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Lateral preoptic and ventral pallidal roles in locomotion and other movements

Suriya Subramanian, Rhett A. Reichard, Hunter S. Stevenson, Zachary M. Schwartz, Kenneth P. Parsley, and Daniel S. Zahm*

Department of Pharmacology and Physiology, Saint Louis University School of Medicine, 1402 S. Grand Blvd., Saint Louis, Missouri 63104

Abstract

The lateral preoptic area (LPO) and ventral pallidum (VP) are structurally and functionally distinct territories in the subcommissural basal forebrain. It was recently shown that unilateral infusion of the GABA_A receptor antagonist, bicuculline, into the LPO strongly invigorates exploratory locomotion, whereas bicuculline infused unilaterally into the VP has a negligible locomotor effect, but when infused bilaterally, produces vigorous, abnormal pivoting and gnawing movements and compulsive ingestion. This study was done to further characterize these responses. We observed that bilateral LPO infusions of bicuculline activate exploratory locomotion only slightly more potently than unilateral infusions and that unilateral and bilateral LPO injections of the GABA_A receptor agonist muscimol potently suppress basal locomotion, but only modestly inhibit locomotion invigorated by amphetamine. In contrast, unilateral infusions of muscimol into the VP affect basal and amphetamine-elicited locomotion negligibly, but bilateral VP muscimol infusions profoundly suppress both. Locomotor activation elicited from the LPO by bicuculline was inhibited modestly and profoundly by blockade of dopamine D2 and D1 receptors, respectively, but was not entirely abolished even under combined blockade of dopamine D1 and D2 receptors. That is, infusing the LPO with bic caused instances of near normal, even if sporadic, invigoration of locomotion in the presence of saturating dopamine receptor blockade, indicating that LPO can stimulate locomotion in the absence of dopamine signaling. Pivoting following bilateral VP bicuculline infusions was unaffected by dopamine D2 receptor blockade, but was completely suppressed by D1 receptor blockade. The present results are discussed in a context of neuroanatomical and functional organization underlying exploratory locomotion and adaptive movements.

*Corresponding author: Tel. (314) 977-8003, Fax (314) 977-6411, daniel.zahm@health.slu.edu.

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Keywords

motivation; GABA; dopamine; ventral tegmental area; bicuculline; muscimol

Introduction

It has been reported for more than thirty years that activating the subcommissural basal forebrain of rats by micro-infusing a GABA_A receptor antagonist, such as picrotoxin or bicuculline (bic), greatly augments locomotion and rearing (Mogenson et al., 1983; 1985; 1993; Shreve and Uretsky, 1989; 1991; Mogenson and Yang, 1991; Kalivas et al., 1991; Wallace and Uretsky, 1991; Johnson et al., 1996; Willens et al., 1992; Gong et al., 1999; Johnson and Napier, 2000; Chen et al., 2001; June et al., 2003; Reynolds et al., 2006; Hubert et al., 2010), whereas similarly localized infusions of a GABA_A agonist, such as muscimol (musc), suppresses these (Mogenson et al., 1980; Mogenson and Nielsen, 1983; Shreve and Uretsky, 1988; Austin and Kalivas, 1989; 1990; 1991) and other (e.g., Hooks et al., 1995; Ma et al., 1996; Numan et al., 2005) behaviors. The subcommissural basal forebrain, in conjunction with parts of the lateral hypothalamus and zona incerta (Sinnamon, 1992; 1993; Mitrofanis, 2005; Yetnikoff et al., 2015), is thought to comprise the final telencephalic link in circuitry conveying information from the prefrontal cortex, hippocampus and amygdala to the motivational circuitry and brainstem motor effectors (Heimer et al., 1985; 1995). Like all parts of brain, the subcommissural region is anatomically and functionally complex (Alheid and Heimer, 1988; Heimer et al., 1991; Heimer and Alheid, 1991; Heimer et al., 1997; Heimer and Van Hoesen, 2006) and it has been reported recently (Zahm et al., 2014) that the remarkably invigorated but otherwise structurally normal locomotion and rearing elicited by infusing bic into one of its subdivisions, the lateral preoptic area (LPO), look nothing like the postural twisting, vigorous pivoting movements, gnawing and compulsive ingesting that result from infusing bic into the ventral pallidum (VP), another, adjacent, subcommissural structure (Heimer, 1972; Heimer and Van Hoesen, 1978; Heimer et al., 1982; Zahm and Brog, 1992; Root et al., 2015).

Stimulating the LPO in the rat invigorates natural appearing, smoothly coordinated actions dominated by forward locomotion and punctuated by much rearing, pausing, observing, and frequent changes in direction, which, aside from the stepped up tempo, resemble spontaneous, 'exploratory' behavior (reviewed in Sinnamon, 1993, and Jordan, 1998), also referred to as 'seeking' behavior (reviewed in Panksepp, 1998, Ikemoto and Panksepp, 1999, and Alcaro et al., 2007). The response to VP stimulation, in contrast, consists of clearly unnatural exaggerations or distortions of adaptive movements. Nonetheless, it is likely that signals conducted by descending axonal projections engage both structures in the service of telencephalic control of adaptive behavior (Alheid and Heimer, 1988; Swanson, 2000; Heimer and Van Hoesen, 2006; Zahm, 2006). The experiments described here were done to further refine our understanding of functional-anatomical substrates underlying both kinds of response.

Methods

Animals

Male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 250–375 g were used in accordance with policy mandated in the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* (<http://grants.nih.gov/grants/olaw/references/phspol.htm>) provided by the U.S. Department of Health and Human Services. The rats were housed in standard conditions on a 12-hour light-dark cycle with *ad libitum* access to food and water in groups of two to four prior to surgeries and singly thereafter.

Placement of guide cannulae

Rats were deeply anesthetized by intraperitoneal injections of a mixture of ketamine (72 mg/kg) and xylazine (11.2 mg/kg) given as a cocktail consisting of 45% ketamine (100 mg/ml), 35% xylazine (20 mg/ml) and 20% saline at 0.16 ml/100 g of body weight and fixed in a Kopf stereotaxic instrument. Incisions were made to expose the skulls in which small burr holes were drilled over intended infusion sites. Guide cannulae, consisting of 13 mm lengths of 22 gauge stainless steel tubing (PlasticsOne, Roanoke, VA) were implanted in the openings unilaterally and bilaterally. Guides aimed at the preoptic area were set at an angle of 20° in the mediolateral plane so as to avoid the lateral ventricle; those aimed at the ventral pallidum were vertical. All were implanted to a depth 2 mm short of the centers of the intended targets and secured with dental cement anchored to stainless steel screws set in the skull. Stainless steel wire obturators were inserted into the guide cannulae to maintain patency. The incisions were closed with wound clips and the rats were kept warm until they awakened. A solution containing lidocaine was infused into the incisions and the rats were given i.p. injections of Buprenorphine SR (1 mg/kg) before they awakened.

Behavioral testing

One week after cannula implantations and at least 20 minutes prior to testing, the rats were brought to a room containing 6 standard activity monitoring chambers, each comprising a square, white floor space (43 × 43 cm) enclosed by clear plexiglass walls 30.5 cm in height (Med Associates, St. Albans, VT). Horizontal rows of 16 point-source infrared illuminators equispaced at 2.54 cm were mounted on the wall on one side of the chambers at heights of 2.54 and 12.7 cm from the floor facing photodetectors mounted on the opposite walls. The lower illuminator-detector bank comprised two sets mounted at a right angle to each other so as to form a grid of 16 × 16 intersecting beams for measurement of horizontal (forward) locomotion, whereas the upper bank consisted of a single set to detect vertical locomotion (rearing). The detectors were connected to a PC and beam breaks were recorded with the aid of Activity Monitor software (Med Associates). The monitors were housed inside dimly illuminated sound attenuating chambers equipped with exhaust fans (Med Associates).

After removing the rats from the home cages and the obturators from the guide cannulae, infusions were done with the aid of 28 gauge stainless steel injector cannulae (Plastics One) cut to lengths of 15 mm so that when fully inserted they protruded 2 mm beyond the ends of the guides. The injectors were connected by a short length of polyethylene tubing (PE 20 0.38/1.09, Stoelting, Wood Dale, IL, cat. # 51155) to the Luer needle of a 1.0 µl Hamilton

syringe mounted in a syringe pump (Harvard Apparatus, Holliston, MA, model '11' plus) calibrated to eject solution at a rate of 0.25 μ l/min.

Drugs

All chemicals and drugs, except as noted, were acquired from the Sigma Chemical Company (St. Louis, MO, USA). The drugs were dissolved in sterile 0.9% sodium chloride (Hospira Inc., Lake Forest, IL), except haloperidol (hal), S(–)-eticlopride hydrochloride (etic) and R(+)-SCH-23390 hydrochloride (SCH), which were dissolved in a vehicle of 20% ethanol, 50% propylene glycol and 30% dH₂O.

Infused drugs—The gamma-aminobutyric acid A (GABA_A) receptor antagonist, 9(R)-(–)-bicuculline methbromide (bic), was prepared at a dilution of 1 mg/3 ml vehicle, which resulted in delivery of 67 ng in 0.25 μ l/60 seconds of infusion. This concentration and rate of delivery produced robust locomotor activation in previous studies (Reynolds et al., 2006; Zahm et al., 2014). The GABA_A receptor agonist, muscimol hydrobromide (musc, Sigma and Tocris Bioscience, Avonmouth, Bristol, UK), was prepared at a dilution of 1 mg/2 ml vehicle, which resulted in delivery of 75 ng in 0.25 μ l/60 seconds of infusion.

Injected drugs—D-Amphetamine hemisulfate salt C-II (amph) was prepared at a dilution of 1.5 mg/ml vehicle and injected at a dose of 1.5 mg/kg. Hal and etic were prepared at a dilution of 2 mg/ml and SCH at 5 mg/ml and these were given at 2 and 5 mg/kg, respectively (see, Discussion, Methodological considerations, below). Hal and etic preferentially bind D2-D3 class relative to D1 dopamine receptors, whereas SCH preferentially binds D1 (Christensen et al., 1984; Hall et al., 1985; Köhler et al., 1986; Leslie et al., 1987 a; b; Sokoloff et al., 1990; Bourne, 2001). A cocktail of hal and SCH was used in order to block D1 and D2 receptors (Zahm, 1992).

Localization of infusion sites

The rats were deeply anesthetized precisely as described above and subjected to transaortic perfusion with 0.01 M Sorenson's phosphate buffer (SPB; pH 7.4) containing 0.9% sodium chloride and 2.5% sucrose, followed by 0.1 M SPB (pH 7.4) containing 4% paraformaldehyde and 2.5% sucrose. The perfused brains were removed and placed in the same fixative for at least four hours and then overnight at 4° C with agitation in 0.01 M SPB (pH 7.4) containing 30% sucrose. The brains were cut on a cryostat into five adjacent series of 50 μ m thick sections of which the first series of sections was thaw mounted on subbed glass slides and the rest were collected and stored in separate glass vials at –20° C in cryoprotectant consisting of 0.01 M SPB containing 30% sucrose and 30% ethylene glycol. The mounted sections were defatted in Coplin jars in 1:1 alcohol/chloroform for at least four hours, immersed in 0.1% cresyl violet solution for 5–10 minutes, rinsed quickly in distilled water, differentiated in 95% ethyl alcohol for 2–30 minutes, dehydrated in 100% ethanol 2×5 min, cleared in xylene 2×5 minutes and coverslipped with Permount. The ends of the infusion cannula tracks, which we regard as the injection sites, were identified by light microscopy with the 2x objective and mapped by reference to an atlas (Paxinos and Watson, 2007) and immunohistochemical preparations archived in our laboratory.

Experimental groups and statistics

During the course of the study guide cannulae were implanted, mainly bilaterally, into the LPO and VP of, respectively, 83 and 56 rats. After a week of recovery, measurements were done on each rat with different combinations of injection (saline, amph, dopamine antagonists) and infusion (vehicle, bic or musc infused unilaterally or bilaterally) on five consecutive days under vigilance for lethargy or other signs of illness, detection of which warranted immediate removal of a rat from the study. Duplicate measurements (same drug-infusion combination more than once in the same rat) were mostly avoided. Sample sizes are given in the illustrated graphs above the bars.

Two test protocols were used. In the first, rats were placed into monitors one minute following infusions into the LPO or VP of bic or musc and locomotion and rearing were monitored for twenty minutes. Alternatively, following injections of amph, hal, etic, SCH or a cocktail of SCH and hal, the rats were returned to the home cage for 10 minutes and then placed in the monitor for 10 minutes, during which locomotion and rearing were monitored under the developing influence of the injected drugs and after which they were removed from the monitors in order for bic, musc or vehicle to be infused into the LPO or VP. Upon completion of unilateral or successive infusions on both sides of the midline, the rats were returned to the monitor for continuing measurement of locomotion and rearing until the monitoring session ended 40 minutes after it began.

Figure 1A and B show representative time-course data acquired during 20 minutes immediately following infusion of vehicle, bic or musc into the LPO or VP bilaterally and unilaterally. For the 40 minute protocol, similar data were collected during a comparable period of 20 minutes beginning two minutes after the rats were returned to the monitors after receiving infusions. This occurred 20–25 minutes after they had received drug or saline injections. Group means of the sums of data collected during these 20 minute windows as shown in Fig. 1C–F were tested using a one-way analysis of variance and the Student-Newman-Keuls post hoc test.

Results

Infusions of bic and musc into the LPO

Zahm et al. (2014) speculated that unilateral and bilateral infusions of bic into the LPO (Fig. 2) produce activations of locomotion and rearing of comparable magnitude, but did not test it. Accordingly, we here directly compared the effects on locomotor activation and rearing of unilateral and bilateral infusions of bic into the LPO. Significant main effects were associated with locomotion ($F_{4,190}=80.786$, $p<0.001$) and rearing ($F_{4,190}=19.323$, $p<0.001$). We observed that both unilateral and bilateral LPO infusions of bic strongly increase locomotion as compared to vehicle with bilateral bic infusions producing slightly greater activation (Fig. 1A and C). Otherwise, nothing apparent distinguished the general structure of horizontal locomotion caused by unilateral and bilateral bic infusions. However, only unilateral LPO bic infusions, as compared to vehicle significantly increased rearing, which, after bilateral LPO bic infusions, approximated baseline levels (Fig 1B and D). Unilateral and bilateral LPO musc infusions suppressed locomotion (Fig. 1C) and rearing (Fig. 1D).

Infusions of musc into the VP

Zahm et al. (2014) reported on unilateral and bilateral infusions of bic into the VP. Similar infusion sites were used in the present study (Fig. 3), but we do not replicate data reported in the earlier study here (but see the control values in Fig. 4) except to note that the slight increase in average locomotion after unilateral VP bic infusions reported in the earlier study was not evident in this one and may have been due to diffusion of bic from VP into the LPO. Here, we observed significant main effects on locomotion ($F_{2,42}=19.514$, $p<0.001$) and rearing ($F_{2,42}=3.041$, $p<0.001$) after infusions of musc into the VP. Whereas baseline locomotion and rearing were not affected by unilateral VP musc infusions, both were suppressed by bilateral VP musc infusions (Fig. 1E and F).

Effects of unilateral and bilateral LPO and VP musc infusions on locomotion and rearing stimulated by amph

Following unilateral and bilateral infusions of musc into the LPO and VP in rats that had received amph injections, significant main effects on locomotion ($F_{3,134}=29.271$, $p<0.001$) and rearing ($F_{3,134}=18.094$, $p<0.001$) were observed. The effects of unilateral and bilateral musc infusions into the LPO did not differ [Student t test - $t = -0.279$ with 53 degrees of freedom. ($P = 0.781$)] and so the values were pooled. Infusions of musc into the LPO, as compared to vehicle, significantly reduced amph-stimulated locomotion (Fig. 4A) and rearing (Fig. 4B). Bilateral infusions into the VP of musc, as compared to vehicle, profoundly suppressed amph-stimulated locomotion (Fig. 4A) and rearing (Fig. 4B) to a degree greatly exceeding that produced by LPO musc ($p<0.001$). In contrast, infusions of musc into the VP on only one side of the midline produced no decrease of amph-induced locomotion or rearing.

Effects of dopamine D2 and D1 antagonists on locomotion and rearing elicited by infusions of bic into the LPO and VP

Receptor-saturating doses of dopamine D2 and D1 antagonists were associated with significant main effects on locomotion ($F_{3,67}=19.242$, $p<0.001$) and rearing ($F_{3,67}=16.900$, $p<0.001$) elicited by infusions of bic into the LPO. The locomotor activating effect of unilateral and bilateral LPO bic infusion was significantly attenuated by pretreatment by hal and, significantly more so, SCH (Fig. 5A). Co-administration of hal and SCH caused a suppression of the response to LPO bic infusion not different from that observed in rats given SCH alone. Rearing after LPO bic infusions was strongly suppressed by hal, SCH and combined administration of the two (Fig. 5B).

The attenuation of LPO bic-elicited locomotion produced by SCH and the SCH/hal cocktail, while severe (Fig. 5A), was not complete. That is to say, some LPO-infused rats pretreated with either SCH or the SCH/hal combination did indeed experience near complete suppression of LPO bic-induced locomotor activation (Fig. 5C and D), but others exhibited sporadic bursts of modest and, occasionally, robust LPO bic-induced locomotion (see, e.g., Fig. 5D, cases 83 and 84). Thus, infusing the LPO with bic was able to cause instances of near normal, even if sporadic, invigoration of locomotion in the presence of saturating dopamine receptor blockade.

Receptor-saturating doses of dopamine D2 and D1 antagonists also were associated with significant main effects on locomotion ($F_{5,63}=17.989$, $p<0.001$) and rearing ($F_{5,62}=3.481$, $p<0.008$) elicited by infusions of bic into the VP. Modest locomotion (Fig. 6A) and rearing (Fig. 6B) associated with bilateral infusions of bic into the VP were similar following administration of vehicle and the dopamine D2 antagonists hal and etic. Stated inversely, bilateral VP infusions of bic relieved (Fig. 6A) the locomotor suppression (catalepsy) associated with administration of the D2 antagonists (Fig. 6A, light gray bar). In contrast, catalepsy caused by SCH given alone or in combination with hal was not relieved by VP bic infusions.

The modest locomotor effects of bilateral VP bic infusions were accompanied by vigorous, obviously abnormal motor behaviors, as has been reported (Zahm et al., 2014). Rats that had received bilateral VP bic infusions would, after a variable delay, lurch suddenly sideways toward the tail or a hindlimb so forcefully as to whip the entire body in a near 360° pivot. Once such pivoting began, the rats frequently assumed a posture with head turned toward the tail or a hind paw, which sometimes were taken in the mouth, from which strenuous bouts of pivoting frequently occurred, commonly constituting five to seven rapidly sequential rotations and, not infrequently, up to twenty. However, despite the vigor of the movement, pivoting mostly was not recorded by the activity monitor as locomotion because pivoting rats' centers of mass remained relatively stationary. Pivots were prominently unidirectional, but invariably accompanied by fewer or, rarely, equivalent numbers contralateral rotations. It was not unusual during the course of a pivoting episode for a rat to turn perhaps five to seven pivots toward one side before suddenly reversing direction to do multiple contraversive pivots. After an infusion, pivoting typically began after a delay of some minutes, peaked at about 10–15 minutes post-infusion and subsided thereafter, presumably in relation to the gradual dissociation of bic from GABA_A receptors. Between pivoting episodes rats sometimes exhibited reverse (i.e., backward) stepping, but also moved around the activity monitor in a quite normal manner and, if provided edibles, compulsively ingested them. [VP effects on ingestion have been extensively reported (e.g., Cromwell and Berridge, 1993; Stratford et al., 1999; Shimura et al., 2006; Smith and Berridge, 2007; Smith et al., 2009; Stratford and Wirtshafter, 2012; 2013; Covelo et al., 2014). We will address our data on ingestion in more detail in a separate communication (Reichard et al., in preparation)].

Hal or etic given alone had no or little effect on abnormal movements elicited bilaterally from the VP, whereas SCH, given alone (Table 1) or in combination with hal completely suppressed pivoting. Notably, however, rats were not rendered paralyzed by SCH. Rather, between pivoting episodes, they repeatedly stretched their necks and upper bodies forward, backward and side to side, all the while whisking and seeming to take great interest in their surroundings; but the hindlimbs remained planted, which rendered the rats immobile, except when, on rare occasions, they would cross the floor of the activity monitor with apparently normal locomotion. They would also on occasion rear up against the chamber walls, particularly at the corners, supported by the forepaws, busily whisking side to side and up and down, and remain in this propped up position sometimes for many minutes. Like controls, SCH treated rats exerted vigorous escape efforts when handled by the investigator.

Discussion

Methodological considerations

Activation of the ionotropic GABA_A receptor produces membrane hyperpolarization due to opening of chloride channels (Coombs et al., 1955; Eccles, 1964; Kaila et al., 1989). Ubiquitous among vertebrates and invertebrates, GABA_A is expressed to some degree by virtually all neurons in the mammalian CNS (Nutt, 2006), such that each, to some degree, is inhibited by the GABA_A agonist, musc, and disinhibited by its antagonists, bic and picrotoxin (Zukin et al., 1974; Dray, 1975; Simmonds, 1982; Krishek et al., 1996). Accordingly, microinfusions of these drugs have been utilized in numerous experiments to make evident the influences on function of specific brain structures or regions. In practice, 'silencing' is frequently effective, whereas 'stimulation' tends more to occlude presumably functionally-specific patterns of neural activity, which creates difficulties in interpretation. Functional localization requires that infused GABA_A ligands act only on structures to which effects are attributed. Because infusion sites are not visible histologically, this was done here with control infusions into several contiguous and nearby structures, including the bed nucleus of stria terminalis, ventral striatum, nucleus of the vertical limb of the diagonal band and olfactory tubercle. None produced behavior resembling that observed after LPO or VP bic and musc infusions. As regards the VP itself, however, only its central subcommissural part has been evaluated so far. Whether characteristic VP-elicited behavioral responses can be generated by infusions in other parts of the VP (Root et al., 2015) is not known.

Behavioral *activation* has occasionally been reported after infusion of musc into the VP (Scheel-Krüger, 1983; Swerdlow and Koob, 1984; Baud et al., 1988; van den Bos and Cools, 1989; 1991), whereas we and others (references in Introduction) have consistently seen only behavioral suppression. We addressed this discrepancy separately by assessing bilateral infusions into the VP of musc at 75, 25 and 10 ng/0.25 µl/side, observing modest activation at the 10 ng dose (unpublished observation), possibly reflecting a presynaptic action of muscimol on GABAergic axon terminals (Yamamoto et al., 2011; Wakita et al., 2012). Infusions of 25 and 75 ng consistently suppressed behavior in our hands.

With the hal-SCH combo used in this study, we sought to replicate complete dopamine depletion based on empirical data showing that an extraordinary effect on the distribution of striatal neurotensin immunoreactivity caused by reserpine (Bean et al., 1989) was reproduced only with a combo of hal and SCH at these doses (Zahm, 1992). Lesser doses of dopamine antagonist and dopamine-depleting 6-hydroxydopamine lesions failed to replicate the unique effect of reserpine, so the drug effect was attributed to the production of CNS extracellular concentrations of antagonist adequate to achieve full blockade of dopamine receptors. Importantly, lesser doses of dopamine antagonists also failed to block pivoting in the present study. A role for serotonin (5-HT) in mediating these effects cannot be excluded, however, insofar as reserpine also depletes serotonin stores and SCH at the high doses used blocks 5-HT₁ and 5-HT₅ receptors (Wamsley et al., 1991; Bourne, 2001). In this regard, the effect of the hal-SCH combo on striatal neurotensin immunoreactivity was not replicated by ritanserin, a potent 5-HT₁ receptor antagonist, either when used alone or in combination with hal (Zahm, 1992).

LPO control of behavior

Our data indicate that locomotion is stimulated by LPO bic and that both basal and amph-stimulated locomotion are attenuated by LPO musc. LPO thus may trigger locomotion via signals conducted by its projections to upper brainstem somatomotor sites, such as, e.g., the subthalamic and midbrain locomotor regions, periaqueductal gray and retrorubral area (Troiano and Siegel, 1975; 1978; Swanson et al., 1976; Saper et al., 1978; Zahm, 2016), which, in turn, project strongly to somatomotor regions in the caudal brainstem and spinal cord (Garcia-Rill et al., 1983; Garcia-Rill and Skinner, 1987; Skinner et al., 1990; Skinner and Garcia-Rill, 1993; Holstege, 1991; 1992; 1996; Caggiano et al., 2018). However, LPO also projects strongly to the VTA (Zahm et al., 2016) and activation (Mogenson et al., 1979; Lavezzi et al., 2014) and suppression (Reynolds et al., 2006; Liu et al., 2008) of VTA activity, respectively, increase and decrease extracellular dopamine in the Acb (Mogenson et al., 1979; 1980; Sotty et al., 2000), which, respectively, stimulates and attenuates locomotion (Kelly et al., 1975), much like LPO bic and musc infusions. In addition, the Acb has strong GABAergic and peptidergic projections to the LPO (Zahm et al., 2013) and other structures aligned along the medial forebrain bundle, including somatomotor sites to which LPO projects (Groenewegen and Russchen, 1984; Heimer et al., 1991; Zahm and Heimer, 1993; Usuda et al., 1998).

Locomotor effects we would like to attribute to LPO stimulation might thus actually be exerted by the Acb. But, our data show that locomotion can be activated, even if in an attenuated, sporadic manner, by LPO bic administered during systemic blockade of dopamine D1 or D2 receptors and, importantly, combined blockade of both, i.e., full blockade of dopamine D1 and D2 receptor signaling. Furthermore, locomotion due to stimulation of the mesoaccumbens dopaminergic pathway is blocked by inhibition of the LPO and VP (Austin et al. and Kalivas, 1989; 1990; 1991; Mogenson et al., 1980) and we also show that locomotor activation elicited by amph is attenuated by inactivation of the LPO, all of which suggests that increased Acb dopamine concentration activates locomotion via the LPO. Indeed the, robust locomotor activation caused by amph occurs despite dopamine autoreceptor-mediated suppression of the firing of VTA dopamine neurons caused by the increase in midbrain extracellular dopamine concentration due to the action of amph (Bunney et al., 1973; Einhorn et al., 1988; Shi et al., 2000a; b; 2004). Independence of amph-evoked dopamine overflow from VTA neuronal firing has received further experimental support in the dorsal striatum (Westerink et al., 1987; Kuczenski et al., 1990), but to our knowledge, no similar determination was made in the Acb. In fact, amph-elicited locomotor activation is attenuated by low dose dopamine agonists, but this presumably is a dopamine autoreceptor effect, also independent of dopamine neuron firing (Costall et al., 1980; Creese et al., 1982; Strombom and Leidman, 1982; Kuczenski et al., 1990; Furmidge et al., 1991; Mogenson and Wu, 1991). Thus, because we observed that locomotion *is* stimulated by LPO activation under dopamine receptor blockade and *is not* stimulated by amph-increased Acb extracellular dopamine if LPO activation is blocked, we conclude that the LPO mediates the locomotor response to increased Acb dopamine, but can activate locomotion, however tentatively, in the absence of dopamine signaling.

Behavior invigorated by LPO stimulation is coherent, integrated and purposeful in appearance. This highly coordinated character of LPO-elicited behavior is surprising because it is counterintuitive that it should be so. Amplification by bic of output transmitted from the LPO to brainstem motor effectors should also render disorganized any functionally important patterning of the impulses. Thus, that the physical structure of locomotion is not disrupted by LPO bic infusions suggests that it is the density of neural activity conducted from the LPO to the brainstem, not its pattern, that matters in LPO modulation of locomotion, consistent with longstanding doctrine holding behavioral pattern to be autonomously controlled by brainstem subject to modulation by descending signals mainly as pertains to initiation, cessation and gain (Ferrier, 1876/1966; Hinsey et al., 1930; Bard and Rioch, 1937; Bard and Macht, 1958; Woods, 1964).

VP control of behavior

In contrast to the accelerated, but, otherwise, putatively ‘normal’ locomotor behavior seen after LPO bic, a collection of distinctly aberrant, unnatural, presumably maladaptive movements, such as pivoting, backing, compulsive gnawing and ingesting while sated, was observed after VP infusions of bic. It is as if the VP can initiate and may provide at least part of the coding for a repertoire of actions, perhaps including turning, gnawing and ingesting, that, in the presence of the disruptive amplification associated with bilateral VP bic infusions, becomes the distorted caricatures of normal movements described here. VP projects to subthalamic and upper brainstem sites also innervated by the LPO (Haber et al., 1985; 1993; Groenewegen et al., 1993) and, thus, like LPO, is neuroanatomically well positioned to modulate movement and locomotion. Like LPO, the VP also strongly innervates the VTA (Groenewegen et al., 1993; 1994). However, Floresco et al. (2003) observed no release of dopamine in the Acb upon VP stimulation, suggesting that the movements are not caused by VP-mediated stimulation of Acb-projecting VTA dopamine neurons. On the other hand, Koshikawa, Cools and colleagues were able to trigger bouts of vigorous pivoting and gnawing with unilateral infusion of dopamine agonists into the Acb shell (Koshikawa et al., 1996; Kitamura et al., 1999; 2001; Ikeda et al., 2003; 2007), which they could block with VP musc infusions (Kitamura et al., 2001; Uchida et al., 2005). While it thus seems unlikely that their effect models VP to VTA-stimulated Acb dopamine release, it nonetheless is difficult to conclude other than that dopamine signaling is in some way required. Consistent with their results, we have shown here that systemic dopamine D1 receptor blockade (but not D2 blockade) prevents the pivoting-gnawing response to bilateral stimulation of the VP. Where in the brain the necessary dopamine signaling occurs remains to be determined; perhaps in the VP itself (Napier and Maslowski-Cobuzzi, 1994; Gong et al., 1999). Considering all the data, it seems fair to speculate that pivots and gnawing are a distortion of a dopamine-dependent functional linkage between the Acb, VP and downstream somatomotor sites that differs fundamentally from locomotor activation associated with LPO stimulation, which also is modulated by dopamine signaling, but can proceed in its absence.

Disinhibition as a mechanism of action

Irrespective of differences in the motoric outcomes of LPO and VP activation, it defies *prima facie* logic that infusion of bic into either structure should *increase* movements,

insofar as the outputs of LPO and VP are commonly thought to be GABAergic – activating them should suppress behavior. The pervasive notion that forebrain outputs are mainly GABAergic likely reflects the high reported percentages of GABAergic neurons in the VP (up to 90%) and LPO (50%) (Mugnaini and Oertel, 1985; Ferraguti et al., 1990; Najlerahim et al., 1990) viewed in the light of earlier experiments showing that at least some descending forebrain efferents utilize GABA as a transmitter (e.g., Brownstein et al., 1977; Gonzales-Vegas and Pardey et al., 1979). However, when markers of GABAergic phenotype were sought in target-specified, i.e., retrogradely labeled, LPO and VP neurons, they were typically found to comprise only about 30% or less (Beckstead and Kersey, 1985; Zahm et al., 1987; Schmued et al., 1989; Ray et al., 1992; Gritti et al., 1994; Veenman and Reiner, 1994; Bell et al., 1995; Mascagni and McDonald, 2009; Barker et al., 2017). This suggests a predominance of other transmitters, which, depending on the specific projection, might be excitatory amino acids (e.g., Geisler et al., 2007; Barker et al., 2017) or acetylcholine (Gritti et al., 1997). However, phenotypic markers of utilization of GABA as a transmitter are notoriously difficult to detect, particularly in neurons that express GABA modestly (e.g., Ribak et al., 1978; Ferraguti et al., 1990; Ray et al., 1992), so the actual numbers of GABAergic LPO and VP outputs may be more than reported. In any event, even small numbers of strategically localized GABAergic synapses can effectively curtail the activity of target neurons – particularly at dendritic branch points, by electrotonic ‘amputation’, and at the cell body and axon initial segment by ‘strangulation’ (Eccles, 1964; Shepherd, 1975, pg. 210). Consequently, the observed tendency for increased movement to be linked to *activation* of the LPO or VP makes sense if LPO and VP GABAergic outputs act to inhibit a local inhibitory network, perhaps in the caudal brainstem, but possibly more widely distributed, that more directly controls the activity of brainstem motor effectors (Kinjo et al., 1990; Mogenson et al., 1993). Conversely, musc mediated *inactivation* of both the LPO and VP results in *suppression* of basal and amph-stimulated locomotion, which in turn makes sense only if inactivating LPO and VP permits said local inhibition to dominate. How excitatory outputs from the LPO and VP modulate locomotion, other than by activating the VTA (e.g., Reynolds et al., 2006), remains to be determined. They might, e.g., bypass the posited inhibitory network to act directly on principle neurons of brainstem somatomotor networks.

Differences in motoric effects elicited from the LPO and VP may reflect, at least in part, differences in how each interacts with aforementioned presumptive downstream inhibitory networks. Tangible manifestations of such interactions might include, e.g., differences we observed in the relative potencies of unilateral and bilateral infusions into the LPO and VP to elicit behavioral responses. That is, both unilateral and bilateral bic infusions into the LPO caused a motor response, whereas only bilateral VP bic infusions did so. Maximal locomotor responses generated by unilateral and bilateral LPO bic infusions were nearly identical, and the large mean response magnitude to bilateral LPO bic infusions only very modestly exceeded that seen after unilateral infusions. Whether this slight advantage reflects a particular mechanism requiring bilateral LPO activations or, alternatively, bilateral infusions simply double the likelihood of hitting previously reported ‘sweet spots’ associated with unilateral LPO stimulation of especially invigorated locomotion (Zahm et al., 2014) is unclear. Either way, the difference is sufficiently small that parsimony favors a simpler conclusion: the mean response magnitudes of both unilateral and bilateral LPO bic infusions

are large and nearly equivalent. Likewise, similar reductions in both basal and amph-stimulated locomotion are produced by unilateral and bilateral infusions of musc into the LPO. Thus, infusions of bic or musc into one or both sides of the LPO exert nearly, if not precisely, the same level of control over locomotor invigoration. This fits well with the concept of autonomous execution of spontaneous locomotion by a dedicated brainstem-spinal somatomotor network controlled by a proximal inhibitory network. LPO input, whether from one or the other side of the midline or both, may initiate disinhibitory signaling that propagates throughout the entire inhibitory network, enabling LPO output frequency to command the vigor of locomotion.

In contrast, only *bilateral* infusions of bic into the VP elicited the aberrant pivoting, backing, gnawing and ingesting characteristic of VP bic infusions and only *bilateral* VP musc infusions produced maximal suppression of basal and amph-stimulated locomotion. Despite resulting from bilateral VP bic infusions, pivoting in one direction or the other typically predominated, but it was almost always accompanied by fewer pivots in the opposite direction and, occasionally, an about even split between the two directions was observed. While we observed no frankly asymmetrical locomotor responses after unilateral VP bic infusions, others have reported wide turning after unilateral VP infusions of opioids (Hoffman et al., 1991; Napier, 1992; Napier et al., 1992) and musc (Kitamura et al., 2001). However, the latter, due to their reported large diameter (>30 cm) and relatively low frequency (about 4 turns/5 minutes max), may have been disrupted by or otherwise gone undetected in our square, 43 cm × 43 cm test space.

Another indication that LPO and VP outputs may have different interactions with presumptive downstream somatomotor inhibitory networks is the much greater suppression of behavior by musc infusion into the VP (when given bilaterally) as compared to LPO (when given unilaterally or bilaterally). That is, the moderate reduction in amph-stimulated locomotion produced by musc inactivation of LPO was outstripped by the near complete cessation of amph-stimulated locomotion and other movements following bilateral VP musc infusions. Thus, modulation of the gain of locomotion by the LPO may proceed under tight regulation by a stronger, permissive, tonically active (Mogenson et al., 1993) VP suppression of the presumptive tonic local inhibition.

This leaves remaining only to attach (even hypothetical) functional significance to the peculiar requirement that the VP be activated or inhibited bilaterally in order to produce the behavioral responses we have observed. Perhaps this goes to the need to select and inhibit competing motor programs to achieve smoothly integrated motor behavior (e.g., Mink, 1996). Distinct functional competencies of the LPO and VP likely compete for access to the same pool of brainstem-spinal premotor and motor neurons. That unilateral stimulation of the LPO is sufficient to trigger a maximal ‘exploratory’ behavioral response, suggests the somatomotor network is powerfully and bilaterally controlled even by unilateral LPO signaling. This is underscored by our earlier observation that infusion of bic into LPO on one side of the midline paired with a bic infusion into the VP on the other always results in an LPO-style locomotor activation (Zahm et al., 2014). Nonetheless, bilateral inhibition of the VP profoundly suppresses both basal and amph-stimulated exploratory locomotion, suggesting that bilateral activation of the VP is necessary (and unilateral activation

insufficient) to supplant LPO possession of the downstream somatomotor network and instead impress said network into service on behalf of discrete, faux-adaptive VP-elicited movements. While highly speculative, it seems possible that such an ‘override’ feature permits exploratory locomotion to be superseded by VP-elicited movements. In the absence of exogenously imposed stimulation and inhibition of the LPO and VP structures, as was done in this study, reported differences in their baseline firing frequencies (Mogenson et al., 1993) are consistent with mechanisms hypothesized here. However, further details of neuroanatomical organization and mechanisms to support such interactions remain to be worked out.

Functional considerations

Locomotor activation elicited by LPO stimulation and blocked by LPO inhibition simulates the acquisitive forward progression sometimes called ‘exploratory’ locomotion, which, in the behaving animal, can proceed independently of salient stimuli or be hastened by the promise of consummation, either remembered or cued by contextual environmental stimuli (Mary Christopher and Butter, 1968; Hotsenpiller et al., 2001). Consistent with responses to mnemonic and environmental cues, LPO receives major telencephalic input from the lateral septum and Acb shell (Zahm et al., 2013), which themselves are dominated by massive inputs from the hippocampus and periamygdaloid, infralimbic, ventral prelimbic and ventral agranular insular cortex (Kelley and Domesick, 1982; Room et al., 1985; McGeorge and Faull, 1989; Groenewegen et al., 1990; Hurley et al., 1991; Berendse et al., 1992; Brog et al., 1993; Groenewegen et al., 1987; Vertes, 2004; Reynolds and Zahm, 2005; Reichard et al., 2017) concerned with contextual, relatively undifferentiated aspects of behavioral synthesis (Heidbreder and Groenewegen, 2003; Bannerman et al., 2004; McHugh et al., 2004; O’Mara et al., 2009; Cooper et al., 2006; Ito and Lee, 2016). Alternatively, stimulation of the VP simulates discrete movements, which, in proper context and undistorted, could be adaptive responses to salient, discrete stimuli. Accordingly, the VP gets quite strong input, via relays mainly in the Acb (Zahm and Brog, 1992; Zahm, 1999), from the dorsal prelimbic, dorsal agranular insular and cingulate cortex (Room et al., 1985; McGeorge and Faull, 1989; Groenewegen et al., 1990; Berendse et al., 1992; Brog et al., 1993; Vertes, 2004; Reynolds and Zahm, 2005) to which have been attributed more so the planning and execution of discrete, stimulus-driven adaptive behavioral responses (Kelley et al., 1997; Balleine and Dickinson, 1998; Kelley, 1999; Heidbreder and Groenewegen, 2003; Vertes, 2004). Thus, although driven absent of meaningful descending input, the respective actions elicited by LPO and VP bic infusions do not differ fundamentally from what in life each structure is called upon to execute by the cortical structures to which it is connected. The distinct functional competencies of the LPO and VP thus may have evolved and developed in close relation to those of the respective cortices to which each is connected.

Clinical note

Mechanisms that underlie the conversion of motivation to movement, while essential to normal adaptive behavior, assume clinical importance when considering addiction, i.e., ‘compulsive repetition of actions known to be self-injurious’. Abstinence during addiction succumbs, as much as to its own persistent aversiveness, to the impossibly constant effort necessary to its maintenance, which must be exerted without expectation of immediate

beneficial consequence. Even ardent motivation to abstain is readily annulled by actions directed toward gratification during even brief lapses in the continuous attention abstinence demands. A better understanding of mechanisms that distinguish automatic from intentional actions, even at the fundamental level considered herein, could lead ultimately to strategies that retard recourse to repetition of self-destructive actions that are the *sine qua non* of relapse in addiction.

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List of Abbreviations

Acb	accumbens
amph	D-amphetamine
bic	9(R)-(-)-bicuculline methbromide
etic	S(-)-eticlopride hydrochloride
GABA	gamma-aminobutyric acid
hal	haloperidol
LPO	lateral preoptic area
musc	muscimol hydrobromide
SCH	R(+)-SCH-23390 hydrochloride
SPB	Sorenson's phosphate buffer
VP	ventral pallidum
VTa	ventral tegmental area

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Figure 1.

Graphs illustrating locomotion and rears, including representative time courses (A and B), during twenty minutes following unilateral and bilateral infusions of vehicle, bicuculline (bic) or muscimol (musc) into the lateral preoptic area (LPO, panels A–D) and unilateral and bilateral infusions of musc into the ventral pallidum (VP, panels E and F). Data describing bic infusions into the VP have been reported (Zahm et al., 2014) and so are omitted in E and F. Numbers above the bars in C and E are n values. Totals for the entire twenty minute period, as shown in C–F, were evaluated statistically using a one way ANOVA, results of

which are given in the text. Asterisks shown beneath the panels reflect statistically significant differences revealed by the Student-Newman-Keuls post hoc test.

Figure 2.

Diagram illustrating representative injection sites in the lateral preoptic area (LPO). Most cases were implanted with bilateral cannulae, but sites are shown on one side only. Dots indicate the tips of injector cannulae as plotted on standardized templates of basal forebrain based on images like that shown in the inset. The asterisks in the inset and panel E indicate the particular injection site plotted from the micrograph shown (inset). Additional abbreviations: ac – anterior commissure; BST – bed nucleus of the stria terminalis; CPu – caudate-putamen; GP – globus pallidus; ox – optic chiasm; SLEA – sublenticular extended amygdala; VDB, vertical limb of the diagonal band; VP – ventral pallidum. Scale bar: 1 mm.

Figure 3.

Diagram illustrating representative injection sites in the ventral pallidum (VP). Most cases were implanted with bilateral cannulae, but sites are shown on one side only. Dots indicate the tips of injector cannulae as plotted on standardized templates of basal forebrain based on images like that shown in the inset. The asterisks in the inset and panel D indicate the particular injection site plotted from the micrograph shown (inset). Additional abbreviations: ac – anterior commissure; BST – bed nucleus of the stria terminalis; CPu – caudate-putamen; GP – globus pallidus; ox – optic chiasm; SLEA – sublenticular extended amygdala; VDB, vertical limb of the diagonal band. Scale bar: 1 mm.

Figure 4.

Graphs showing effects on locomotion (A) and rearing (B) invigorated by subcutaneous administration of D-amphetamine (1.5 mg/kg) of infusion of muscimol (musc) into the lateral preoptic area (LPO) and ventral pallidum (VP). Rats were injected with amph, returned to the home cage for ten minutes and then were placed in activity monitors. After measurement of baseline activity for ten minutes, they were removed, musc was infused and they were returned to the activity monitors for twenty minutes during which total locomotion and rearing were recorded (for a graph of the time course see Fig. 5C). Numbers above the bars in A are n values. Totals for the twenty minute period are shown and were evaluated statistically using a one way ANOVA, results of which are given in the text. Asterisks shown beneath the panels reflect statistically significant differences revealed by the Student-Newman-Keuls post hoc test.

LPO bic, dopamine receptor antagonists

Figure 5.

Graphs showing effects on locomotion (A) and rearing (B) invigorated by infusions of bic into the lateral preoptic area (LPO) of subcutaneous administration of haloperidol (2 mg/kg), SCH23390 (5 mg/kg) or co-administration of the two. Rats were injected with antagonist, returned to the home cage for ten minutes and then were placed in activity monitors. After measurement of baseline activity for ten minutes (C), they were removed, bic was infused and they were returned to the activity monitors for twenty minutes during which total locomotion and rearing were recorded (for a graph of the time course see panel C). For reference, broken horizontal lines in the white bars indicate baseline locomotion (A) and rearing (B), i.e., in the absence of bic infusions, transposed from Figure 1. Numbers above the bars in A are n values. Totals for the twenty minute period are shown and were evaluated statistically using a one way ANOVA, results of which are given in the text. Asterisks shown beneath panels A and B reflect statistically significant differences revealed by the Student-Newman-Keuls post hoc test. C. Results for seven individual cases (12179–12184), indicating that SCH23390 frequently failed to suppress locomotion elicited by LPO bic

infusions. D. Total horizontal counts for more such cases. Case numbers are on the abscissa. Values of some of the bars are given above the bars.

VP bic (bilateral), dopamine receptor antagonists

Figure 6.

Graphs showing effects on locomotion (A) and rearing (B) following infusions of bicuculline (bic) or vehicle (veh) into the ventral pallidum (VP) of subcutaneous administration of haloperidol (2 mg/kg), SCH23390 (5 mg/kg) or co-administration of the two. Rats were injected with antagonist, returned to the home cage for ten minutes and then were placed in activity monitors. After measurement of baseline activity for ten minutes (C), they were removed, bic was infused and they were returned to the activity monitors for twenty minutes during which total locomotion and rearing were recorded (for a graph of the time course see panel 5C). The figure legend format is 'drug injected, compound infused into the VP'. For reference, broken horizontal lines in the white bars indicate baseline locomotion (A) and rearing (B), i.e., in the absence of bic infusions, transposed from Figure 1. Numbers above the bars in A are n values. Totals for the twenty minute period are shown and were evaluated statistically using a one way ANOVA, results of which are given in the text. Asterisks shown beneath panels A and B reflect statistically significant differences revealed by the Student-Newman-Keuls post hoc test. The hal, VP veh data are given to reference the severity of hal induced catalepsy in the absence of VP bic.

Means $\pm$ SEM of full pivots observed during 30 minutes following infusions of bicuculline into the ventral pallidum on both sides of the midline preceded by the indicated pretreatments.

Table 1

<u>Pivot direction</u>	<u>Pivot parameters</u>	<u>Pretreatments</u>			
		vehicle (n=10)	eticlopride 2 mg/kg (n=5)	haloperidol 2 mg/kg (n=7)	SCH- 23390 5 mg/kg (n=5)
Total pivots	pivots	110 $\pm$ 21	106 $\pm$ 48	51 $\pm$ 15	0
	episodes	33 $\pm$ 5.5	27 $\pm$ 8.8	28 $\pm$ 8.5	0
	pivots/episode	3.3 $\pm$ 0.4	4.1 $\pm$ 1.6	1.9 $\pm$ 0.4	0
CCW pivots	pivots	48 $\pm$ 20	19 $\pm$ 16	27 $\pm$ 9.5	0
	episodes	10 $\pm$ 3.7	12 $\pm$ 8.6	14 $\pm$ 4.4	0
	pivots/episode	2.5 $\pm$ 0.6	2 $\pm$ 1.2	1.6 $\pm$ 0.4	0
CW pivots	pivots	62 $\pm$ 15	87 $\pm$ 53	24 $\pm$ 10	0
	episodes	23 $\pm$ 4.8	15 $\pm$ 7	12 $\pm$ 4.1	0
	pivots/episode	2.4 $\pm$ 0.4	4.3 $\pm$ 2.1	1.5 $\pm$ 0.5	0