforced, though could also be “foraging” on a radial arm maze, or an appetitive Pavlovian paradigm, where a CS signals the availability of a food UCS. Indeed, in many such tests, dopamine agonists are poor stimulators of direct consumption of food but in some cases will increase operant responding for food (for review see Baldo & Kelly, 2007) and lesions of the ventral tegmental area and dopamine antagonists reduce operant responding for food and other approach behavior for food, but not the consumption of the food itself: indeed, the effect of dopamine antagonism on operant responding is positively related to the amount of instrumental effort required to produce reinforcement (Salamone et al., 2007). These studies are all compelling because they show that the consumption of the commodity is itself not altered (or even enhanced) when made freely available, by a manipulation that reduces the effortful, appetitive behavior directed toward producing the opportunity to ingest. In anticipation of our later argument, one would predict that an endogenous inhibitor of mesolimbic dopamine, such as galanin perhaps, would also produce decreased instrumental behavior without decreasing or perhaps even stimulating consummatory behavior.

6. Galanin and Dopamine

Establishing some relationship between galanin and mesolimbic dopamine is a necessary, though not sufficient, condition for linking galanin to instrumental behavior. Indeed, some anatomical evidence associates galanin and mesolimbic dopamine. Classic autoradiographic receptor binding studies showed galanin-like binding in both the core and shell of the nucleus accumbens and ventral tegmental area (Skofitsch, Sills & Jacobowitz, 1986). The ventral tegmental area also expresses galanin mRNA and mRNA for the GalR2. One known noradrenergic input to ventral tegmental area is from the locus coeruleus, which is likely to also contain galanin, but other inputs could also arrive from known ventral tegmental area inputs regions that express galanin receptors and immunoreactivity, such as lateral hypothalamus, interpeduncular nucleus or central nucleus of the amygdala (Saper & Loewy, 1980; Akmaev, Kalimullina & Sharipova, 2004). However, no systematic studies using

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colabelling and anterograde/retrograde tracers to look at galanin inputs to ventral tegmental area and nucleus accumbens have been conducted to confirm this association.

Physiological and biochemical studies also provide some, albeit largely indirect, evidence showing that galanin modulates mesocorticolimbic dopamine activity. Galanin reduced levels of tyrosine hydroxylase protein and attenuated dibutyryl cAMP-induced TH-immunoreactivity in ventral mesencephalon cell culture. This effect was correlated with a sizable increase in GalR1 mRNA expression (Counts et al., 2002). Another report showed reduced dopamine synthesis in ventral tegmental area following galanin treatment (Ericson & Arlenius, 1999). Tsuda et al. (1998), reported that galanin inhibited evoked DA release in striatal slice preparation. However, the only published study using *in vivo* microdialysis to measure galanin effects on dopamine release microinjected galanin into the paraventricular nucleus of the hypothalamus and observed an increase in nucleus accumbens dopamine levels (Rada, Mark & Hoebel, 1998). Together, these data suggest that a galanin modulatory influence may be complex and may involve several pathways, though the conclusive studies have not been conducted.

7. Galanin and Instrumental behavior Processes: Behavioral Evidence

The most straightforward evidence in favor of galanin modulation of instrumental behavior comes from behavioral experiments of the sort described above and used to demonstrate a selective role for dopamine in instrumental behavior, where appetitive and consummatory behavior are clearly separated procedurally and where dissociations between response-contingent and free access consumption can be made.

The first such lines of evidence came from a reanalysis of some of the secondary measures from a line of research conducted in our lab examining the effects of galanin on various operant tasks (described in Brewer, Echevarria, Langel & Robinson, 2005). The primary focus of these experiments was to look at the effects of galanin on measures of working memory, executive and motor processes. Early studies had shown that galanin consistently impaired performance of delayed non-matching to sample and delayed matching to sample tests at even short memory delays. These multi-component operant tasks are usually described as measuring working memory, but also tap other psychological constructs such as perseveration, visual discrimination, and motor skills. This “delay-independent” pattern of impairment is usually thought to indicate disruption of task relevant processes other than working memory capacity, as performance is impaired even when little or no working memory appears to be needed. After replicating delay-independent delayed matching-to-position deficits produced by centrally administered galanin, follow up studies were able to rule out galanin-induced disruption of motor initiation or sustained responding (Brewer, Langel & Robinson, 2004) and simple and conditional discriminations (Echevarria et al., 2005; Saccone et al., unpublished) as explanations.

The common element of each of these tasks was that the rats were water restricted for twenty-three hours prior to the test session and responding was reinforced by the delivery of 0.1 ml of water and the consistent effect of galanin across all of the tasks was to reduce the number of trials completed (and therefore, reinforcers received) in each session (shown in Table 1). For example, one study compared the effects of galanin on free access to water, both when presented in a cup in a tub cage or as free-droplets on a fixed time FT20 sec schedule, as well as responding on a progressive ratio schedule of reinforcement (Brewer, Langel & Robinson, 2005). A progressive ratio 1 (PR1) schedule increases the number of responses required per reinforcer on each subsequent reinforcer, and the “break point” measure, which is the point where the animal ceases to respond, is used commonly as a test of reinforcer strength. On the PR1 schedule, a substantially decreased break point was observed at a 5μg dose of galanin that

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produced no reduction in consumption of the free water droplets on the FT schedule. These data clearly indicate reduced strength of the reinforcer, but only suggest that the effect of galanin on the instrumental response is added on top of the effect on reduced water consumption, rather than clearly dissociated. That is, when the experimental paradigm was made more complicated by including an instrumental response component, the effect of the galanin is observed at a lower dose. While this may simply reflect an additive effect of both an endocrine response (i.e., "thirst"), as discussed above, and an inhibition of mesolimbic dopamine appetitive activation, it does not provide a clear theoretical dissociation.

While these data are consistent with some sort of "effort-dependency" of the galanin effect, the clearest way to tease apart these two explanations is to perform the same experiments again with a food rather than a water reinforcer. Here, the nature of galanin provides the opportunity for a very compelling test. Since galanin stimulates eating, one could predict that galanin was affecting instrumental behavior through actions on the palatability or neurohormonal signals for the primary reinforcer, then here it would **enhance** instrumental behavior strength and the rats would persist **longer** on the progressive ratio schedule. In essence, if the commodity is valued more, they should "pay" more for it. Alternatively, a galanin-induced reduction in instrumental behavior should be independent of the properties of the food reinforcer, so one would predict less persistent responding on the progressive ratio schedule but a galanin **stimulation** of consumption of the food when made freely available. Indeed, it is the latter that was observed, regardless of whether standard lab chow pellets were used in both the free access conditions (Brewer & Robinson, In press) or if a high fat (15% fat) milk-cream product was used (shown in Figure 1). The addition of the PR1 response requirement abolished the galanin-induction of feeding observed in the free-access condition, consistent with a selective inhibition of dopamine-mediated instrumental behavior.

Together, the findings from these varied operant and free consumption experiments paint a picture of galanin playing three regulatory roles: the simulation of food consumption, the reduction of deprivation-induced water consumption, and an inhibition of appetitive instrumental behavior, all by dissociable mechanisms.

8. Galanin & Instrumental Behavior: Theoretical Models

So let us consider the mechanism of this galanin-mesolimbic dopamine interaction. Two theories could be offered to explain these findings, each of which predicts fundamentally different connection networks. Specifically, they differ in the direction of the interaction.

A. Galanin inhibits dopamine

In this model, galanin, perhaps through the widespread and hyperpolarizing GalR1, inhibits dopamine-mediated appetitive activation at the ventral tegmental area or in nucleus accumbens. This might be accomplished directly by galanin from locus coeruleus, or indirectly by upstream inhibition by galanin of inputs to ventral tegmental area/nucleus accumbens from hippocampus, hypothalamus, central amygdala, or even medial prefrontal cortex. In this manner, galanin functions as a peptide neuromodulator of dopamine, adding nuance to the dopamine response.

B. Dopamine inhibits galanin

This model may not be as intuitive, but would fit the existing data as well. In this model, the addition of the high operant response requirement creates a condition in which mesolimbic dopamine activity is increased (e.g. increased release, burst firing). Here dopamine synapses on hypothalamic nuclei (e.g. paraventricular, lateral or arcuate), and blocks galanin induction of feeding and potentiates galanin reduction of drinking. In this model, the role of dopamine

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in determining the elasticity of demand conditions is further articulated by linking it to galanin regulated consumptive functions.

C. Tests of the Theories

The critical evaluation of these models is dependent upon considerable amounts of information that does not yet exist in the literature, and a goal of this discussion is to stimulate new work to test them. While a decisive *experimentum crucius* is unlikely to emerge, data that could support or undermine both of these alternatives could be provided from several different approaches. While this is not an exhaustive list of possible experiments, they demonstrate the heuristic value of two theories in generating novel lines of work.

The most obvious first piece would be a substantial amount of anatomical work detailing the exact relationship between galanin and dopamine neurons. In particular, studies such as those of Barerra et al. (2004) that employed retrograde tracers and double labeling for galanin markers and tyrosine hydroxylase would help elucidate specific points of galanin–dopamine interaction. However, other pathways where galanin and dopamine may interact indirectly will be more complicated to establish.

Given the potentially numerous areas of interaction, and the difficulties of determining the specific relationships between neurotransmitter systems at the system, synaptic and intracellular levels, this anatomical work would be unlikely to serve as a strong test of either theory. However, anatomical evidence, in conjunction with site-specific microinjections would also help delineate the relevant systems and complement the anatomical studies. Therefore, the demonstration of direct effects of galanin and galanin antagonists on mesolimbic DA overflow as measured by *in vivo* microdialysis, voltametry and electrophysiology in conscious animals are essential. For example, if galanin is inhibitory of mesolimbic dopamine, then one might expect galanin microinjected into the ventral tegmental area or nucleus accumbens to reduce tonic dopamine firing rates, burst events, or dopamine overflow in target regions. Galanin antagonists might also have a facilitative action, which would support an endogenous role for galanin more strongly than the application of exogenous galanin. Inhibition of dopamine by intracerebroventricularly-administered galanin, in the absence of direct effects in VTA or accumbens, would point to indirect modulator pathways. A failure to observe direct effects of galanin on dopamine physiology and neurochemistry would bode poorly for a theory of galanin inhibition of dopamine. Overall, this work would expand upon and potentially reconcile the interesting but unclear direct and indirect measures of mesolimbic dopamine tone discussed previously (e.g. Counts et al., 2001; Ericsson & Arlenius, 1999; Rada et al., 1998; Tsuda et al., 1998).

Direct tests of the second theory, whose premise is that dopamine inhibits galanin, requires first that dopaminergic drugs be shown to affect galanin. Reliable measurement of galanin release *in vivo* is difficult but possible (Morilak et al., 2002), and would be the most direct way to elucidate the effects of dopamine agonists or antagonists on galanin overflow in specific brain regions. This influence of dopamine on galanin could also be examined less precisely by measuring gene expression of preprogalanin or galanin receptor subtype mRNA.

Showing anatomical or physiological interactions between galanin and dopamine enables but does not firmly establish the specific role in instrumental behavior that we have discussed previously. For this, various behavioral pharmacological and lesion experiments could also be conducted along the lines of dopamine devaluation experiments that showed that inhibition or loss of dopamine only reduced instrumental responding for food, but not the consumption of food made freely available (e.g. Salamone, Correa, Farrar & Mingote, 2007). For example, if galanin inhibits the dopamine that is maintaining instrumental responding for food, then galanin administration is like a pharmacological blockade of dopamine or a dopamine-specific

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lesion. Following from this argument, one could predict that dopamine agonists co-administered with galanin might offset the galanin-induced suppression of instrumental responding. Reciprocally, one could also predict that dopamine antagonism or 6-OHDA lesions would not impair galanin-induced feeding. If, according to the second theory of dopamine inhibiting galanin induced feeding, adding a response produces dopamine system activation that in turn inhibits galanin in hypothalamaus, then systemic or microinjected dopamine agonists would inhibit galanin-induced free-feeding by simulating response contingent feeding conditions.

A third line of research would establish the generality of the effects of galanin on instrumental behavior, and follows from the broader assumption that mesolimbic dopamine mediated appetitive activities should not be limited to food and water reinforced instrumental behaviors, but should generalize to other known operant reinforcers, such as sucrose and saccharine solutions, turning on a heat lamp in a cold environment, and avoiding shock and other aversive (negative) reinforcers. Other operants, such as wheel running for food or eating to gain access to wheel running in the style of the transposable response-instrumental behavior paradigms (reviewed in Dunham, 1976), also pose interesting challenges, such as whether galanin would stimulate versus inhibit eating to gain access to wheel running. Determining the effects of galanin on instrumental behavior for acquired, secondary reinforcers are also a fascinating potential experiments, given the importance of acquired reinforcers in motivating human activities.

A final and highly interesting set of tests also comes from the evaluation of drugs of abuse as reinforcers. A common theory is that the instrumentally energizing (reinforcing) effects of drugs of abuse are at least partially due to the activation of mesolimbic dopamine in a manner similar to that of “natural” rewards like food and sex (see Hyman, Malenka & Nestler, 2006, for a recent review). If examined in detail, this theory can generate some very complex discussions beyond the scope of the present review. However, it is not a point of debate that drugs of abuse can maintain operant behavior, and therefore one can make predictions about how galanin might affect instrumental responding for these substances. Some indirect evidence exists from transgenic mouse models that suggest that galanin chronically modulates the actions of several classes of drugs of abuse. For example, mice overexpressing galanin showed a diminished locomotor response to amphetamine challenge (Kuteeva, Hökfelt & Ögren, 2005) and galanin knockout mice showed increased activity and place preference to morphine (Hawes et al., 2007). Theses findings, when placed in the context of previous pharmacological tests with opiates that also showed that galanin inhibited the formation of opiate place preference and opiate withdrawal (Zachariou, Parikh & Picciotto, 1999; Zachariou et al., 2003), demonstrate that galanin may be an endogenous inhibitor of both opiate and dopamine systems. From this, one could suggest that it might also inhibit the self-administration of these (i.e. instrumental responding), especially at high response requirements, but not on a continuous reinforcement schedule (e.g. fixed-ratio 1). However, establishing the experimental conditions that would allow the dissociation between response contingent versus non-contingent consumption are not as straightforward as for food because of the difficulty of determining what free consumption levels of amphetamine or morphine would be and what “deprivation” means in this context.

The effects of galanin on the free-consumption of another drug of abuse, ethanol, is known. Galanin microinjected into the paraventricular nucleus of the hypothalamus or third ventricle has been shown to stimulate consumption of a 4% ethanol in ethanol preferring rats (Rada et al., 2004; Schneider, et al., 2007), and voluntary ethanol consumption or ethanol loading also stimulate galanin expression in the hypothalamus (Leibowitz et al., 2003). These authors suggest that this stimulation of ethanol consumption by galanin is related to galanin stimulation of fat consumption. So, one could predict that making ethanol consumption contingent upon

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a response requirement, would, as with food, show galanin reducing rather than increasing ethanol consumption.

9. Conclusions

The goal of this review was to point to an underappreciated relationship between galanin, dopamine and instrumental behavior. Clearly, the current state of this proposed role for galanin in instrumental behavior awaits much future work. However, what makes this role especially interesting as a target of investigation is that galanin may be involved in both the appetitive/instrumental and the consummatory aspects of motivation. Assessment of galanin involvement in the "hedonic", non-homeostatic aspects of food intake, perhaps through interactions with opiate systems in the nucleus accumbens and hypothalamus (e.g. Kelly et al., 2005; Barton, York, & Bray, 1996; Dube et al., 1994), should also be further explored, since galanin may play a unique integrative function in these systems as well. These data serve to further illustrate the unique position of galanin in multiple aspects of motivation, all questions of central importance to neuroscience.

Acknowledgements

The authors would like to recognize the important contributions of the experimental studies of Dr. David Echevarria and Phillip Saccone to the development of this thesis. We would also like to thank Professor Ülo Langel for many discussions that have enriched this work. J.K.R. thanks Professors Sven Ove Ögren and Tomas Hökfelt for graciously hosting his sabbatical at the Karolinska Institutet during which this article was prepared. This work was supported in part by the National Institute on Aging (1 R03 AG21295-01).

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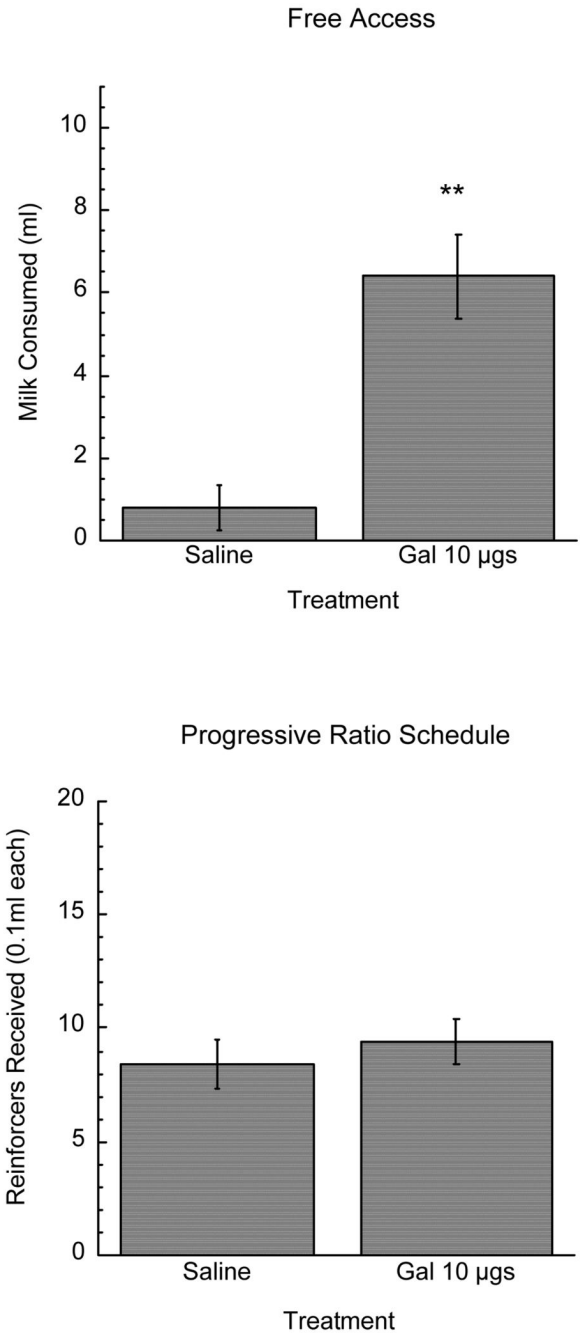

Figure 1.
Galanin (10µg i.c.v.) stimulated consumption of a high-fat milk solution when it was made freely available in a dish in a tub cage (top panel, ** = p<.001) but not when consumption was based upon the completion of a progressive ratio reinforcement schedule (bottom panel).

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Table 1

Effects of galanin (i.c.v) on measures of water consumption. Across a variety of instrumental and response-independent test, galanin consistently reduced the persistence of responding and/or amount of water consumed. In the operant tasks, no instance of a separable effect on the main performance measures (i.e. discrimination, working memory) were observed, consistent with an interpretation that the primary effects of galanin across all of the tasks was on the incentive value of the reinforcer and not secondary to the impairment of discrimination, non-matching, working memory and such. All studies were conducted in twenty-three hour water restricted rats. nd = not determined.

Behavioral Test	Measure	Galanin 5 μg i.c.v. (% Baseline)	Galanin 10 μg i.c.v. (% Baseline)	Galanin 20 μg i.c.v. (% Baseline)
Differential Reinforcement of High Rate of Response (DRH)[1]	Responses/session	nd	73	48
Simple Light-Dark Discrimination[2]	Trials/session	nd	72	73
Nonmatch-to-Position Conditional Discrimination[2]	Trials/session	nd	63	62
Match-to-Position Conditional Discrimination[2]	Trials/session	nd	68	69
Delayed Match-to-Position (DMTP)[2]	Trials/session	nd	63	39
Delayed Nonmatch-to-Position (DNMTP)[3]	Trials/session	51	nd	nd
Sustained Attention[5]	Trials/Session	83	nd	80
Progressive Ratio (PR) operant schedule[4]	Reinforcers obtained/session	79	68	72
Fixed Time (FT) response-independent schedule[4]	Reinforcers/session	103	nd	62
Free water access[4]	Water consumed/10 min	88	nd	75

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[2] Echevarria, Brewer, Manuzon, Langel & Robinson, 2005

[3] Robinson & Crawley, 1993a

[4] Brewer, Langel & Robinson, 2005

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