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Individual Differences in Behavioral Measures: Correlations With Nucleus Accumbens Dopamine Measured by Microdialysis

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BRADBERRY, C. W., R. J. GRUEN, C. W. BERRIDGE AND R. H. ROTH. *Individual differences in behavioral measures: Correlations with nucleus accumbens dopamine measured by microdialysis.* PHARMACOL BIOCHEM BEHAV **39**(4) 877–882, 1991.—Rats were placed in one of two novel test environments for behavioral observation. In one, exploratory behavior (assessed by hole pokes) and locomotion were assessed during a 10-min test session. In the other, the chewing of varied objects on the cage floor was rated over a 20-min session. Within 2–18 days, animals were anesthetized and microdialysis probes were implanted into the nucleus accumbens for measurement of basal and d-amphetamine-stimulated levels of dopamine (DA). These measures were then correlated with the individual behavioral rating collected earlier from the drug-free animals. We found a significant correlation between duration of exploratory behavior and amphetamine-induced DA release. Locomotor activity did not correlate with either basal or amphetamine-stimulated DA release. Duration of chewing episodes correlated with basal levels of DA, as well as with amphetamine-induced DA release. Our studies indicate that differences in the dopaminergic responsivity of the nucleus accumbens (or other circuitry influencing nucleus accumbens DA function) may contribute to individual differences in certain behaviors displayed by the animals when placed in a novel environment.

Dopamine release Exploratory behavior Microdialysis Amphetamine Locomotion Novelty
Chewing behavior Individual differences

IN rodents, the behavioral response elicited upon exposure to novelty generally involves a combination of locomotor activity and focused investigation (sniffing, licking, and manipulation with forepaws) with the specific responses observed depending on the environment. In general, there exists a wide degree of variability across animals in the relative amount of each possible individual behavioral component observed.

The neural systems regulating the behavioral response to novelty, and the factors that account for the variability in this response across animals are poorly understood. Motor behavior (both locomotion and other) is thought to be dependent on central dopaminergic systems. For example, reports based on 6-hydroxydopamine lesions (14,33) indicate that the dopaminergic innervation of the nucleus accumbens (NA) plays a necessary role in the normal function of exploratory behavior and locomotion. Systemic administration of psychostimulants such as amphetamine, which cause the release of DA (among other actions), increase both exploratory behavior and locomotion (19), and at least some of these effects are due to actions at the NA as shown by microinfusion studies (27).

A dopaminergic involvement in oral movements is also possible, though most work has focused on stereotypies induced by psychostimulants (7, 21, 30), and so-called purposeless chewing induced by long-term administration of neuroleptics (11, 17, 29).

In the present report, we have studied exploration (as assessed by hole pokes), locomotion, and chewing, upon exposure of rats to novel environments. We wished to determine the extent to which variation in the nucleus accumbens dopaminergic system may underlie individual variability in the expression of these three behaviors. To test this, we correlated the behavioral response of individual subjects to a novel environment with microdialysis measures of basal and amphetamine-induced DA release in the anesthetized animals 2–18 days following the behavioral testing.

METHOD

Locomotion and Exploration

Subjects consisted of two groups of male Sprague-Dawley rats (250–275 g upon arrival from CAMM, Wayne, NJ, n = 17 in each group). Subjects were housed in a soundproof chamber (lights on 0600, off 1800) upon arrival in groups of two or three,

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and were allowed to acclimate to the light-dark cycle before exploratory and locomotor behavior were assessed using a 4-hole board apparatus as previously described (15). The apparatus was a dark grey box (floor dimensions: 66 × 54 cm; walls: 35 cm) with a single hole in each wall (2.5 cm in diameter). The floor was sectioned into a 3 × 3 grid by one inch lines painted on the floor. All animals were tested without any drug treatment. The test session was between 1830 and 2100 hours to avoid errors attributable to variations in motor activity and head-dipping at different points during the activity cycle (13). The test room was darkened and the apparatus dimly illuminated with a red light sufficient to permit videotaping of the session. To ensure that the ratings of locomotor behavior (No. line crossings) were accurate, two separate raters viewed the videotaped sessions independently. The interrater reliability, as reflected by the Pearson correlation between raters was .960, indicating a reliable measure of locomotor activity was made.

Each test session was 10 min long. Five variables were scored. These included 1) the time elapsed before the first head dip; 2) the total number of head dips made into any of the four holes; 3) the total time spent head dipping; 4) the total number of different holes into which the animal dipped its head at least once (range 1–4); 5) the total number of lines crossed (as an animal moved from one grid to another), taken as a measure of locomotor activity.

The mean duration of exploratory behavior was calculated as the total time spent head dipping divided by the number of head dips. A head dip was scored if the animals's eyes were not visible when it placed its head into a hole.

Chewing Behavior

These observations were made on a separate group of animals (n = 12). Subjects were individually placed into a novel, well-illuminated plastic cage (floor 56 × 34 cm; walls 18 cm). Various objects were scattered on the floor of the cage such as small bits of wood, cotton swabs, plastic foam, aluminum foil, and food pellets. The number of well-defined chewing episodes over the 20-min test session were noted and timed, and a mean duration per episode calculated. The animals did not appear to favor any of the various objects present, and treated the food pellets the same as the nonedible objects.

Microdialysis

Concentric-style microdialysis probes were constructed as previously described (4) using Cuprophan (Enka, West Germany) hollow fibers (300 μm i.d., 330 μm o.d.) housed in a section of 23-gauge stainless steel tubing. The fiber extended approximately 2.0–2.5 mm beyond the tip of the tubing exposing an active surface of 1.5–2.0 mm. Perfusion buffer (in mM: KCl 2.4, NaCl 137, $CaCl_2$ 1.2, $MgCl_2$ 1.2, NaH_2PO_4 0.9, Na_2HPO_4 1.4, ascorbic acid 0.3, pH 7.4) was pumped through a section of vitreous silica tubing (150–170 μM o.d.) which extended to the tip of the hollow fiber.

Animals were anesthetized with chloral hydrate (400 mg/kg IP), and placed in a stereotaxic apparatus in the flat skull position. The coordinates to which the tip of the dialysis probe was lowered vs the top of the skull at bregma were +1.7 A, 1.3 L, and 8.3 V, corresponding to the nucleus accumbens (23). The probe was always placed into the right hemisphere, avoiding the possible additional variability due to differences between the left and right hemispheres. Body temperature was maintained using a heating pad and monitored by a rectal temperature probe. Supplemental chloral hydrate was given as needed in order to maintain deep anesthesia. Once a stable baseline was attained (approximately four hours after probe placement), 3 mg/kg *d*-amphetamine-sulphate was administered IP. While stable at this point, some previous studies suggest that basal release is not entirely calcium dependent (34). Following each experiment, the brain was removed and stored in formalin for later sectioning and staining for verification of probe placement in the nucleus accumbens.

Determination of DA was accomplished using liquid chromatography with electrochemical detection (4, 5, 20). Ten × 2.1 mm i.d. columns were packed with 3-micron C-18 particles (ODS2 material from Phase Separations, Norwalk, CT). Mobile phase used for the experiments described herein was 0.05 M dibasic sodium phosphate, 350 mg/liter sodium octanesulfonate, 0.1 mM disodium EDTA, 300 microliters/liter triethylamine, and 150 ml/liter methanol, pH 5.0. A laboratory constructed potentiostat was used to apply a potential to the amperometric glassy carbon working electrode (Bioanalytical Systems, West Lafeyette, IN) and convert the resulting current to a voltage for output to a strip chart recorder. A pneumatic displacement fluid pump was used for pumping mobile phase through the column, allowing for extremely smooth flow. The routine limit of detection attained with this system is 2–3 fmol injected in a volume of 40 microliters.

The microdialysis probes were calibrated in vitro prior to use by placing in perfusion buffer with 0.1 micromolar DA added; perfusion buffer was pumped through the probes at 2 microliter/min at room temperature. The calibration was done in order to permit normalization of differences between the probes (not to estimate an actual extracellular DA concentration). Basal levels of DA were calculated for each animal as the mean of the three (recovery adjusted) DA dialysate levels preceding amphetamine administration. DA levels were adjusted for probe recovery by dividing the absolute fmol/microliter by the fractional recovery for that probe. Peak DA levels were the maximum corrected values during a sampling period following amphetamine administration. An alternative method to observing peak DA would be to use the area under the release curve. This method yields essentially the same correlations with peak DA and behaviors as those presented below.

Data Analysis

Data were analyzed using correlational techniques. Pearson's correlations were computed for basal DA values and the various behavioral parameters to determine any relationship and also between all the various behavioral measures in each experiment. Partial correlations were used in analyzing the relationship between behavioral parameters and peak DA levels, controlling for baseline levels of extracellular DA (6). This procedure corrects for variability in peak DA associated with basal DA levels.

RESULTS

Locomotion and Exploration

Subjects consisted of two groups of animals. Results for both groups yielded statistically significant correlations, thus data from the two groups were collapsed for this presentation.

In the behavioral assessment, all subjects obtained a score of 4 on the number of different holes explored (range 1–4); thus this variable was excluded from further analysis. Table 1 presents the mean and standard errors of all the biochemical and behavioral variables. Table 2 summarizes all the correlations between the behavioral variables. Significant correlations were obtained between total duration and mean duration, total duration

TABLE 1

SUMMARY OF MEAN BIOCHEMICAL AND EXPLORATION/LOCOMOTION VALUES (n = 34)

Variable	Mean	SEM
Total number holes	21.8	± 1.2
Total duration (s)	58.9	± 5.1
Mean duration (s)	2.6	± 0.1
Latency (s)	47.4	± 5.0
Total number crossings	177	± 5.7
Basal DA (fmol/μl)	19.6	± 2.4
Peak DA (fmol/μl)	169	± 18

and total No. holes, and mean duration and total No. holes. A significant negative correlation was found between the total No. line crossings and mean duration.

Table 3 presents data relating the measures of exploratory and locomotor behavior to the biochemical measurements. Basal DA did not significantly correlate with any of these behavioral measures, while peak DA (controlling for basal DA) significantly correlated with total duration ($R = .358$, $n = 34$, $p = 0.038$), as well as mean duration ($R = .406$, $n = 34$, $p = 0.017$) of exploration. Figure 1 is a scatter diagram illustrating the correlation between mean duration of exploration and peak DA. Peak DA residuals are plotted in this figure. These values represent the difference between actual peak DA, and peak DA calculated by the least squares best fit line for the correlations of peak DA and basal DA. Thus this value represents variability not predicted by basal DA. Peak levels of DA were found to correlate very highly with basal DA levels obtained from the same animals ($R = .735$, $n = 34$, $p < 0.001$).

Chewing Behavior

Table 4 presents the mean values and standard errors for the behavioral and biochemical measures. The Pearson correlations between the behavioral parameters are as follows: the total duration of chewing correlates with the mean duration per episode ($R = .636$, $n = 12$, $p = 0.026$) and with the number of episodes ($R = .647$, $n = 12$, $p = 0.023$), however, the mean duration did not correlate with the number of episodes ($R = -.156$, $n = 12$, $p = 0.629$).

Basal DA levels correlated significantly with mean duration of chewing, in contrast to the locomotor/exploration study in which basal DA did not correlate with any of the behavioral parameters. Figure 2 illustrates the Pearson correlation between basal DA and mean duration of chewing. The partial correlation between peak DA and mean chewing, like that between peak DA and mean duration exploration, was significant, and is presented in Fig. 3, controlling for basal DA. As in the exploration/locomotion groups, basal DA correlated with peak DA ($R = .672$, $n = 12$, $p = 0.017$).

TABLE 2

PEARSON CORRELATIONS BETWEEN BEHAVIORAL MEASURES (n = 34)

	T. Dur.	M. Dur.	Latency	Cross
T. Holes	.788	.321	−.0075	.0066
	$p < 0.001$	$p = 0.064$	$p = 0.966$	$p = 0.970$
T. Dur.		.821	.0162	−.265
		$p < 0.001$	$p = 0.928$	$p = 0.130$
M. Dur.			.0548	−.379
			$p = 0.758$	$p = 0.026$
Latency				.128
				$p = 0.470$

TABLE 3

CORRELATIONS BETWEEN EXPLORATION/LOCOMOTION AND DA MEASURES (n = 34)

	Basal DA (Pearson correlation)	Peak DA (partial correlation)
T. Holes	−.0162	.214
	$p = 0.927$	$p = 0.225$
T. Dur.	−.0264	.358
	$p = 0.882$	$p = 0.038$
M. Dur.	.0342	.406
	$p = 0.848$	$p = 0.017$
Latency	−.111	.096
	$p = 0.532$	$p = 0.564$
Cross	−.0169	−.201
	$p = 0.924$	$p = 0.255$

DISCUSSION

In this study, we wished to determine if inherent differences in the dopaminergic innervation of the nucleus accumbens between individuals (due to genetics or environment) influence behavior. We addressed this question by looking for differences in basal and amphetamine-stimulated extracellular DA, following behavioral testing, using microdialysis. These biochemical measures were then correlated with the previously obtained behavioral data from the same individuals. By carrying out the microdialysis experiments in the anesthetized animal at a later time, we were able to eliminate any variability present in the testing environment, and more importantly, the stress of surgery

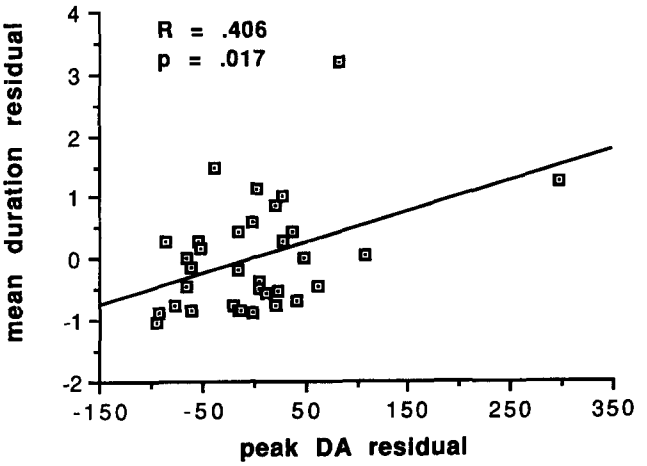

FIG. 1. Partial correlation of peak DA, controlling for basal DA, with mean duration of exploration, n = 34 animals.

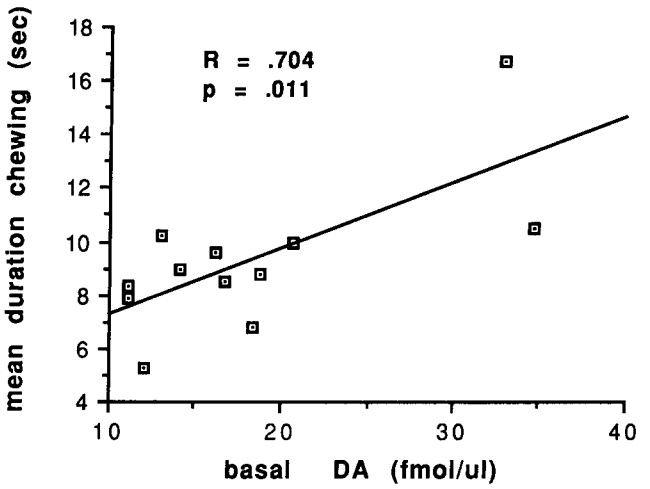

FIG. 2. Pearson correlation of basal DA with mean duration chewing behavior, n = 12 animals.

and harnessing necessary to carry out the experiments in an awake animal. The dopamine system has been shown to be extremely sensitive to stress, undergoing long-term alterations including changes in sensitivity to amphetamine (2). While simultaneous measurement of DA levels and behavior in the awake animal would provide the strongest evidence of functional linkage, it is also possible that the stress of surgery would induce changes in the dopaminergic system large enough to obscure subtle preexisting differences.

Our results indicate that individual variations in the dopaminergic innervation of the nucleus accumbens correlate with, and hence may impact upon behavior expressed by animals in a novel environment. Differences observed at the time of the behavioral testing several days prior to microdialysis experiments were later reflected either by the amount of DA released by a standard dose of amphetamine (exploration), or by both basal DA levels as well as amphetamine-induced DA release (chewing). In the case of exploratory behavior, it is interesting that the basal levels of DA do not correlate at all with the behavioral measures, but do correlate with peak DA levels. This suggests

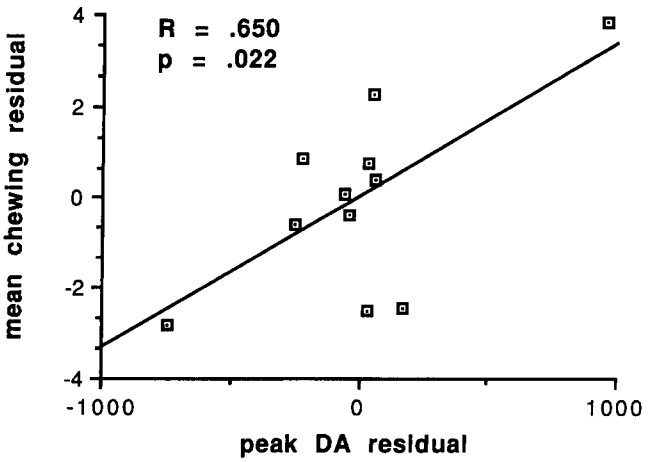

FIG. 3. Partial correlation of peak DA with mean chewing, controlling for basal DA, n = 12 animals.

TABLE 4

SUMMARY OF MEAN BIOCHEMICAL AND CHEWING BEHAVIOR VALUES (n = 12)

Variable	Mean	SEM
Episodes	14.2	± 1.6
Total duration (s)	130	± 17
Mean duration (s)	9.3	± 0.8
Basal DA (fmol/μl)	18.3	± 2.3
Peak DA (fmol/μl)	355	± 150

that a biological variable which influences the exploratory behavior displayed by animals in our test apparatus also affects the extent to which amphetamine can induce DA release, yet has no impact on basal DA release in the anesthetized animal. The fact that basal release correlated very highly with amphetamine-induced release indicates that there are common factors which influence both basal and peak DA.

In contrast to exploratory behavior, chewing behavior correlated with both basal DA and amphetamine-stimulated DA. This suggests that novelty-associated chewing is influenced by some factor(s) associated with both basal DA and peak DA, as opposed to exploratory behavior, which is influenced by a factor which appears to regulate peak DA, but not basal DA.

There have been other recent reports on the investigation of individual behavioral and biochemical differences and the actions of amphetamine (16, 21, 22, 24, 26, 30, 32). Piazza et al. (26) divided subjects into groups which were high responders or low responders with respect to locomotion in a novel environment. Significant differences between the locomotor response of the two groups was seen with subsequent amphetamine administration. Because locomotor activation induced by amphetamine appears to be linked to release of DA in the NA (27,31), it was expected that we would see a positive correlation between locomotion and subsequent DA release in NA. Interestingly, we saw a nonsignificant trend in the opposite direction. However, nosepoking could be seen as a competing behavior with locomotion, and the apparatus used by Piazza et al. (26) did not have holes which the animals could interact with. Because our behavioral testing apparatus is different, and our release studies were carried out in the anesthetized animal, it is difficult to compare the results from the two studies. In their more recent work, this group has shown that there are differences in DA metabolism in both the prefrontal cortex and basal ganglia depending on whether animals fall into a high- or low-responding group with respect to locomotor activation by amphetamine (24).

Segal and Kuczenski have also explored some possible biochemical correlates to individual differences in behavioral responsiveness to amphetamine. While slightly different from our work in that we were observing spontaneous as opposed to drug-induced behavior, there are some intriguing comparisons to be made. They demonstrated (30) substantial individual differences in behavioral response to an intermediate dose of amphetamine (1.75 mg/kg free base, SC). When split into two subgroups, differences in whole tissue measures of DA and its metabolites were seen in response to systemic amphetamine in the NA and frontal cortex. In another study, Kuczenski and Segal (21) performed microdialysis measures in awake unrestrained animals simultaneously with behavioral observations and amphetamine administration. In this case the microdialysis probe was sampling the caudate-putamen. Significant correlations between behavior and DA levels were seen during certain phases of the behavioral response, though it was suggested that mismatches in the tem-

poral patterns of the behavior and DA release indicated more complex interrelations involving other neurotransmitters, e.g., 5-HT, and altered receptor sensitivity. An intriguing difference between the results of Segal and Kuczenski and our own was the lack of correlation between basal DA and amphetamine-induced increases seen by these authors. We consistently found a significant correlation between basal DA and amphetamine-stimulated levels. Whether this is a result of anesthesia or differences between the caudate-putamen and NA is currently being investigated.

There are interesting similarities between amphetamine administration, and one feature of the exposure to novelty, namely the apparent stress undergone by the animal. Exposure to novelty has been shown to be a significant stressor (3,10) and stress has been shown to elevate DA release from the nucleus accumbens (1, 8, 9, 12). Also, daily exposure to stressful conditions will enhance the motor stimulant effect of amphetamine (2,28), believed to be mediated by DA release. If the release of DA in response to a stress challenge is increased by prior stress as has been suggested (18), the alterations in regulatory control of DA neuronal firing responsible, e.g., changes in somatodendritic release of DA (18) might also influence amphetamine-induced DA release. The stress potentiation of amphetamine-induced hyperlocomotion (2) and rotational behavior (28) suggests this is possible, as does the stress-induced increase in acquisition of amphetamine self-administration (25). The differences in peak DA levels between the two groups of animals in our study could reflect differences in the level of stress induced by the different behavioral paradigms. One paradigm was carried out in a brightly illuminated cage, while the other was conducted in a darkened setting.

In summary, we have demonstrated significant correlations between behavioral measures in rats, and measurements of basal, and amphetamine-stimulated extracellular DA in the nucleus accumbens. These results appear to suggest that individual differences in the behaviors observed have some physiological basis in variations of nucleus accumbens DA function.

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