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Relationships between locomotor activation and alterations in brain temperature during selective blockade and stimulation of dopamine transmission

P. Leon Brown, David Bae, and Eugene A. Kiyatkin*

Cellular Neurobiology Branch, National Institute on Drug Abuse - Intramural Research Program, National Institutes of Health, DHHS, 333 Cassell Drive, Baltimore, MD 21224, USA

Abstract

It is well known that the dopamine (DA) system plays an essential role in the organization and regulation of brain activational processes. Various environmental stimuli that induce locomotor activation also increase DA transmission, while DA antagonists decrease spontaneous locomotion. Our previous work supports close relationships between locomotor activation and brain and body temperature increases induced by salient environmental challenges or occurring during motivated behavior. While this correlation was also true for psychomotor stimulant drugs such as methamphetamine and MDMA, more complex relationships or even inverted correlations were found for other drugs that are known to increase DA transmission (i.e., heroin and cocaine). In the present study we examined brain (NAcc), muscle and skin temperatures together with conventional locomotion during selective interruption of DA transmission induced by a mixture of D1 and D2 antagonists (SCH23390 and eticlopride at 0.2 mg/kg, sc) and its selective activation by apomorphine (APO 0.05 and 0.25 mg/kg, iv). While full DA receptor blockade decreased spontaneous locomotion, it significantly increased brain, muscle and skin temperatures, suggesting metabolic brain activation under conditions of vasodilatation (or weakening of normal vascular tone). In contrast, APO strongly decreased skin temperature but tended to decrease brain and muscle temperatures despite strong hyperlocomotion and stereotypy. The brain temperature response to APO was strongly dependent on basal brain temperature, with hypothermia at high basal temperatures and weak hyperthermia at low temperatures. While supporting the role of DA in locomotor activation, these data suggest more complex relationships between drug-induced alterations in DA transmission, behavioral activation and metabolic brain activation.

Keywords

SCH23390; eticlopride; apomorphine; metabolic brain activation; vasoconstriction and vasodilatation; behavioral activation; functional role of the dopamine system

It is generally believed that locomotor activation results from brain activation, which manifests as an excitation of central neurons and an increase in cerebral metabolism. While different neurochemical mechanisms are involved in brain activation, dopamine (DA) appears to play an essential role (see Le Moal and Simon, 1991; Salamone et al., 2005 for review). Various

* Correspondence should be addressed to: Dr. Eugene A. Kiyatkin at the above address; phone: (410) 550 5551; fax: (410) 550-5553; e-mail: ekiyatki@intra.nida.nih.gov..

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environmental challenges that induce locomotor activation also increase DA transmission, while pharmacological blockade of DA transmission inhibits spontaneous locomotion and greatly attenuates behavioral activation, independent of its triggering mechanisms (see Kiyatkin, 2002 for review). Hyperlocomotion and stereotypy also occur during pharmacological increase in DA transmission induced by both direct (i.e. bromocriptine, apomorphine or APO) and indirect (i.e. amphetamine, methamphetamine, cocaine) DA agonists (see Wise and Bozarth, 1987; Jackson and Westlind-Danielsson, 1994 for review).

Our previous work supports a relationship between locomotor activation and increased metabolic activity manifested as brain temperature increase. Brain temperature rapidly increases, along with locomotor activation, during exposure to various salient environmental challenges, the performance of natural motivated behavior and the initiation of intravenous (iv) heroin and cocaine self-administration (see Kiyatkin, 2005 for review). Similarly, brain hyperthermia occurs together with locomotor hyperactivity and stereotypy following systemic administration of meth-amphetamine (Brown et al., 2003) and MDMA (Brown and Kiyatkin, 2004). While brain temperatures generally correlate with body temperatures, in each case the increase in the brain is more rapid and stronger, suggesting metabolic brain activation as a primary source of brain hyperthermia. However, the relationships between locomotor activity and brain temperature changes were more complex with other drugs and in other experimental conditions. For example, repeated heroin self-injections induce transient freezing and hypoactivity, but these behavioral effects occur at high and relatively stable brain temperatures (Kiyatkin and Wise, 2002). Although iv cocaine increases both locomotion and brain temperatures, these changes do not correlate following a single injection (Brown and Kiyatkin, 2005) and show a negative correlation during self-administration (Kiyatkin and Brown, 2003). Therefore, it may be assumed that the relationship between drug-induced behavioral and metabolic brain activation is far from being a simple positive correlation.

To clarify the possible relationships between metabolic activation and behavioral activation, we examined alterations in brain, muscle, and skin temperatures together with conventional locomotion during selective pharmacological interruption of DA transmission induced by a mixture of D1-like and D2-like DA antagonists (SCH23390 and eticlopride) and its selective activation induced by APO, a selective, directly acting DA agonist with high affinity to both D1- and D2-like receptors (Jackson and Westlind-Danielsson, 1994). Taking into account the known role of the DA system in brain activational processes, we predicted that brain hyperthermia would accompany the locomotor activation induced by APO and hypothermia would accompany locomotor inhibition induced by DA antagonists. Such results would imply a close link between metabolic and behavioral changes. In contrast, our results failed to support this prediction, pointing at more complex relationships between drug-induced behavioral and metabolic brain activation. These data also suggest a multi-faceted role for DA in the central organization and regulation of brain activational processes.

Materials and Methods

Subjects

Forty one Long-Evans male rats (Taconic, Germantown, NY), weighing 420–480 g and housed in a 12 h light cycle (lights on at 0700) with *ad libitum* food and water, were used. Protocols were performed in compliance with the Guide for the Care and Use of Laboratory Animals (NIH, Publications 865-23) and were approved by the Animal Care and Use Committee, NIDA-IRP.

Surgery

All animals were implanted with three thermocouple electrodes as previously described (Kiyatkin and Brown, 2003). Animals were anesthetized with Equithesin (3.3 ml/kg i.p.) and mounted in a stereotaxic apparatus. Holes were drilled through the skull over the NAcc shell (1.2 mm anterior to bregma, 0.9 mm lateral to bregma) using the coordinates of Paxinos and Watson (1998). The dura matter was retracted and a thermocouple probe was slowly lowered to the desired target depth (7.4 mm). A second thermocouple probe was implanted subcutaneously along the nasal ridge with the tip approximately 15 mm from bregma. A third thermocouple probe was implanted in deep temporal muscle (*musculus temporalis*). The probes were secured with dental cement to three stainless steel screws threaded into the skull. Animals used in APO experiments were implanted with a jugular iv catheter during the same surgery session. For jugular catheter implantation, a 10 mm incision was made in the neck to expose the jugular vein. A catheter was then inserted into, and secured to, the vein, and the catheter was run subcutaneously to the head mount and secured with dental cement. Rats were allowed three days recovery and one day of habituation (6 h session) to the testing environment before the start of testing.

Experimental Protocol

All tests occurred inside a Plexiglas chamber (32x32x32 cm) equipped with four infrared motion detectors (Med Associates, Burlington, VT, USA), placed inside of a sound attenuation chamber. Rats were brought to the testing chamber at 09:00 and attached via a flexible cord and electrical commutator to thermal recording hardware (Thermes 16, Physitemp, Clifton, NJ, USA). The catheter extension was also attached to the internal catheter, thereby allowing remote, unsignalled iv injections. Temperatures were recorded with a time resolution of 10 s and movement was recorded as the number of infrared beam breaks per 1 min.

In Experiment 1 (DA antagonists), each rat (n=8), following a habituation session (Day 1), received a sc injection of saline (0.3 ml) or a combination of DA antagonists (SCH at 0.2 mg/kg and ETI at 0.2 mg/kg in 0.3 ml saline), once on Day 2 or 4. Day 3 was a free day to minimize the possible influence of the previous injection. These injections were made after at least a 3-hour habituation to the recording chamber and their order was counter-balanced. SCH-23390 [R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, or SCH] and eticlopride (ETI) have strong antagonistic activity at D1-like or D2-like DA receptors, respectively (relative D1:D2 affinity, SCH=2,500:1 and ETI 1:51,400; Neve and Neve, 1997). Both these drugs were obtained from Sigma (St. Louis, MO) and dissolved in saline immediately before use. Our previous studies suggests that the combination of these drugs at 0.2 mg/kg (0.7 and 0.6 μ M, respectively) provides effective blockade of DA transmission for at least two hours as tested by the antagonism of striatal neuronal responses to iontophoretic DA (Kiyatkin and Rebec, 1999) as well as significantly inhibits spontaneous locomotion for at least three hours (Kiyatkin and Brown, 2005).

In experiment 2 (APO), rats (n=8), following a habituation session (Day 1), received identical APO treatment on Day 2, 3 and 5. After at least a two-hour habituation period, rats received three iv injections of APO (0.2 ml dissolved in 0.1% ascorbic acid in saline over 16 s) at 10, 50 and 250 μ g/kg with at least 90-min inter-injection intervals. The external catheter was refilled for each injection. An additional 30-min period was added to eliminate the possible influence of this procedure on locomotion and temperature. On Days 2 and 3, room temperature was maintained at $23.0 \pm 0.5^\circ\text{C}$ and on Day 5 at $28.5 \pm 0.5^\circ\text{C}$. Although the latter ambient temperature is close to normothermia in rats (Romanovsky et al., 2002) and has minimal effects on basal temperatures, it strongly potentiates brain hyperthermia induced by various drugs and stimuli that induce vasoconstrictive effects (see Kiyatkin, 2005 for review). APO [R(-) apomorphine hydrochloride hemihydrate; obtained from Sigma] is a selective, directly acting

DA agonist with high affinity to both D1-like and D2-like receptors (Neve and Neve, 1997). 50 and 250 µg/kg of APO were chosen in this study as “small” and “large” doses because of the known dose differences with respect to activation of auto- and postsynaptic DA receptors (Jackson and Westlind-Danielsson, 1994) and the dose range self-administered by rats (Yokel and Wise, 1978; Roberts, 1989). A dose of 10 µg/kg was chosen as a sub-threshold dose, eliminating the need for a control vehicle administration.

Histology and Data Analysis

When recording was completed, all rats were anesthetized, decapitated, and had their brains removed for sectioning and confirmation of probe placement. Brains were cut on a cryostat into 50µ slices and placed on glass slides. All probes were located within the NAcc shell, as described in Paxinos and Watson (1998).

Temperature and movement data were analyzed with 1- and 3-min time bins and were presented as both absolute and relative changes with respect to the moment of drug administration. ANOVA with repeated measures, followed by post-hoc Fisher tests, was used for statistical evaluation of drug-induced changes in temperature and movement. Student's t-test was used for comparisons of between-site differences in temperature and locomotion. Correlation (Pearson's *r*) and regression analyses were also used to assess the relationships between temperatures recorded from different sites and the dependence of drug-induced temperature change upon basal temperatures.

Results

1. Changes in locomotion and temperatures following blockade of DA transmission by SCH23390 and eticlopride

Fig. 1 shows changes in locomotion and temperatures in the NAcc, temporal muscle and skin after sc injections of either a mixture of SCH and ETI or saline. As shown, both treatments resulted in significant changes in temperature and locomotion. NAcc and muscle temperature rapidly increased after SCH+ETI injection and remained elevated for the entire period of observation. Skin temperature transiently decreased but then significantly increased (Fig. 1A). Locomotor activity rapidly increased immediately after drug injection but then decreased below baseline (Fig. 1C). In the case of the saline injection (Fig. 1B), brain and muscle temperatures also increased (~0.5 °C), while skin temperature rapidly decreased (~0.6 °C). In addition, rats showed a transient locomotor response for about 15–20 min.

To represent the effect of DA antagonists, we calculated the difference in temperatures after SCH+ETI and saline treatment (Fig. 1D). As can be seen, brain and muscle temperatures for the two groups did not differ significantly for the first 20 minutes after the injection, but then the group difference (for both brain and muscle) became significant and relatively similar in amplitude for both sites (0.6–0.7°C increase in SCH+ETI group vs. control). In contrast, a transient skin hypothermia seen in both groups was weaker after SCH+ETI and the between-group difference became significant at 6 min post-injection. While in control animals skin temperature returned to basal values at about 20 min, in the DA antagonist group it increased above baseline. Between-group differences in skin temperature were evident for the entire 120-min analysis interval.

Temperature changes induced by DA antagonists had high individual variability with strong increases (>1.5°C), virtually no change, and even slight decreases in different animals (Fig. 2A). As shown in Fig. 2B (n=33), the brain temperature response (assessed at the 30th min post-injection) was significantly negatively correlated with basal brain temperatures ($r = -0.492$, $p < 0.01$). When NAcc temperatures were low at baseline, DA antagonists induced

strong temperature increases. When basal temperatures were high, the response was minimal or even absent. The regression line crossed the line of no effect at about 38.1°C; this value is at the upper range of normal variability and is more than 2 SD larger than mean basal NAcc temperature (36.80 ± 0.10 °C, $SD = 0.56$ °C). The temperature-increasing effect of DA antagonists was significant in each of the 5 groups and was highly significant if combined into one group (37.41 ± 0.10 °C; $p < 0.001$). The mean increase was 0.61 ± 0.11 °C vs. baseline.

2. Changes in locomotion and temperatures following stimulation of DA transmission by APO at normal and warm ambient temperatures

Figure 3 shows relative changes in temperature and locomotion following iv APO injections in different doses at normal room temperatures (23 °C). As can be seen, APO at 10 µg/kg had virtually no effect on locomotion or temperatures in the brain and muscle, but transiently decreased skin temperature for 8–10 min after administration (A and B). APO at a moderate dose (50 µg/kg) phasically increased locomotion for about 10 min. During this period, mean values of brain and muscle temperature remained stable, but skin temperature transiently decreased, showing an inverse correlation with locomotion. Temperatures in both NAcc and muscle significantly decreased from ~15 min post-injection. APO at a large dose (250 µg/kg) strongly increased locomotion and induced stereotypy for about 30 min. During this period, mean NAcc and muscle temperatures showed biphasic fluctuation with an initial decrease followed by increase. However, these changes were not significant because of large individual variability. Skin temperature decreased dramatically (~1.2 °C) after the injection and did not return to baseline within the 60 min analysis period. Skin temperature showed an inverse correlation with locomotion. Both brain and muscle temperatures decreased below baseline from ~30 min post-injection.

Because APO-induced changes in temperature showed high individual variability, we examined how the change in brain temperature depends on basal values. As shown in Fig. 4 (A: basal values vs. values at 10th min post-injection and B: basal values vs. temperature change at 10th min post-injection), these parameters were highly negatively correlated for both drug doses. At low basal NAcc temperatures, APO at 50 and 250 µg/kg increased temperature, while it consistently decreased temperature at higher basal values. The correlation was strong ($r = -0.725$ and -0.853 for each dose, respectively; $p < 0.001$) and similar for both drug doses. In contrast to DA antagonists, regression lines crossed the line of no effect at about 36.7–36.8 °C, i.e. at about average basal NAcc temperatures (36.80 ± 0.10 °C). In contrast to brain temperature response, locomotor activation and skin hypothermia induced by APO (50 µg/kg) were independent of basal brain temperature ($r = 0.197$ and 0.04 , respectively). Skin temperature response was also independent of basal skin temperature ($r = -0.192$).

Fig. 5 shows relative changes in temperature and locomotion following iv APO injections at different doses at 29°C ambient temperatures. As can be seen, rats at warm temperatures exhibited similar locomotor responses to APO, but these effects were slightly weaker than at normal room temperature, especially at the 50 µg/kg dose. Under these conditions, rats also showed similar dose-dependent decreases in skin temperature, and effect was also weaker than at 23 °C. At 29 °C, APO at both 10 and 50 µg/kg had no effects on brain and muscle temperature, but significantly increased them at the 250 µg/kg dose. Animals tested at 29°C had similar spontaneous locomotion as those tested at 23 °C (2.1 ± 0.5 vs. 2.3 ± 0.5 counts/min, respectively; evaluated as an average of three pre-injection baselines), but had higher basal temperatures in each recording location. The differences were greatest for skin (36.03 ± 0.15 vs. 35.22 ± 0.24 °C, $p < 0.01$), lower for muscle (36.53 ± 0.19 vs. 35.87 ± 0.18 ; $p < 0.05$) and smallest for NAcc (37.17 ± 0.09 vs. 36.88 ± 0.19 °C; $p > 0.05$).

Discussion

The present study produced several unexpected findings. First, we found that DA antagonists, which strongly inhibit spontaneous locomotion, moderately increase brain, muscle and skin temperatures, suggesting some kind of metabolic activation associated with peripheral vasodilatation. The temperature-increasing effects of DA antagonists in the brain, moreover, were dependent upon basal brain temperatures, with strong effects at low temperatures and virtually no effects at higher temperatures. Second, APO, which induced powerful locomotor activation and stereotypy, strongly decreased skin temperature, suggesting vasoconstriction, but had differential effects on brain temperature. At low basal values, brain temperatures increased slightly with APO, while it decreased with APO at higher basal values. Third, APO administered at warm ambient temperatures induced similar, but apparently weaker, locomotor activation and skin hypothermia, but moderately increased brain and muscle temperatures. These results suggest that DA has state-dependent effects on brain metabolism and points at the role the DA system plays in both driving and regulating brain activational processes.

1. Metabolic brain activation induced by DA antagonists

Although DA receptor blockade strongly inhibited spontaneous locomotion, this hypoactivity was associated with an increase in brain, muscle and skin temperatures. Such a response pattern contrasts sharply with those induced by true sedative drugs. For example, sodium pentobarbital at an analgesic dose (50 mg/kg) induces profound hypothermia in the brain, body core and skin surfaces (Kiyatkin and Brown, 2005). Relative to body core, temperature decrease after pentobarbital is stronger in brain sites (suggesting primary inhibition of brain metabolism) and weaker in skin (suggesting vasodilatation and enhanced heat loss). The pattern of temperature changes induced by DA antagonists also differs from that induced by salient environmental stimuli (Kiyatkin et al., 2002), as shown in this study with sc saline injection. This mild stressogenic procedure induces hyperactivity, increases brain and muscle temperatures, and transiently decreases skin temperature. In this and other cases of natural arousing stimulation, temperature rises more quickly and more strongly in the brain than in the muscle, suggesting metabolic neural activation as a primary factor behind brain hyperthermia, as well as a factor determining (via sympathetic pathways) subsequent increase in body metabolism and body hyperthermia. A transient decrease in skin temperature—a typical response to various arousing stimuli (Baker et al., 1976; Kiyatkin, 2005) points towards vasoconstriction and diminished heat loss to the external environment.

Because skin temperature during DA receptor blockade was higher than in control conditions, indicating vasodilatation and enhanced heat dissipation, it appears that brain and body hyperthermia following this treatment results from central activation and subsequent enhanced heat production. In contrast to metabolic brain activation following arousing stimuli, the source of this heat production is less clear because temperature increases were weaker, slower but more prolonged, with brain and muscle showing a virtually similar time-course. As skin temperature depends upon both vessel tone and the temperature of arterial blood supply, a relative increase in this parameter may reflect both vasodilatation and the inflow of warmer blood from the body core. Because DA antagonists clearly diminished the temperature decrease associated with sc injection (see Fig. 1), this relative skin warming appears to result not from vasodilatation *per se*, but from the loss of natural vessel tone. Taken together with brain and muscle hyperthermia, this finding suggests that pharmacological interruption of DA transmission results in mild and prolonged metabolic brain activation.

While metabolic brain activation coupled with locomotor hypoactivity is an atypical combination for physiological and behavioral conditions, several lines of neurophysiological evidence suggest that many central neurons become hyperactive following DA receptor blockade. First, this procedure results in compensatory hyperactivity of DA neurons and

increased DA release (Freeman et al., 1985; Imperato and DiChiara, 1985). Second, striatal neurons lacking normal DA input have higher discharge rates and are more sensitive to glutamate than drug-free animals (Calabresi et al., 2000; Kiyatkin and Rebec, 1999). Third, DA receptor blockade results in heavy *fos* expression in the NAcc, dorsal striatum, substantia nigra, pars reticulata (SNr), globus pallidus, entopeduncular nucleus, central amygdala, and midline thalamic nuclei (Ma et al., 2003; Wirtshafter and Asin, 1995, 1999, 2003). Neuronal activation evaluated by this parameter was evident within the entire system of basal ganglia and some of its important afferent and efferent structures, embracing massive numbers of neural cells. This neuronal hyperactivity may reflect the loss of natural, restraining influence of tonic DA release on striatal activity, a factor important in mediating hypodynamia and behavioral hyporesponsiveness seen during various conditions associated with DA deficit.

The temperature-increasing effects of DA antagonists were inversely related to basal brain temperatures, being stronger at lower temperatures and weaker at higher temperatures. These effects, however, were evident within the full range of basal NAcc temperatures (mean $\pm$ 2SD or 35.68–37.92°C; see Fig. 2), but disappeared during hyperthermia (>38.0°C) associated with behavioral and metabolic brain activation. Therefore, it appears that the effects of DA receptor blockade on brain and body metabolism are state-dependent, with a stimulatory action present only at low levels of basal metabolic activity.

2. Inhibiting effect of APO on brain metabolism

Although APO induced powerful motor activation and stereotypy that should increase body heat production (Margaria et al., 1963; Schmidt-Nielson, 1997), temperatures in both NAcc and muscle on average slightly decreased. This effect is even more paradoxical because APO strongly decreased skin temperature, suggesting vasoconstriction and decreased heat loss to the external environment. These effects were seen with 50 and 250 μ g/kg, and weak skin hypothermia occurred even with 10 μ g/kg, when locomotion and temperatures in the brain and muscle remained stable. Such stable or slightly decreased brain temperatures during enhanced body heat production, due to locomotion, and body heat retention, due to vasoconstriction, can be reasonably assumed to result from decreased metabolic brain activity and thus decreased intra-brain heat production. While this response pattern was unexpected, a dose-dependent hypothermic effect of APO coupled with hyperlocomotion was reported in previous studies (Lapin and Samsonova, 1968; Fuxe and Sjoqvist, 1972; Grabowska et al., 1973; Scheel-Kruger and Hasselager, 1974; Cox and Lee, 1978; Weiss et al., 1984; Faunt and Crocker, 1987; Verma and Kulkarni, 1993). Similarly, it was reported that APO-induced hypothermia in rats is related to decreased metabolism and diminished metabolic heat production (Lin et al., 1979). Metabolic inhibition also occurred following direct APO injection in ventricles, preoptic anterior hypothalamus, striatum, and globus pallidus (Lin et al., 1982) and during electrical stimulation of SNc (Lin et al., 1992)—a situation that should selectively increase DA transmission. Body temperature also decreased following systemic injection of bromocriptine (Calne et al., 1975), as well as intracerebral or intra-hypothalamic injections of DA itself (Cox et al., 1978).

While it appears that selective enhancement of DA transmission has an inhibiting effect on brain metabolism, decreasing brain and body temperature *despite* increased heat production due to locomotion and *despite* diminished heat dissipation due to peripheral vasoconstriction, temperature dynamics become altered under conditions of diminished heat dissipation. While APO tested at 29 °C, only 6 degrees higher than normal room temperatures (23 °C) and close to normothermia in rats (Romanovsky et al., 2002), had similar, albeit slightly weaker, effects on locomotion and skin temperatures, changes in brain and muscle temperature differed from those seen at 23 °C (see Fig. 5). In contrast to weak decreases seen at 23 °C, both these parameters were either stable (50 μ g/kg) or significantly increased (250 μ g/kg). Therefore, it

appears that under conditions of diminished heat dissipation in a warm environment, APO may increase brain and muscle temperatures *despite* its inhibiting effect on brain metabolism and decreased intra-brain heat production. This is a typical decompensation when metabolic heat generated during locomotion cannot be properly dissipated from the body, resulting in brain and body hyperthermia. Such atypical hyperthermic effects of APO were previously reported in rats at warm ambient temperatures (30 °C) and it was shown that they result from increased body heat production and decreased heat loss (Lin et al., 1979).

Although the effects of APO on locomotion and skin temperatures were similar at different basal brain temperatures, the pattern of changes in brain temperatures was quite different. When basal brain temperatures were higher than its mean values (>37 °C), APO clearly decreased them, but weak increases were seen at lower temperatures. While the exact mechanisms underlying this state-dependent action of APO on brain temperature remain unclear, these data may suggest that DA is able to decrease brain metabolism only when it is previously increased due to metabolic brain activation. This inhibiting action, moreover, became progressively stronger, depending on the degree of previous activation. In contrast, this inhibiting action is absent at very low levels of background metabolic activity (full inactivity, sleep) and under these conditions DA may slightly increase brain metabolism.

3. Conclusions and speculations on the role of the DA system in the organizing and regulating brain activational processes

Behavioral deficits following DA cell degeneration or pharmacological interruption of DA transmission and the tight link between enhanced DA transmission and behavioral activation suggest the importance of DA in driving and organizing brain activational processes that are essential for adaptive behavior. The effects of DA on its target cells, however, are generally inhibitory in its nature (Bloom et al., 1989; Kiyatkin and Rebec, 1995, 1999; Mercuri, 1985; Moore and Bloom, 1978; Nicola and Malenka, 1997; Siggins, 1977; Windels and Kiyatkin, 2006; see, however, Gonon and Sundstrom, 1996 and Gonon, 1997 for alternative evidence), while DA receptor blockade or DA denervation is often associated with hyperactivity of these cells (see above). These data are consistent with primarily regulatory or modulatory functions of DA with respect to other neurochemical systems involved in brain activational processes. While DA transmission is enhanced under numerous conditions associated with brain activation, its primary function may be to regulate this activity, driving it at low levels and inhibiting it at higher levels.

Our present data appear to support this “homeostatic” view on DA functions in relation to brain activation and brain metabolism.

First, they suggest that selective interruption of DA transmission, despite its powerful inhibiting effects on spontaneous locomotion and behavioral responses to salient environmental stimuli, does not inhibit the brain. In contrast, the brain without functional DA appears to be metabolically more active and warmer despite the enhanced heat loss due to peripheral vasodilatation. This change parallels electrophysiological findings, suggesting that most DA-sensitive central neurons become more active, albeit disorganized, without DA input and mostly inhibited by DA itself (see above). Because most cells receiving DA input are GABA-ergic, interruption of this restraining influence of DA and subsequent hyperactivity of these cells may be the primary factor determining behavioral inhibition following DA deficit independent of its cause.

Second, our data suggest that selective stimulation of DA transmission by APO has an inhibiting effect on brain metabolism despite intense hyperlocomotion and strong vasoconstriction that, respectively, increase body heat production and decrease heat dissipation. Importantly, these inhibiting effects of enhanced DA transmission on brain

metabolism were evident only when it was increased, i.e. under conditions associated with behavioral activation and naturally occurring DA release. Therefore, it appears that DA has its specific modulatory effects on activational processes when activation is present and DA is released. Because APO had weak temperature-increasing effects at low basal temperatures that are consistently associated with deep inactivity or sleep, it may be suggested that DA may also have an excitatory effect on brain metabolism. The relevance of this effect to natural conditions, however, is questionable because during behavioral inactivity and sleep, DA release is maintained at low levels.

Third, our data suggest that the tight association between locomotor activation and increased brain metabolism that appears to exist under physiological and behavioral conditions (see Kiyatkin, 2005 for review) does not hold for drug-induced behavioral activation. APO-induced hyperlocomotion appears to be related to inhibition of brain metabolic activity, while locomotor inhibition following DA receptor blockade is accompanied by metabolic brain activation. While this uncoupling looks surprising, it is typical of other drugs. For example, iv heroin induces transient freezing and hypoactivity but brain and muscle temperatures strongly increase (Kiyatkin and Wise, 2002). Transient episodes of hypoactivity consistently occur after each repeated heroin self-injection, but brain temperature remains strongly elevated without evident phasic decreases or increases. Locomotor activation induced by a single iv cocaine injection occurs much quicker and is much shorter than increases in brain and muscle temperatures (Brown and Kiyatkin, 2005). Although repeated cocaine self-injections result in bouts of hyperlocomotion, brain and muscle temperatures transiently decrease during these episodes (Kiyatkin and Brown, 2003). Therefore, it may be suggested that naturally occurring locomotor activation (searching, grooming, rearing) and inhibition (rest, sleep) differ in its basic underlying mechanisms from similar behaviors induced by drugs.

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Fig. 1.

Changes in temperature (A and B; °C relative to the last pre-injection value) and locomotion (C; counts/3 min) induced by sc injection of DA antagonists (SCH23390 and eticlopride at 0.2 mg/kg each) and saline in awake rats. Filled symbols show values significantly different ($p < 0.05$; Scheffe F-test following one-way ANOVA with repeated measures) from the last pre-injection values. n=number of rats in groups. D shows temperature difference between the experimental and control groups (SCH+ETI – saline). Significant between-group differences (Student's t-test) are shown as filled symbols. Vertical hatched lines in all graphs show the moment of the injection (0 min). Basal temperature levels (0 °C) are shown as horizontal hatched lines. For clarity, error bars are omitted from the temperature graphs.

Fig. 2.

Relationships between basal NAcc temperatures and its changes induced by DA antagonists (SCH23390 and eticlopride at 0.2 mg/kg each). A shows the relationships between temperatures before and 30 min after the injection of DA antagonists. B shows the relationships between basal temperatures and its relative change after injection of DA antagonists. Data were obtained in 33 rats in 5 experiments. Each graph shows a regression line, line of no effect (hatched), coefficient of correlation, and regression equation. B in addition shows mean basal values (vertical half-line) and mean temperature increase (0.61 °C) after DA antagonists (horizontal half-line).

Fig. 3.

Relative changes in temperatures in each recording location (A, °C vs. baseline) and changes in locomotion (B, counts/min) after unsignalled iv injections of apomorphine at three doses at normal room temperatures (23°C). Filled symbols show values significantly different from baseline ($p < 0.05$; Scheffe F-test following one-way ANOVA with repeated measures).

Fig. 4.

Relationships between basal NAcc temperatures and its changes induced by apomorphine at 50 (left) and 250 µg/kg (right). A shows the relationships between temperatures before and 10 min after apomorphine injection. B shows the relationships between basal temperatures and its relative change after apomorphine injection. Data were obtained in 8 rats. Each graph shows a regression line, line of no effect (hatched), coefficient of correlation, regression equation, and basal NAcc values at which regression lines crosses the line of no effect (vertical hatched half-lines).

Fig. 5.

Relative changes in temperatures in each recording location (A, °C vs. baseline) and changes in locomotion (B, counts/min) after unsignalled iv injections of apomorphine at three doses at warm ambient temperatures (29°C). Filled symbols show values significantly different from baseline ($p < 0.05$; Scheffe F-test following one-way ANOVA with repeated measures).