

Special Issue on Galanin

Assessment of new functional roles for galanin in the CNS

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Abstract

There is considerable evidence that galanin plays an important role in food intake, nociception, stress reactivity, sexual behavior, and learning. However, its involvement in other important behavioral processes, especially higher cognition, has not been systematically investigated. This review summarizes our recent efforts to explore the role of galanin in executive processes as well as in fundamental motivational and motor productive processes that are essential to the behavioral assessment of cognitive constructs in rodents. Our work points to a role in reward processes and physiological water balance regulation, and argues against a role for galanin in fine motor production and maintenance, simple visual discrimination, and perseveration.

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1. Introduction

Galanin is generally thought to be important to several psychological processes, including pain sensation, feeding, sexual behavior, and learning and memory (Kahl et al., 2002). However, little work has looked at potential roles for galanin in many important cognitive processes implicated by biochemical, physiological or anatomical evidence. Additionally, galanin involvement in fundamental motivational and motor productive processes essential to the behavioral assessment of cognitive constructs in rodents has also not been assessed.

Our recent efforts have sought to address this issue by conducting an expanded assessment of the effects of exogenously administered galanin on behavior (summarized in Table 1). To be systematic, we have constrained this investigation to psychological constructs implicated by anatomical, physiological, and biochemical evidence, such as the presence of ¹²⁵I-galanin binding sites and

other markers in medial prefrontal cortex, caudate-putamen substantia nigra motor regions, hypothalamus (Melander et al., 1986; Skofitsch and Jacobowitz, 1985), the co-expression of galanin in AVP producing cell bodies in the magnocellular hypothalamic neurons (Melander et al., 1986), and the galanin inhibition of the actions of vasopressin (Kondo et al., 1991).

Our investigations have also been guided by the finding that intracerebroventricular (i.c.v.) administration of galanin impairs the performance of the operant delayed nonmatch-to-position task (DNMTP) in a “delay-independent” manner in rats (Robinson and Crawley, 1993a; McDonald and Crawley, 1996). In this procedure, a rat who has had limited access to water is first presented with a sample stimulus (the illumination of one of the front panel lights in an operant chamber followed by a barpress to the corresponding lever by the rat) followed by a variable *delay* (i.e., retention interval). After the completion of the retention interval, both front cue lamps are illuminated and the rat is required to press the response lever that was not pressed (i.e., nonmatch) during the sample phase to receive a small water reinforcer (see Fig. 1).

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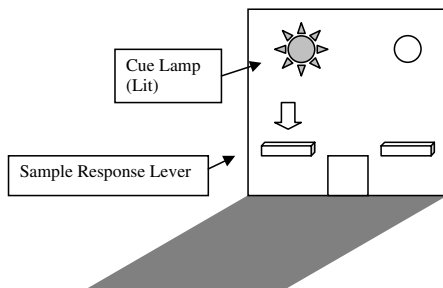
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Table 1
Summary of the behavioral effects of galanin described in the text

Construct measured	Behavioral task	Finding and dose of galanin
<i>Executive functions</i> (from Echevarria et al., submitted)		
Discrimination/Response perseveration	Simple light-dark discrimination w/ non-random stimulus presentation	↔ (5–20 µg)
Response strategies	Non-match and match-to-position conditional discriminations	↔ (5–20 µg)
Working memory/multiple constructs	Delayed match-to-position	↓ (10 µg; delay-independent)
<i>Motor processes</i> (from Brewer et al., 2004)		
Response initiation	Operant reaction time	↔ (10–20 µg)
Sustained responding	Differential reinforcement of high rate of responding (DRH)	↔ (10–20 µg)
<i>Motivational processes</i> (from Brewer et al., submitted)		
Thirst	Free water consumption Fixed time, response-noncontingent ↓ (20 µg) reinforcement schedule (FT 20 s)	↓ (20 µg)
Reward strength	Progressive ratio (PR) schedule of reinforcement	↓ (5–20 µg)

↔, no effect; ↓, impaired performance.

Step 1. Sample Response



Step 2. Delay (Retention Interval 0-15 s)

Step 3. Non-Match Choice Response

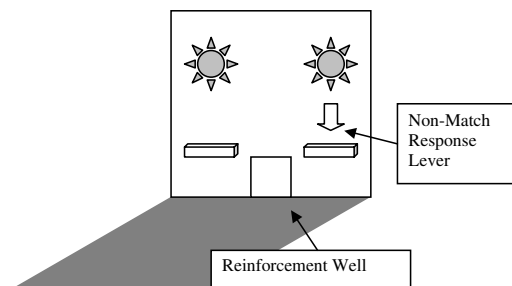


Fig. 1. Rat's eye view of the front panel of the operant chamber used for the delayed nonmatch-to-position (DNMTP) task and the other operant procedures described in the text.

The delay-independent pattern of impairment, in which non-matching accuracy is impaired even when little remembering is required of the rat, suggests that other psychological processes are affected by galanin infusion *in addition to* or *instead of* working memory. Though the DNMTP is often described as a *memory* task, there are many other processes involved that are required for successful performance including attending to the sample stimulus, response alternation (non-

matching), proficient motor production and motivation for a water reward. For our studies, we have broken the DNMTP into these subcomponents through a process of *fractionation*, originally developed by 19th century psychophysicist Oswald Kulpe (Sahakian, 1975), and studied the effects of galanin on each process separately. In doing this we have also adopted a logical *screening off* approach (Salmon, 1984), in which we have attempted to rule out in broad strokes the involvement of some theoretical constructs by using a wide dose range of galanin administered i.c.v. so that we would detect an effect of galanin if one was to be detected in a particular task.

2. Galanin and executive processes

Our first experiments (Echevarria et al., submitted) isolated the non-matching rule of the DNMTP and linked it to the well-described symptom of frontal lobe dysfunction, *perseveration* (Milner, 1982). Perseveration would manifest itself as an inability to follow a cued response on the left lever, for example, with another cued response on the right lever. Similarly, the “if you pressed the left lever during the sample phase, the right lever is the correct press during the choice phase” non-match conditional discrimination that is the core of the DNMTP might be impaired. We tested these hypotheses in three procedures. The first experiment employed a simple operant light–dark discrimination test in which the rat pressed the cued lever to receive a reinforcer. Each trial was separated by a 10 s intertrial interval, and stimuli would appear in extended sequences on one side to increase the likelihood of the rat developing a position habit. Galanin (5–20 µg, i.c.v.) produced no impairment of discrimination responding regardless of whether the correct response switched sides or was the same as the previous trial. Next we tested rats in a nonmatch-to posi-

tion (NMTP) and match to position (MTP) conditional discriminations. These were the DNMT procedure without the retention interval. If rats perseverated, one might expect the NMTP to be impaired but not the MTP, where a “perseverative” response is required. Galanin produced no impairment in either the NMTP or MTP task. Finally, we tested whether galanin would impair the *delayed match*-to-position task, since this is identical to the DNMT with the exception of the underlying non-match rule. Galanin impaired DMTP in a similar delay-independent, non-specific manner as the DNMT. Together, these experiments argue against galanin-induced response perseveration.

3. Galanin in motor processes

Many of the behavioral tests that have been used to study the involvement of galanin in complex behavioral processes involve the ability to initiate responses and maintain sustained response sequences. Therefore, we next examined the effects of galanin on two highly sensitive operant tasks designed to detect galanin-induced alteration of these capabilities (Brewer et al., 2004). Response initiation was studied using a light-dark discrimination reaction time task that required a correct response within 2.5 s of a spatially and temporally uncertain stimulus onset. The ability to perform high local rates of responding was studied using an operant differential reinforcement of high rate (DRH) of responding task. Galanin (10–20 µg, i.c.v.) did not alter reaction time or inter-response time distributions in either task.

4. Galanin in motivational processes

Many experiments that have reported galanin-induced impairments in the performance of tasks thought to measure learning and memory, including the DNMT, have used water restriction routines and water reinforcers to maintain responding (e.g., Givens et al., 1992; Robinson and Crawley, 1993a,b). Therefore, we next examined the effects of galanin on water consumption and water-reinforced operant behavior. We first used a free water access test in which rats deprived of water for 23.5 h were placed in tub cage in the presence of 10 ml of water in a secured cup. To confirm that this finding would generalize to the operant chamber environment, we also looked at the number of “free” rewards the rats consumed when they were delivered one every 20 s on a fixed time schedule (FT 20). A high (20 µg, i.c.v.) dose of galanin reduced water intake in both of these settings. Next, to determine what effects galanin would have on response-contingent drinking, we employed an operant progressive ratio (PR) schedule, a standard test used to assess reinforcer strength

in which the number of responses required for each reward is raised on each subsequent trial and the point at which the rat ceases to respond is indicative of the “strength” of the response-reinforcer relationship or “motivation” for the reward. Galanin (5–20 µg, i.c.v.) reduced the persistence of the rats on this schedule. Finally, we simulated the effects of a galanin-induced decrease in water reinforcer efficacy by allowing the rats access to water prior to testing in an operant delayed non-matching to position (DNMT) task. Pre-session access to water reduced the number of trials per session in the DNMT but did not significantly reduce non-matching accuracy. Together, these experiments suggest that galanin may play a role in regulating water intake and reinforcement processes. However, the data also suggested that DNMT choice accuracy deficits observed previously could not be attributed to a galanin-induced change in reinforcer efficacy.

5. Conclusions and future directions

The main conclusion of our findings is that galanin appears to play a role in reward processes and physiological water balance regulation. Additionally, we have been able to rule out a role for galanin in fine motor production or maintenance, simple visual discrimination, and perseveration.

Future work will include further examination of galanin involvement in reward and water intake. These would include site-specific microinjection of physiologically relevant doses of galanin and antagonists, as well as receptor specific ligands. Furthermore, studies assessing galanin involvement in additional executive processes such as attention are underway. It is our hope that these experiments will both expand our basic knowledge of galanin and psychological processes, as well as provide a broader range of reliable and discriminating behavioral screens for galanin pharmacology.

Acknowledgements

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