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Research paper

GABA-induced inactivation of dorsal midline thalamic subregions has distinct effects on emotional behaviors

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HIGHLIGHTS

- Inactivation of the paraventricular thalamic subregions reduces locomotor activity.
- Novelty-induced activity is more influenced by posterior paraventricular thalamus.
- Inactivation of posterior not anterior paraventricular thalamus increases anxiety.

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ABSTRACT

The paraventricular nucleus of the thalamus (PVT) is a key node integrating information about emotion and relaying output to other limbic structures influencing motor behavior. With recent studies showing the anterior (aPVT) and posterior (pPVT) subregions of this nucleus to have different anatomical connections and functions in ingestive behavior, the present study investigated whether they also make different contributions to emotional behaviors. Rats were microinjected in the aPVT or pPVT with saline vehicle or the $GABA_B$ + $GABA_A$ agonists, baclofen + muscimol (bac + mus; 0.3 + 0.03 nmol), to inhibit neural activity and were then tested between-subject for differences in emotional behavior. In a novel activity chamber, bac + mus significantly reduced locomotor activity, with this change somewhat larger after injection in the pPVT than the aPVT. In a familiar activity chamber, bac + mus again reduced locomotor activity but induced similar changes after injection in the aPVT and pPVT. In an elevated plus maze, bac + mus significantly decreased open arm time and entries, although this was observed only after injection in the pPVT. Thus, while both PVT subregions are necessary for general locomotor activity, the pPVT appears to have a greater function in both novelty-induced activity and anxiety-like behavior, indicating that this subregion makes a greater contribution than the aPVT to reactions to stressful stimuli.

1. Introduction

The paraventricular nucleus of the thalamus (PVT) is a key node integrating information about emotion, hunger, memory, pain, and arousal and relaying output to other limbic structures influencing motor behavior [12,24]. As this nucleus spans the anterior–posterior extent of the dorsal midline thalamus, it is typically divided into anterior (aPVT) and posterior (pPVT) subregions, which show differences in their afferent and efferent connections [11,12]. For example, while the aPVT receives its largest input from the prelimbic cortex and hippocampal subiculum, the pPVT receives its heaviest innervation from the infralimbic and anterior insular cortices in addition to the prelimbic cortex [12]. Also, whereas the aPVT projects widely to areas such as the nucleus accumbens core and shell, hypothalamic nuclei, and regions of the amygdala, the pPVT has more restricted projections that are particularly dense to the amygdala and bed nucleus of the stria terminalis [11,24].

Due to their connections, the subregions of the PVT are in a prime position to affect behavioral responses to arousing and stressful conditions. Recent evidence suggests that the pPVT in particular is critically involved in the expression of conditioned fear [8,14,19]. Additionally, through a series of microinjection studies involving this subregion, Kirouac and colleagues have shown that the exci-

Abbreviations: aPVT, anterior paraventricular nucleus of the thalamus; bac + mus, baclofen + muscimol; EPM, elevated plus maze; OX, orexin/hypocretin; PVT, paraventricular nucleus of the thalamus; pPVT, posterior paraventricular nucleus of the thalamus; SEM, standard error of the mean.

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tatory neuropeptide, orexin/hypocretin (OX), inhibits locomotor activity in both a novel and familiar chamber [15], decreases exploration of a novel object and the center area of an open field [16], and reduces open arm time and entries in an elevated plus maze (EPM) [17], while blockade of OX is anxiolytic, particularly in rats previously exposed to stress [9,17]. These results support the idea that activation of neurons in the pPVT, which has strong connections with regions involved in fear and pain, leads to a decrease in locomotor activity in association with an increase in arousal and anxiety. While similar studies of the aPVT have yet to be performed, research involving ingestive behavior shows this subregion to affect different behaviors than the pPVT. Specifically, OX promotes binge drinking of alcohol after injection in the aPVT but not the pPVT, and it stimulates intake of palatable food after injection in the pPVT but not the aPVT [2,6]. This evidence leads us to question whether the two PVT subregions might also diverge in their control of emotional behaviors.

To investigate the respective contributions of the aPVT and pPVT to emotional behavior, the present study examined their roles in locomotor activity in a novel or familiar chamber and also in anxiety in an EPM. To do this, we temporarily inactivated each subregion through microinjection with the $GABA_B$ receptor agonist baclofen together with the $GABA_A$ receptor agonist muscimol, with both receptor classes known to exist in the PVT [4,10]. We tested the hypothesis that inactivation of the pPVT, opposite to results with OX, would decrease anxiety while increasing locomotor activity, and inactivation of the aPVT, which has weaker connections with fear- and anxiety-regulating nuclei, would have little effect on EPM behavior but would also increase locomotor activity.

2. Materials and methods

2.1. Animals

Adult, male Long–Evans rats ($N = 32$; 201–225 g, Charles River Laboratories International, Inc., Kingston, NY, USA) were individually housed in an AAALAC-accredited facility, on a 12-hour reversed light/dark cycle (lights off at 0900 h). They were given at least one week to acclimate to the facility prior to surgery and were handled daily. Rats received *ad libitum* chow (PicoLab Rodent Diet 20 5053, Lab Diet, St. Louis, MO, USA) and water throughout the study. Experiments were approved by the Institutional Animal Care and Use Committee of The Rockefeller University and followed the NIH Guide for the Care and Use of Laboratory Animals and the European Commission Directive 86/609/EEC.

2.2. Drugs

Baclofen and muscimol were purchased from Sigma–Aldrich (St. Louis, MO, USA) and dissolved together in 0.9% saline (Baxter International Inc., Deerfield, IL, USA) at a dose of 0.3 nmol baclofen and 0.03 nmol muscimol per 0.3 μl of solution. This dose is commonly used to inactivate limbic nuclei [13,21].

2.3. Microinjections

Rats were cannulated in the aPVT ($n = 16$) or pPVT ($n = 16$), with each subregion serving as an anatomical control for the other. After anesthesia with 75 mg/kg ketamine and 10 mg/kg xylazine (i.p.), 10 mm stainless steel guide shafts (21-gauge) were implanted perpendicularly, aimed at the aPVT (1.7 mm posterior to bregma, ±0.2 mm lateral to midline, 4.6 mm ventral to the level skull) or pPVT (3.4 mm posterior to bregma, ±0.2 mm lateral to midline, 4.6 mm ventral to the level skull) [18], with the midsaggital sinus moved to the side prior to implantation. To prevent occlusion, 26-gauge stainless steel stylets were left in the guide shafts between injections. Rats were given at least one week of recovery after surgery. During this time, they continued to be handled daily, and their stylet was removed and replaced to acclimate them to the procedure.

For injections, baclofen + muscimol (bac + mus) or saline vehicle was administered 5–10 min prior to behavioral testing, in a between-subject design. The order of injections was counterbalanced for each rat over the three behavioral tests and half of the subjects who received bac + mus in one test then received saline in the next. Solutions were administered through concentric microinjectors of 26-gauge stainless steel outside and fused-silica tubing inside (74 μm ID, 154 μm OD; Polymicro Technologies, Phoenix, AZ, USA) that protruded 1.5 mm beyond the guide shafts. A syringe pump (Harvard Apparatus, Holliston, MA, USA) delivered 0.3 μl of solution over 30 s, and the microinjector remained in place for another 30–60 s to allow for diffusion.

2.4. Behavioral testing

Behavioral testing was conducted in a sound-attenuated room under low ambient red light, starting 45 min into the dark cycle. The aPVT and pPVT groups were tested on separate days. First, rats were tested for novelty-induced locomotor activity. Following injection with bac + mus or saline, each rat was placed in a novel 43.2 cm × 43.2 cm activity test chamber (Med Associates, Inc., St. Albans, VT, USA) while ambulatory distance, time, counts (number of infrared beam breaks), and episodes, average and total velocity, and vertical counts were recorded over 15 min. Following this test, the rats were given three additional exposures to the chambers over three consecutive days and on the next day were tested for locomotor activity. They were injected and placed in the same test chamber with measurements recorded as before over 15 min. Eleven days later, the rats were tested for anxiety in an EPM. Following injection, they were placed in the center of the maze, alternately facing an open or closed arm, and left on the maze for 5 min while videotaped. The maze consisted of four arms (10 × 50 cm each), 55 cm above the floor, with two opposite arms enclosed by 30 cm-high opaque walls. An observer blind to treatment condition later scored the videotape for time in arms and number of arm entries, with the criterion for entry being both forepaws into an arm.

2.5. Histology

To verify injection location, rats were injected with 0.3 μl methylene blue dye (Sigma–Aldrich), anesthetized with ketamine and xylazine (100 mg/kg and 13 mg/kg, i.p.), and decapitated. Brains were post-fixed in 4% paraformaldehyde for 72 h at 4 °C, transferred to 25% sucrose for 3–4 days at 4 °C, and then frozen at −80 °C. They were cut in coronal 30 μm sections and slide-mounted for microscopic examination. One animal in the aPVT group and two from the pPVT group had a probe more than 0.5 mm from the target region, so data from these rats were discarded. One additional rat in the aPVT group began to exhibit poor health during the study and was removed prior to EPM testing.

2.6. Data analysis

Data were analyzed using a repeated-measures ANOVA, with brain area and drug injection as between-subject factors and behavioral measures in each test as the within-subject factor. Significant main effects of group (brain area + drug injection) were followed up with multiple comparisons using Tukey's HSD, and significant interaction effects were followed up by unpaired, two-tailed t-tests. Significance was determined at $p < 0.05$. Data are reported as mean ± standard error of the mean (SEM).

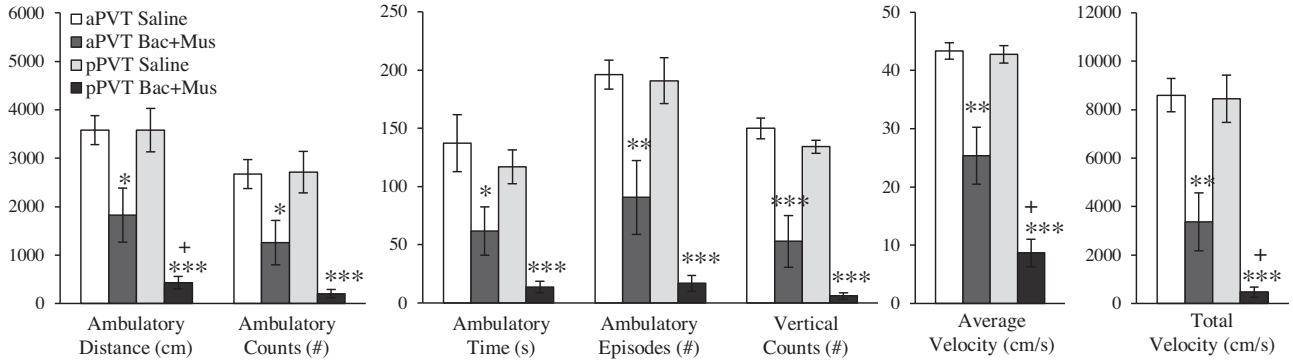

Fig. 1. Baclofen + muscimol (bac + mus, 0.3 +0 .03 nmol in 0.3 μl) compared to saline vehicle (0.3 μl) reduces novelty-induced locomotor activity when injected into the anterior paraventricular thalamus (aPVT) (bac + mus: $n = 8$, saline: $n = 7$) or posterior paraventricular thalamus (pPVT) (bac + mus: $n = 7$, saline: $n = 7$), causing a greater decrease when injected into the pPVT. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs. respective saline; $^{+}$ $p < 0.05$ vs. aPVT bac + mus.

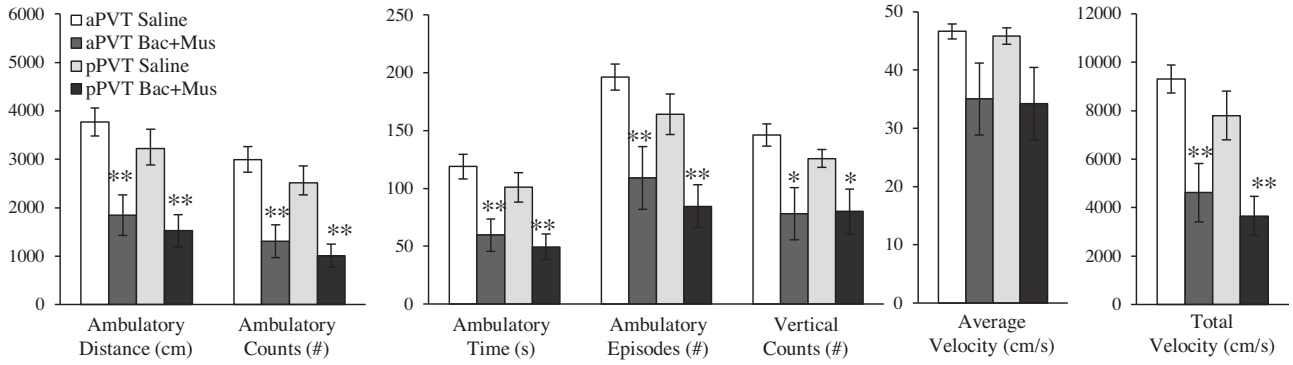

Fig. 2. Baclofen + muscimol (bac + mus, 0.3 + 0.03 nmol in 0.3 μl) compared to saline vehicle (0.3 μl) reduces locomotor activity in a familiar activity chamber, with similar effects observed after injection into the anterior paraventricular thalamus (aPVT) (bac + mus: $n = 8$, saline: $n = 7$) and posterior paraventricular thalamus (pPVT) (bac + mus: $n = 7$, saline: $n = 7$). ** $p < 0.01$, * $p < 0.05$ vs. respective saline.

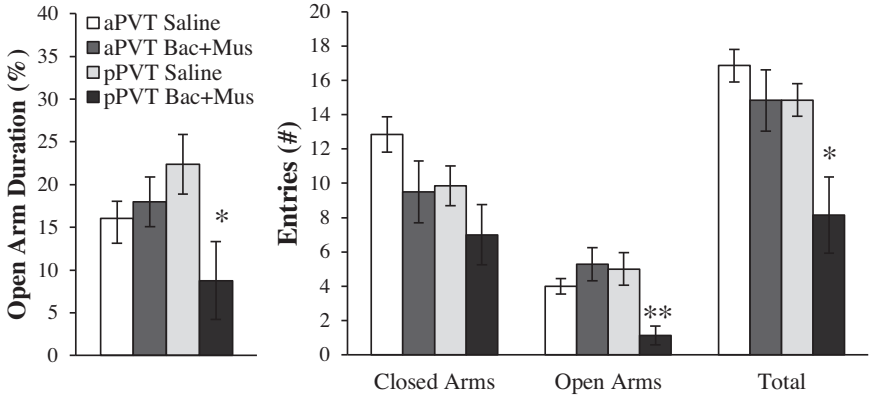

Fig. 3. Baclofen + muscimol (bac + mus, 0.3 + 0.03 nmol in 0.3 μl) compared to saline vehicle (0.3 μl) increases anxiety-like behavior in an elevated plus maze when injected into the posterior paraventricular thalamus (pPVT) (bac + mus: $n = 7$, saline: $n = 7$), but not the anterior paraventricular thalamus (aPVT) (bac + mus: $n = 7$, saline: $n = 7$). ** $p < 0.01$, * $p < 0.05$ vs. respective saline.

3. Results

In the novel activity chamber, drug injection in the PVT subregions significantly affected locomotor activity [F (3,25) = 18.94, $p < 0.001$] (Fig. 1). Multiple comparisons revealed that this was due to a significant reduction in activity after bac + mus compared to saline in both the aPVT ($p < 0.01$) and pPVT subregions ($p < 0.001$), with a trend for a difference between the aPVT and pPVT groups after bac + mus injection ($p = 0.09$) but, importantly, no significant difference between these groups after injection of saline vehicle ($p = 1.00$). With a significant interaction effect detected between group and behavioral measure [F (18,150) = 20.52, $p < 0.001$], bac + mus compared to saline in both the aPVT and pPVT was found to significantly reduce all recorded locomotor activity measures, namely ambulatory distance, time, counts, and episodes, average and total velocity, and vertical counts ($p < 0.05$). Comparison of bac + mus in the pPVT vs. the aPVT showed that it caused a significantly greater decrease in ambulatory distance and also average and total velocity ($p < 0.05$), and it led to a strong trend for a greater decrease in ambulatory time, counts, and episodes ($p = 0.06$) as well as vertical counts ($p = 0.08$).

In the familiar activity chamber, injection of bac + mus compared to saline in the PVT subregions again significantly affected locomotor activity [$F(3,25) = 9.29$, $p < 0.001$] (Fig. 2). Multiple comparisons showed this again to reflect a significant reduction in activity with drug injection in both the aPVT ($p < 0.01$) and pPVT ($p < 0.05$), but in contrast to the significant group differences when the chamber was novel, these comparisons when the chamber was familiar revealed no differences between the aPVT and pPVT groups after bac + mus ($p = 0.64$). As before, there were no significant differences between the aPVT and pPVT groups after saline injection ($p = 0.89$). The significant interaction effect between group and behavioral measure [$F(18,150) = 8.63$, $p < 0.001$] was due to a significant reduction, after bac + mus compared to saline, in both the aPVT and pPVT subregions in the measures of ambulatory distance, time, counts, and episodes, total velocity, and vertical counts ($p < 0.05$), with a trend for a reduction in average velocity ($p = 0.07$ for aPVT, $p = 0.09$ for pPVT).

In the EPM, injection of bac + mus compared to saline in the PVT subregions significantly affected behavior [$F(3,24) = 4.01$, $p < 0.05$] (Fig. 3), although this time multiple comparisons indicated that this was due solely to a significant change in the pPVT group ($p < 0.05$) but not the aPVT group ($p = 1.00$), with no significant differences between the groups after injection of saline ($p = 0.80$). A significant interaction effect revealed that the change in the pPVT group after injection of bac + mus compared to saline differed according to the behavioral measure [$F(9,72) = 2.40$, $p < 0.05$]. Specifically, bac + mus in the pPVT significantly increased anxiety-like behavior, as reflected by a smaller percentage of time spent in the open arms ($p < 0.05$) and less frequent open arm entries ($p < 0.01$). It had no effect on spontaneous motor behavior in the maze as measured by closed arm entries ($p = 0.20$), although it did result in a significant reduction in the number of total arm entries ($p < 0.05$) due to the large decrease in open arm entries, which suggests that some aspects of locomotor activity were reduced by bac + mus.

Histological examination showed that aPVT injections were made between bregma −1.44 mm and −1.92 mm, and pPVT injections were between bregma −3.00 mm and −3.48 mm (Fig. 4). The 0.3 μl methylene blue dye injected in the aPVT never reached the pPVT, and vice versa, having a radial spread of approximately 0.5 mm.

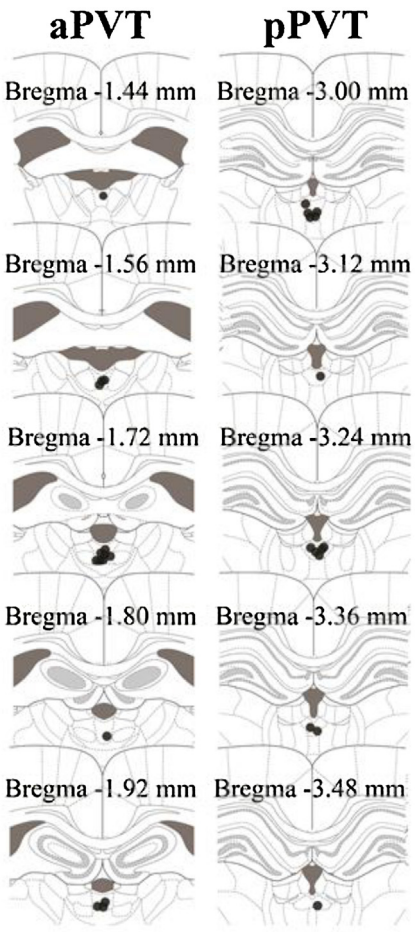

Fig. 4. Injection sites (black dots) of baclofen + muscimol (0.3 + 0.03 nmol in 0.3 μl) or saline vehicle (0.3 μl) for animals included in the analyses. A. Sites in the anterior paraventricular thalamus (aPVT) ($N = 15$). B. Sites in the posterior paraventricular thalamus (pPVT) ($N = 14$). Adapted from [18], with permission from Elsevier.

4. Discussion

The results of this study suggest that, while both the aPVT and pPVT are necessary for general locomotor activity, the pPVT has a greater role in novelty-induced activity and is the only subregion necessary for the expression of anxiety-like behavior. These results confirm our original hypothesis that both subregions contribute to emotional behavior and that the pPVT plays a greater role in reactions to stressful stimuli, but the direction of effects induced by GABA agonists is contrary to that expected from published results with OX.

The participation of the aPVT and pPVT in emotional behavior can largely be understood in light of their connections with other brain areas. Both subregions are likely involved in locomotor activity due to their similar inputs from nuclei that affect movement and emotional regulation, including the reticular thalamic nucleus, periaqueductal gray, and dorsal raphe nucleus [12], to their shared outputs, likely glutamatergic [20], to nuclei that coordinate movement and motivation, such as the nucleus accumbens and dorsal striatum [24], and to their reciprocal connections with the circadian pacemaker, the suprachiasmatic nucleus [24]. The greater participation of the pPVT than aPVT, in the responses to a novel chamber and EPM may reflect the denser input to the pPVT from brain regions that process fear and pain, including the infralimbic and anterior insular cortices [12], and also the stronger output of this subregion to the amygdala and bed nucleus of the stria terminalis that process fear and anxiety [11,24]. The idea that the pPVT plays a greater role in stressful situations is further supported by studies examining neuronal activation, which show this subregion generally to exhibit an earlier or greater rise than the aPVT in levels of c-Fos in response to restraint, noxious mechanical stimulation, or food deprivation [3,5,23].

An unexpected finding of the present study is the direction of the changes in locomotor and anxiety-like behaviors induced by pPVT injection of inhibitory GABA agonists, which were similar rather than opposite to those induced by pPVT injection of excitatory OX [15,17]. It is interesting that, in studies of ingestive behavior, inhibition of the pPVT also alters behavior in similar ways to injection of OX. Intake of laboratory chow or sucrose pellets is increased by muscimol injection as well as by lesioning of the pPVT [14,22], and the drinking of sucrose is also increased by pPVT injection of OX [2] just as intake of a high-fat diet is reduced by pPVT knockdown of the OX 1 receptor [6]. These similar effects of GABA and OX within the same subregion would presumably occur if receptors for these neurochemicals lie on distinct neuronal populations with different efferent projections.

While this study utilized exogenous injection of GABA agonists, it should be noted that endogenous GABA in the PVT comes from outside rather than within this nucleus, which apparently does not contain GABAergic interneurons [1]. Endogenous GABA may be released, for example, from the suprachiasmatic nucleus or

reticular thalamic nucleus, regions that are known to send GABAergic projection neurons to the PVT [12,25]. Thus, under natural conditions, the PVT subregions may be inactivated by GABA from areas involved in arousal and attention.

Some of the effects in this study may have occurred due to the spread of injections to adjacent thalamic nuclei, which also contain GABA receptors [7]. However, GABA agonists in the mediodorsal, centromedial, or intermediodorsal nuclei are found to stimulate rather than inhibit locomotor activity, with this effect diminishing as these injections approach the PVT [7]. Similarly, feeding behavior is affected in opposite directions with muscimol injection into the PVT vs. the mediodorsal nucleus [22]. Collectively, these findings show that the effects of GABA agonists in the dorsal midline thalamus are highly subregion-specific.

Taken together, the present findings lend further support to the idea that the PVT plays a role in the expression of emotional behaviors and indicate that inhibition of its neuronal activity can decrease locomotor activity and induce anxiety. Importantly, they introduce the new idea that subregions of the PVT, the aPVT and pPVT, make distinct contributions to these emotional behaviors.

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