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Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the "shell" as compared with the "core" of the rat nucleus accumbens

(addiction/drug abuse/microdialysis/self-administration)

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ABSTRACT **The nucleus accumbens is considered a critical target of the action of drugs of abuse. In this nucleus a "shell" and a "core" have been distinguished on the basis of anatomical and histochemical criteria. The present study investigated the effect in freely moving rats of intravenous cocaine, amphetamine, and morphine on extracellular dopamine concentrations in the nucleus accumbens shell and core by means of microdialysis with vertically implanted concentric probes. Doses selected were in the range of those known to sustain drug self-administration in rats. Morphine, at 0.2 and 0.4 mg/kg, and cocaine, at 0.5 mg/kg, increased extracellular dopamine selectively in the shell. Higher doses of cocaine (1.0 mg/kg) and the lowest dose of amphetamine tested (0.125 mg/kg) increased extracellular dopamine both in the shell and in the core, but the effect was significantly more pronounced in the shell compared with the core. Only the highest dose of amphetamine (0.250 mg/kg) increased extracellular dopamine in the shell and in the core to a similar extent. The present results provide *in vivo* neurochemical evidence for a functional compartmentation within the nucleus accumbens and for a preferential effect of psychostimulants and morphine in the shell of the nucleus accumbens at doses known to sustain intravenous drug self-administration.**

Central dopamine (DA) neurotransmission is currently recognized as a common target of drugs and substances of abuse (1–3). Thus, drugs of abuse of different pharmacological classes (psychostimulants, opiates, ethanol, nicotine, and phencyclidine) increase extracellular DA concentrations in the rat striatum as estimated by brain microdialysis by different mechanisms (4–7).

On the basis of these and other findings on the behavioral effects of experimental manipulations of DA transmission, it has been hypothesized that DA is a common substrate for the abuse liability and addictive properties of drugs and substances of abuse (1–4, 7).

After nearly a decade from the formulation of this hypothesis, however, the precise role of DA in drug abuse remains elusive (7). Major difficulties in the experimental elucidation of such a role arise from the fact that DA is, in general, critical for the motor expression of motivated (including drug-motivated) behavior such that an acute impairment of its function can disrupt responding independently from an action on the primary motivational properties of the drug (7–9). It is notable however that various drugs of abuse are more effective in raising extracellular DA in the nucleus accumbens (NAc), a major terminal area of the mesolimbic DA neurons, compared with the dorsal caudate putamen, the site of termination of nigrostriatal DA neurons (4–6). In view of the role in emotion and motivation assigned to the NAc (10), these observations fit with the hypothesis that stimulation of DA transmission in the NAc plays a role in the motivational properties of drugs of abuse (7).

More recently, however, the notion itself of NAc as a unitary structure has been thoroughly revised following the observation of compartments within this area differing in neurochemical and connectional properties (11–13). On this basis two functionally different components have been distinguished: a medioventral part, the NAc "shell," strictly related to the limbic "extended amygdala," and a laterodorsal part, the NAc "core," viewed as part of the striatopallidal complex (14, 15). The two subdivisions of the NAc have been assigned different functions, with the shell playing a role in emotional and motivational functions and the core being involved in somatomotor functions (14, 15). Recently, shell/core differences in the response to stress and to drugs affecting DA transmission (reserpine, α-methyltyrosine, haloperidol, and clozapine) have been reported in postmortem studies of DA turnover (16).

Given these premises, it was of interest to compare the effect of drugs of abuse on *in vivo* DA transmission in each of these subdivisions on the NAc. Therefore, we studied the effect of amphetamine, cocaine, and morphine on extracellular DA in animals vertically implanted with two concentric dialysis probes: one aimed at the shell, and the other aimed at the core of the NAc. In view of the fact that these drugs are often abused by humans and are self-administered by animals by the i.v. route and in view of the reported differences between i.v. and i.p. administration of certain drugs of abuse—e.g., cocaine (17)—drugs were administered i.v. through chronically implanted catheters at unit doses in the range of those known to maintain i.v. drug self-administration in rats (18–22).

MATERIALS AND METHODS

Animals. Male Sprague–Dawley rats (Charles River Breeding Laboratories) (280–300 g) were housed in groups of six under standard conditions of temperature and humidity and under an artificial light–dark cycle (light from 6 a.m. to 6 p.m.). Concentric dialysis probes were prepared with AN69 fibers (Hospal Dasco, Bologna, Italy) by a modification of the method described by Di Chiara *et al.* (23). Major changes were the reduction of the dialyzing length of fiber to 1.5 mm and the assembly of the two components of the probe—i.e., dialysis fiber and silica capillary tube—before mounting it on the stereotaxic holder, thus making unnecessary the use of a tungsten mandrel to lower the fiber into the brain.

Surgery. Rats were anesthetized with 100 mg of ketamine per kg i.p. (Ketalar, Parke–Davis) and placed in a stereotaxic

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Abbreviations: DA, dopamine; NAc, nucleus accumbens.

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apparatus. The skull was exposed, and a small hole drilled to expose the dura on each side. Each rat was implanted with two probes, one on each side, aimed respectively at the NAc shell and core according to the atlas of Paxinos and Watson (24) (coordinates: shell; A = +2.0, L = 1.2, and V = 8.0; core; A = +1.2, L = 2.0, and V = 7.8).

During the same session, the right femoral vein was exposed, and a polyethylene catheter was inserted in the vein and tunneled subcutaneously to exist at the nape of the neck according to the method of Crane and Porrino (25).

Experiments were performed on freely moving rats 24 h after probes were implanted. Ringer's solution (147 mM NaCl/2.2 mM $CaCl_2$/4 mM KCl) was pumped through the dialysis probe at a constant rate of 1 μl/min. Samples were taken every 10 min and analyzed.

Analytical Procedure. Dialysate samples (10 μl) were injected without purification into an HPLC apparatus equipped with a reverse-phase column (LC-18 DB, 15 cm, 5-μm particle size; Supelco) and a coulometric detector (ESA, Coulochem II, Bedford, MA) to quantitate DA. The first electrode of the detector was set at +130 mV (oxidation) and the second at −175 mV (reduction).

The composition of the mobile phase was 50 mM NaH_2PO_4/5 mM Na_2HPO_4/0.1 mM Na_2EDTA/0.5 mM n-octyl sodium sulfate/15% (vol/vol) methanol, pH 5.50. The mobile phase was pumped with an LKB 2150 pump at a flow rate of 1.0 ml/min. The sensitivity of the assay for DA was 5 fmol per sample.

Histology. At the end of the experiment, rats were transcardially perfused with 100 ml of saline (0.9%) and 500 ml of a 4% formaldehyde/1% calcium acetate/100 mM NaCl solution. The probes were removed, and brains were cut on a Vibratome in serial coronal slices oriented according to the atlas of Paxinos and Watson (24). The sections were processed alternatively for Luxol fast cresyl violet stain and calbinding immunohistochemistry (26) by using antibodies kindly provided by C. R. Gerfen (National Institute of Mental Health, Bethesda, MD). In this manner, the location of the probes were reconstructed and referred to the atlas of Paxinos and Watson (24).

Behavior. The behavior of the rats was rated every 10 min for 20 min before drug administration and for the duration of the subsequent dialysis session according to the scale of Scheel-Krüger (27): 0 = sleeping or sedated; 1 = alert, usually not moving, occasional grooming; 2 = short-lasting locomotion and some intermittent spells of sniffing at the air; 3 = increased continuous locomotion, rearing and sniffing; 4 = stereotyped behavior consisting only of very active continuous sniffing at restricted areas of the floor with side to side head movements; and 5 = stereotyped and continuous licking or gnawing.

Drug. D-Amphetamine sulfate (MW 368.5), cocaine hydrochloride, and morphine hydrochloride, obtained from Sigma, were dissolved in saline and injected i.v. (0.2 ml/100 g) within 5 sec.

Statistics. Statistical analysis was carried out by "Statgraphics" software (5TSC-PLUS*WARE, Rockville, MD). One-way or two-way analysis of variance for repeated measures was applied to the data obtained from the serial assays of DA after each treatment. Results from treatments showing significant overall changes were subjected to post-hoc Tukey's test with significance for $P < 0.05$. Basal values were the means of three consecutive samples differing by no more than 10%.

RESULTS

Fig. 1 shows the location of the dialysis probes in the animals utilized in the present study. NAc shell placements corresponded to the anterior and medial aspect of the NAc; core placements also enchroached on the ventral part of the shell and on a transition zone of the core with the ventral caudate putamen. Of 36 rats implanted, 3 were not included in the calculations because the NAc shell probe was shown to be in the core (see below), and 2 were discarded because of failure to reach stable values of DA output.

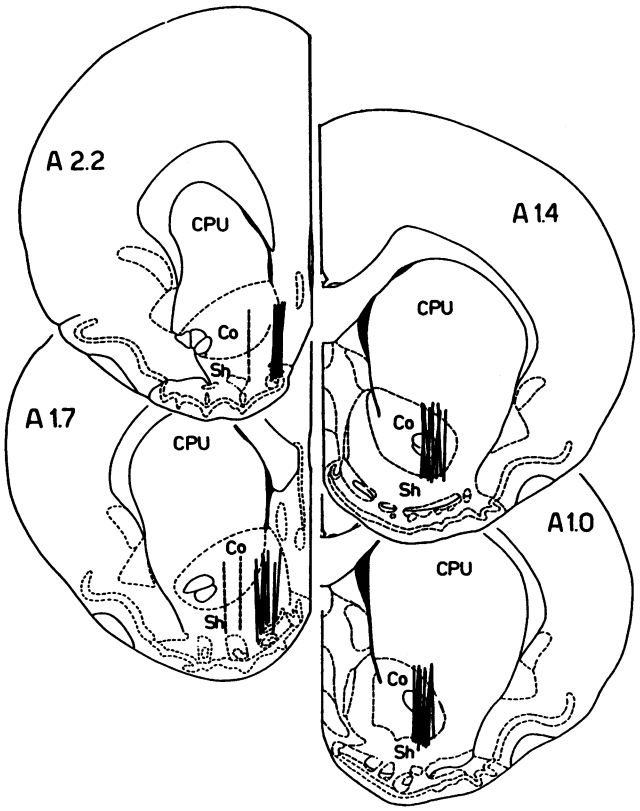

FIG. 1. Localization of dialysis probes (dialyzing portion) within the NAc and their relationship with shell and core as referred to in the atlas of Paxinos and Watson (24). Stippled lines refer to probes aimed at the shell but residing in the core.

Basal output of DA was not significantly different in the two subdivisions of the NAc, being 64 ± 6 fmol per sample in the shell and 62 ± 6 fmol per 10-min sample in the core (mean ± SEM of 22 rats).

Cocaine (Fig. 2) elicited a time-related change of DA output in dialysates from the NAc shell at both doses tested (0.5 and 1.0 mg/kg) ($F_{6,14} = 9.343$, $P < 0.005$; and $F_{6,28} = 8.596$, $P < 0.001$, respectively). Post-hoc Tukey's test revealed a significant increase of DA output over basal levels from the shell at 10, 20, and 30 min after either dose of cocaine (Fig. 2). With either dose of cocaine, the peak increase of DA in the shell occurred during the first 10 min, when maximal behavioral stimulation was obtained. Behavioral stimulation, however, did not exceed a score of 1 after 0.5 mg/kg and a score of 2 after 1.0 mg/kg. Behavior was characterized by arousal and intermittent locomotion with sniffing at the air. Cocaine elicited time-related changes in extracellular DA also in the core after doses of 0.5 and 1.0 mg/kg (maximum of +36% and +53% at 10 min) ($F_{6,14} = 14.073$, $P < 0.001$; and $F_{6,28} = 8.576$, $P < 0.001$, respectively), but this effect did not result in a significant increase over basal levels on post-hoc analysis except after the highest dose tested (1 mg/kg) at 10 and 20 min postdrug. At both doses, the changes in the shell were significantly different compared with the values in the core (0.5 mg/kg, $F_{1,40} = 10{,}252$, $P < 0.005$; 1.0 mg/kg, $F_{1,68} = 10.067$, $P < 0.005$). Post-hoc analysis revealed a significantly higher increase in the shell compared with the core at 10 and 20 min postcocaine (Fig. 2).

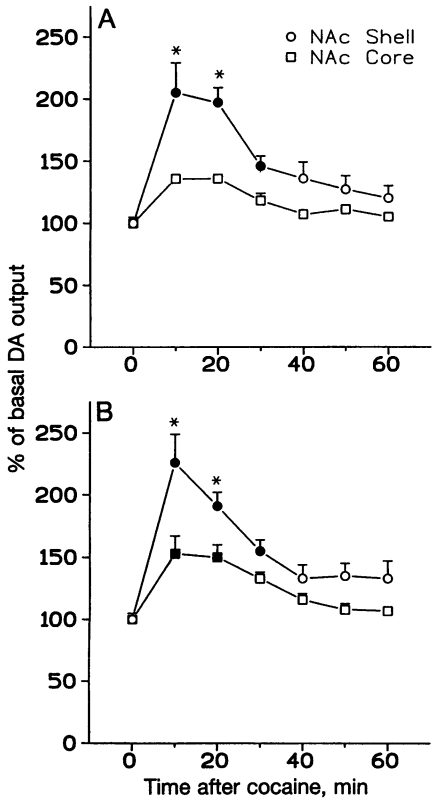

FIG. 2. Effect of i.v. cocaine on DA output in dialysates from shell and core subdivisions of the NAc of freely moving rats. (*A*) Cocaine, 0.5 mg/kg i.v. (*B*) Cocaine, 1.0 mg/kg i.v. Results are means ± SEM of the amount of DA in each sample expressed as the percent of basal values. Basal values expressed as fmol per sample were as follows: shell, 64 ± 7; core, 60 ± 6 (means ± SEM of 8 rats). Filled symbols indicate a significant increase over basal ($P < 0.05$; Tukey's test) levels. *, $P < 0.05$ as compared with the corresponding sample in the core.

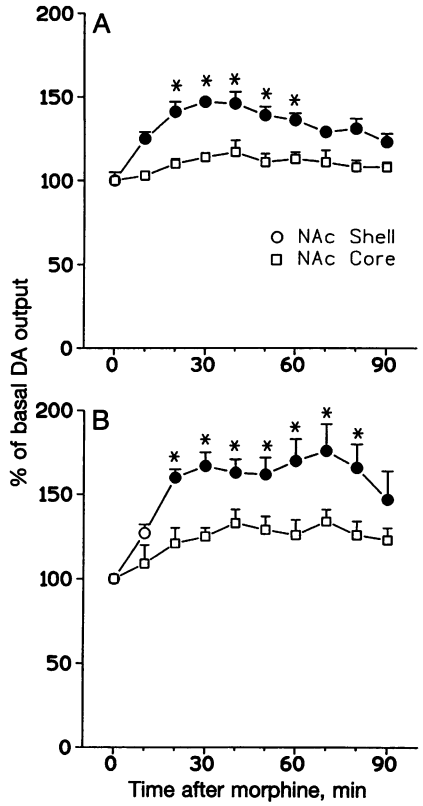

FIG. 3. Effect of i.v. morphine on DA output in dialysates from shell and core subdivisions of the NAc of freely moving rats. (*A*) Morphine, 0.2 mg/kg i.v. (*B*) Morphine, 0.4 mg/kg i.v. Results are means ± SEM of the amount of DA in each sample expressed as the percent of basal values. Basal values expressed as fmol per sample were as follows: shell, 60 ± 7; core, 62 ± 7 (means ± SEM of 8 rats). Filled symbols indicate a significant ($P < 0.05$; Tukey's test) increase over basal levels. *, $P < 0.05$ compared with the corresponding sample in the core.

Morphine (Fig. 3) elicited a time-related change in DA output from the shell at both doses tested (0.2 and 0.4 mg/kg) ($F_{9,30} = 7.197$, $P < 0.001$ and $F_{9,20} = 4.656$, $P < 0.005$, respectively), whereas it failed to change DA output from the core. Post-hoc analysis showed that the increase of DA in the shell was sustained between 10–20 min and 90 min postdrug. At both doses of morphine, stimulation of DA output in the shell was significantly higher than in the core (0.2 mg/kg, $F_{1,78} = 58{,}381$, $P < 0.001$; 0.4 mg/kg, $F_{1,58} = 30.013$, $P < 0.001$). Post-hoc analysis revealed a significantly higher output of DA from the shell compared with the core over 10–80 min postdrug. Morphine administration resulted in mild arousal with a maximum score of 1 after 0.2 mg/kg and a maximum score of 2 after 0.4 mg/kg.

Amphetamine (Fig. 4) elicited a time-related change in DA output after both doses in the shell (0.125 mg/kg, $F_{6,21} = 33.440$, $P < 0.001$; 0.256 mg/kg, $F_{6,14} = 14.980$, $P < 0.001$) and in the core (0.125 mg/kg, $F_{6,21} = 3.002$, $P < 0.05$; 0.2 mg/kg, $F_{6,14} = 9.800$, $P < 0.001$). Post-hoc analysis revealed a significant increase over basal levels between 10 and 30 min both in the shell and in the core after both doses of the drug. The peak increase of DA was observed between 10 and 20 min in the shell, while in the core, the effect was shallow between 10 and 50 min. A significant difference in DA output in the shell with respect to the core was observed following administration of 0.125 mg of amphetamine per kg ($F_{1,54} = 8.262$, $P < 0.01$), whereas no difference between the shell and the core was obtained with 0.250 mg/kg ($F_{1,40} = 0.232$, $P > 0.63$). Post-hoc analysis showed a significantly higher output of DA in the shell compared with the core after a dose of 0.125 mg of amphetamine per kg but not after an amphetamine dose of 0.25 mg/kg. Amphetamine administration resulted in arousal, sniffing at the air, and intermittent locomotion without stereotypies (score 2) after 0.125 mg/kg and locomotion with intermittent sniffing directed toward the floor (score 3) after 0.250 mg/kg.

In the three rats in which the probe aimed at the shell was placed in the core, neither cocaine (0.5 mg/kg) nor morphine (0.2 and 0.4 mg/kg) significantly changed DA output with respect to basal levels.

DISCUSSION

The present study shows that acute i.v. administration of amphetamine, cocaine, or morphine preferentially increases extracellular DA output in the shell subportion of the NAc compared with the core.

Mediolateral differences in the response of the NAc to subcutaneous administration of amphetamine were previously reported by us (23); however, in that study, the use of dialysis probes with a 2.2-mm (rather than 1.5-mm) exposed surface made the assignment of the observed differences to a shell/core subdivision difficult. Moreover, that study did not directly compare in each animal shell with core probe placements (23).

Evidence for a functional hetereogeneity in the NAc in response to psychostimulants (cocaine and amphetamine) has been recently provided by a 2-deoxyglucose study showing that acute i.v. administration of psychostimulants preferentially increases rates of glucose utilization in the NAc shell compared with the core of freely moving rats (28). Such correspondence between changes in glucose utilization and changes in extra-

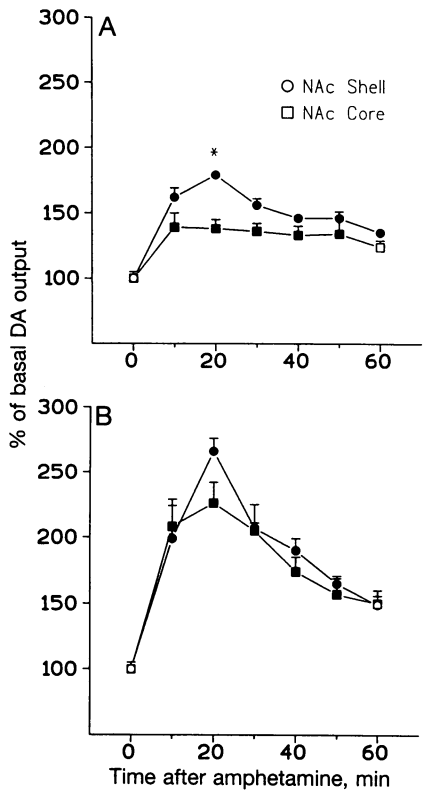

FIG. 4. Effect of i.v. amphetamine on DA output in dialysates from shell and core subdivisions in the NAc of freely moving rats. Results are means ± SEM of the amount of DA in each sample expressed as the percent of basal values. Basal values expressed as fmol per sample were as follows: shell, 68 ± 7; core, 64 ± 7 (means ± SEM of 8 rats). Filled symbols indicate a significant ($P < 0.05$; Tukey's test) increase over basal levels. *, $P < 0.05$ compared with the corresponding sample in the core.

cellular DA elicited by psychostimulants in the NAc might be an aspect of a more general relationship between DA transmission and local brain energy metabolism. In relation to this, the apparent correspondence between the ability of psychostimulants to preferentially increase extracellular DA concentrations in the NAc compared with the dorsal caudate putamen (4) and their ability to selectively stimulate glucose metabolism in the NAc at low doses and in the dorsal caudate putamen at high doses is notable (29, 30). The reason why stimulation of DA transmission in the striatum should be associated with activation of local glucose metabolism is obscure and should be further investigated by combined 2-deoxyglucose/microdialysis studies.

It is notable that in the present study selective or preferential increases of extracellular DA in the shell were obtained at i.v. doses of drugs that are known to sustain self-administration behavior in rats (18–22). It is also important to point out that a preferential effect in the shell does not seem related to a specific neurochemical mechanism of drug action. Thus, increased DA output in the shell was obtained with the DA reuptake blocker cocaine; the DA releaser amphetamine, which also inhibits the firing of DA units; and the opiate morphine, which releases DA by stimulating the firing activity of DA neurons (2).

The increase in extracellular DA in the NAc core, when present, was weaker and limited to the phase of peak action of the drug, with the exception of the highest dose of amphetamine (0.250 mg/kg), which increased extracellular DA to a similar extent in the shell and in the core. It appears, therefore, that drugs of abuse when given by a route, such as the i.v. one, that corresponds to that commonly used for self-administration, primarily stimulate DA transmission in the NAc shell, whereas activation of DA transmission in the NAc core occurs only at higher doses. At the doses which elicited preferential or selective increase of extracellular DA in the NAc shell, no stereotypy (sniffing, licking, or gnawing) and only mild arousal was observed. Since stereotypies are elicited by high doses of psychostimulants which fully increase extracellular DA in the dorsal caudate putamen (31), it is possible that stereotypies are related to stimulation of DA transmission in the NAc core as well as in the dorsal caudate putamen as parts of the striatopallidal system (15).

A notable observation of the present study was the similarity of the range of the increase in extracellular DA in the NAc shell after i.v. administration of amphetamine or cocaine at doses that maintain self-administration in the rat. This contrasts with the large (5- to 10-fold) difference in the increase of extracellular DA elicited by amphetamine as compared with cocaine when these drugs are administered i.p. at doses which induce a similar degree of motor stimulation (31). These differences can be explained as due in part to pharmacokinetic differences between i.v. and i.p. cocaine (17) and in part to the much higher i.p. and s.c. doses of amphetamine commonly utilized in studies of motor behavior (31) compared with those which maintain i.v. self-administration.

The present results demonstrate the remarkable topographic specificity of the action of low doses of drugs of abuse on the DA system and in turn confirm previous suggestions on the need to meet strict topographic criteria within the NAc to obtain functionally and behaviorally meaningful changes in DA transmission after administration of drugs of abuse (32). Failure to observe differences in the DA-stimulating properties of amphetamine between the dorsal caudate putamen and the NAc (33) can be explained, in the light of the present results, as due to failure to confine the placement of NAc probes to the shell. In the case of opiates, the present results would predict that failure to target NAc probes precisely to the shell might even result in failure to observe change in DA release in rats responding for opiate self-administration, as in the case of a recent study by Hemby *et al.* (34).

The observation that DA transmission in the NAc responds to acute i.v. administration of drugs of abuse in a topographically heterogeneous manner suggests that the generic notion of the NAc as a preferential target of drugs of abuse may not be accurate, as it should be specifically referred to its shell and core subdivisions. This heterogeneity might in turn reflect different roles of DA in behavior.

At least two separate properties can be attributed to DA as to its role in behavior: a motivational property, related to its ability to positively influence motivational state, and an activational property, related to its ability to facilitate the emission of motor responses. Interaction between these two properties would result in the incentive effects that are characteristic of stimulation of DA transmission (7). On the basis of anatomical data, one might speculate that the motivational properties of DA are encoded in the NAc shell and processed through reciprocal interconnections within the "extended amygdala" to be expressed via projections to the lateral hypothalamus, central gray, and mesopontine tegmentum (14, 15). Through this highly integrated network, DA transmission in the NAc shell might affect arousal, visceral functions, and energy balance, thus influencing motivational state. Activational properties of DA, instead, would be encoded in the core of the NAc and expressed through the traditional ventropallidal system. If the shell of the NAc is a transition area of the extended amygdala, which includes DA-rich regions as the central amygdala and bed nucleus of the stria terminalis (15), these areas might turn out to be among the most sensitive targets to the action of drugs of abuse. These hypotheses are testable by correlating changes in DA transmission in the shell and core of the NAc and in specific subdivisions of the

extended amygdala to the behavioral effects of psychostimulants.

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