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Differential Behavioral Responses to Dopaminergic Stimulation of Nucleus Accumbens Subregions in the Rat

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SWANSON, C. J., S. HEATH, T. R. STRATFORD AND A. E. KELLEY. *Differential behavioral responses to dopaminergic stimulation of nucleus accumbens subregions in the rat.* PHARMACOL BIOCHEM BEHAV **58**(4) 933–945, 1997.— The following experiments investigated the behavioral response to local microinfusion of dopamine (DA) and selective DA agonists into the core and shell subregions of the nucleus accumbens. Rats were implanted with chronic indwelling cannulae aimed at these subregions. Two experiments were conducted. In experiment 1, the response to DA (0, 2, 5, 10 μg/0.5 μl/side), the D-1 agonist SKF-82598 (0, 0.1, 1.0 μg), the D-2/3 agonist quinpirole (0, 1, 5, 15 μg) and the D-3 preferring agonist pramipexole (0.1, 1.0, 10.0 μg) was examined in photocell activity cages. Locomotor (horizontal) and rearing (vertical) activities were measured. DA and SKF-82958 induced relatively greater increases in activity following stimulation of the shell as compared with the core. Quinpirole induced a dose-dependent suppression of activity after infusion into both sites, although the core was more sensitive to the suppressive effect than the shell. Pramipexole induced time-dependent, biphasic effects that were small in magnitude and did not differentiate between site. In experiment 2, an observation procedure was used to record behaviors (locomotion, rearing, feeding, drinking). Dopamine (0, 2, 10 μg) elicited greater increases in rearing and feeding behavior in the shell than in the core. SKF-82958 (0, 0.75 μg) enhanced locomotion and rearing to a similar extent in both subregions in this test, whereas a mixture of a low dose (0.25 μg) of the D-1 and D-2 agonists selectively induced behavioral activation in the shell. In contrast to the results in the activity cage test, quinpirole (0, 1, 5 μg) increased motor activity at the lower dose when infused into the shell but not into the core. No alterations in feeding were observed following infusion of selective agonists, and no changes in drinking were found with any of the treatments. In summary, the shell appears to be relatively more sensitive to the motor activating effects of DA agonists than the core. Moreover, circuits associated with shell may be preferentially involved in feeding. © 1997 Elsevier Science Inc.

Nucleus accumbens Locomotor activity Striatum Dopamine receptors Feeding behavior

THE NUCLEUS ACCUMBENS, located within the ventral striatum, is conceptualized as a neural interface where information processing within corticolimbic structures is integrated and relayed to the motor system (44). It is thought to play a critical role in the selection and execution of adaptive behaviors. For example, neurotoxic lesions of this structure disrupt exploratory behavior, spatial and locomotor activity, complex instrumental responses and certain motivationally specific behaviors such as feeding, food hoarding, sexual and adjunctive behaviors (3,5,35,58,60). The nucleus accumbens also has been implicated as a brain structure associated with the motor activating and reinforcing effects of psychostimulant drugs (20,36,78). Many drugs that are self-administered by animals and abused by humans, such as cocaine and amphetamine, cause a marked increase in extracellular dopamine (DA) within this structure (20,28).

Administration of dopaminergic agonists to rats increases the expression of many behaviors including locomotion, rearing, grooming and oral stereotypies (4,17,22,31,46,52). In general, infusion of DA or DA agonists into the nucleus accumbens enhances coordinated motor activity and appetitive behaviors, whereas injection of these compounds into dorsal

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or lateral striatal sites elicits motor stereotypies (9,15,18,65). The recent extensive characterization of the D-1 (D-1, D-5) and D-2 (D-2, D-3, D-4) families of DA receptors (12,63,67, 68,71) has allowed a more thorough investigation of the mechanisms underlying DA-induced behaviors. It is well established, for instance, that stimulation of D-1-like receptors activates adenylate cyclase and increases cyclic AMP production. Conversely, D-2-like receptors have been reported to either inhibit adenylate cyclase or to have no effect on its activity (33,66). Many studies have evaluated the effects of selective D-1 and D-2 agonists on behavior. D-2 agonists have been shown to elicit locomotion and stereotypies (9,22,24,45,59), and they serve as a positive stimulus in place conditioning and self-administration paradigms (29,62,77,80). In fact, for years it was thought that D-2 receptors were principally responsible for most of the classic behavioral effects resulting from increased dopaminergic transmission. However, D-1 agonists also have been shown to induce DA-like effects, such as locomotion, grooming and oral dyskinesias (10,11,34,40,45,46), and recent studies have suggested a critical role for D-1 receptors in reinforcement (13,47,56). Currently, it is generally accepted that concurrent stimulation of D-1 and D-2 receptors is necessary for the full expression of DA-like behaviors (10,47,74,76). This synergistic interaction appears to result from an "enabling" mechanism whereby D-1 stimulation is required for full expression of D-2-mediated effects (74,75). Moreover, studies with selective antagonists also have shown that both receptor subtypes are involved in the rewarding and activating effects of stimulants (33,57,79).

Most previous studies investigating the effects of DA agonists in the nucleus accumbens (9,16,22,24,41,54) have not taken into account the recent evidence for functional and anatomical heterogeneity within this structure. Indeed, an important emerging concept regarding the nucleus accumbens is that of compartmentalization, which postulates a functional dichotomy between the more rostrally located "core" and the more caudomedially located "shell" subregions of this structure (82). This dichotomy is based on anatomical, behavioral, neurochemical and electrophysiological data. For example, anatomical studies have shown that the core subregion preferentially sends efferent projections to motor-related structures such as the globus pallidus and the dorsolateral ventral pallidum, whereas the shell projects primarily to more limbic-related structures such as the ventral tegmental area, lateral hypothalamus, ventromedial ventral pallidum and brainstem autonomic centers (3,19,25,26). Immunohistochemically, the core and shell subterritories can be delineated based on the distribution of substance P, enkephalin, and calcium-binding protein (72). It has also been shown that the shell contains greater concentrations of DA than the core (19,25,73). Moreover, the shell is more sensitive to stress in terms of DA turnover (19), and studies with repeated administration of cocaine have indicated that the shell may be more affected by these treatments than the core (51,53). In addition, infusion of a DA agonist into the shell, but not the core, elicits oral motor behavior such as chewing, sniffing and grooming (55). Electrophysiological analysis of the two main subregions has demonstrated differences in basal membrane properties and in the response to DA (49,50).

Such variation between the nucleus accumbens subterritories seems to imply functional differentiation in the modulatory effects of DA. The purpose of the present experiments was to investigate possible differences between core and shell subregions of the nucleus accumbens in relation to behavioral effects of local infusion of DA agonists. Compounds chosen for this study were the full, selective D-1 receptor family agonist SKF-82958 (48), the selective D-2/3 family agonist quinpirole (63), the D-3-preferring agonist pramipexole (14) and the endogenous transmitter DA, which has a high affinity for both receptor subtypes. Main behaviors measured were locomotion and rearing. However, because recent studies have suggested that the shell may have a unique role in ingestive behavior (38), feeding behavior was also evaluated in the second study.

EXPERIMENTAL PROCEDURES

Animals and Surgery

A total of 152 male rats (Harlan–Sprague–Dawley, Indianapolis) weighing 275–300 g upon arrival were used in the present study. Subjects were housed in a temperature-controlled environment with a 12-h light–dark cycle (light period was 6:00 AM–6:00 PM). Food and water were available ad libitum. All animals were handled daily to reduce stress. Several days after arrival, animals were anesthetized with a ketamine/xylazine mixture (100 mg/kg ketamine, 9 mg/kg xylazine) and placed in a stereotaxic frame. Stainless steel guide cannulae (23 gauge, 10 mm) were implanted bilaterally and aimed at the nucleus accumbens core or shell subregion. Coordinates (with toothbar set at 5.0 mm above the interaural line) for core placements were (in mm) +3.3 from bregma (anterior-posterior axis; A-P), ±1.9 from midline (lateral-medial axis; L-M) and −5.3 from skull (dorsal-ventral axis; D-V) for the guide cannulae. Shell coordinates were +3.3 A-P, ±1.0 L-M and −5.3 D-V. A self-curing dental cement, light curable resin (Dental Supply Co. of New England, Boston, MA) and stainless steel screws were used to secure guide cannulae to the skulls of the animals. Wire stylets were placed in the guide cannulae to prevent occlusion. Animals were allowed at least a 3-day recovery period following surgery, before the beginning of behavioral testing.

Drugs and Microinfusion

The drugs used in this study were DA hydrochloride (Sigma, St. Louis, MO), (±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide (D-1 agonist; SKF-82958, Research Biochemicals International, Natick, MA), and trans-(−)-4aR-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H-pyrazolo [3,4-g] quinoline hydrochloride (D-2/3 agonist, quinpirole; Research Biochemicals) and (S)-2-amino-4,5,6,7-tetrahydro-6-propylamino-benzathiazol-dihydrochloride (D-3 agonist, pramipexole, gift of Pharmacia & Upjohn, Kalamazoo, MI). All drugs were dissolved in 0.9% (isotonic) sterile saline.

Infusions were made with stainless steel injector cannulae (30 gauge), extending 2.5 mm below the guide, and were attached to a Harvard microdrive pump apparatus via polyethylene tubing (PE-10). In all cases, the injectors reached a final D-V coordinate of −7.8 mm from skull. During the procedure, the animals were gently wrapped in a small towel and infused bilaterally with a volume of 0.5 μl at a rate of 0.32 μl/min. Injectors were left in place for an additional minute to allow for diffusion of the drug. Following the microinfusion, the injectors were removed, the stylets were replaced and the subjects were placed immediately in the testing apparatus. A preliminary saline injection was administered to all animals prior to the experiment to habituate them to the injection procedure.

Behavioral Testing

For all experiments, animals were well adapted to the test rooms and test cages. Two behavioral paradigms were used.

For experiment 1, rats were tested in photocell activity cages. The activity cages were clear polycarbonate cages measuring 19 × 10.5 × 8 in. Photocells were mounted along the long axis to measure locomotor (horizontal) activity and along the top of the cage to measure rearing (vertical) activity. The photocells were interfaced to a microcomputer that recorded activity automatically (Stimtek, Arlington, MA). Animals were always adapted to the cages for 1 h on test days, followed by a 2-h test session. Horizontal and vertical activities were measured continuously and recorded at 10-min intervals.

In experiment 2, an observational procedure was used in which general spontaneous motor activity and ingestive behaviors were measured by an observer blind to treatment. Animals were tested in cages similar to the home cage, and preweighed food and water were made available to sated rats. Before experimental testing, animals were well adapted to these cages; on the test day, they were infused and put directly into the cages, whereupon testing began. Animals were evaluated for 30 min for feeding, locomotion (crossing of the center line), rearing and drinking with an event recorder linked to a microcomputer (Paul Fray LTD, Cambridge, England). Frequency and duration of behavior were recorded for all but locomotion, for which no duration was recorded. Bouts were recorded each time the animal picked up a food pellet and began eating. Paper was placed below the wire grid floor of the test cage to catch any food spillage. At the end of the period, the food and spillage were removed and weighed, and intake in grams was calculated.

Experimental Design

The effects of DA, SKF-82958, quinpirole and pramipexole were evaluated in separate groups of animals for different drugs and for core and shell subregions. All drugs were administered in a volume of 0.5 μl/side. The doses of DA were 0, 2, 5 and 10 μg for the activity test (core, $n = 8$; shell, $n = 13$) and 0, 2 and 10 μg for the feeding test (core, $n = 14$; shell, $n = 10$). Doses for SKF-82958 were 0, 0.1 and 1 μg for the activity test (core, $n = 14$; shell, $n = 8$) and 0 and 0.75 μg for the feeding test (core, $n = 8$; shell, $n = 8$). In this group, after adminis-

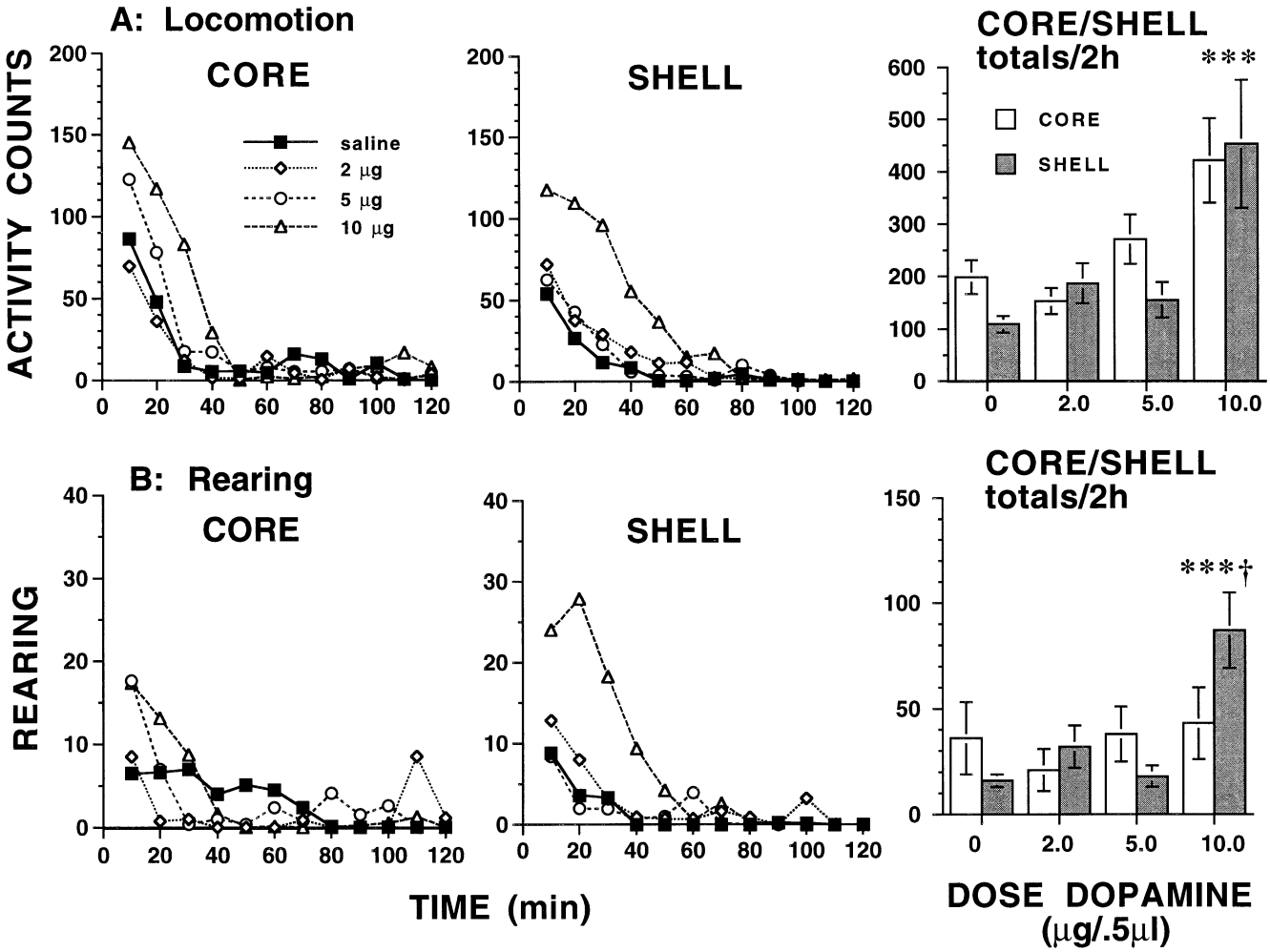

FIG. 1. Locomotor and rearing scores, in the photocell activity cage test, in response to dopamine infusion into core ($n = 8$) and shell ($n = 13$) subregions of nucleus accumbens. Left and middle panels show time course of behavior (symbols indicate means); right panel shows mean totals ± SEM over the 2-h session. ***$p < 0.001$, dose effect; †$p < 0.05$, dose × site interaction.

tration of the SKF-82958 and saline, all animals were given an infusion of a mixture of a low dose of both the D-1 agonist and quinpirole (0.25 μg of each). This dose did not elicit activation with sole administration of either compound in pilot tests. Quinpirole doses for the activity test for the core ($n = 8$) and shell ($n = 7$) were 0, 1, 5 and 15 μg, and the quinpirole doses for the feeding test (core, $n = 9$; shell, $n = 10$) were 0, 1 and 5 μg. For pramipexole, which was only tested in the activity cages (core, $n = 12$; shell, $n = 14$), the doses were 0, 0.1, 1.0 and 10.0 μg. Dose ranges were chosen based on previous pilot experiments and the existing literature. For all experiments, order of dose was counterbalanced across test days to minimize sensitization or order effects. Each animal within a group received all doses of a given compound.

Histology

With completion of testing, the rats were perfused transcardially with 0.9% saline followed by 10% formalin. Brains were immediately removed and placed in formalin. Brains then were immersed in a 10% sucrose-formalin solution for at least 1 day prior to cutting. Brains were frozen and 60-μm sections were taken through the injection site. Sections were mounted on slides and subsequently stained with cresyl violet to verify correct anatomical placement of injection sites. Representative sections were photomicrographed.

Substance P Immunohistochemistry

Because substance P (SP) immunoreactivity very clearly delineates the core and shell regions, in middle and posterior regions of accumbens (25), the brains of two unoperated rats were processed for the immunohistochemical localization of SP to help identify these subregions and provide approximate location of injection sites within these boundaries. The rats were placed under deep anesthesia and were perfused transcardially with approximately 100 ml of 0.15 M saline containing 100 units of heparin (SoloPak Laboratories, Elk Grove Village, IL). The saline rinse was followed by 200 ml of 4% paraformaldehyde in acetate buffer (pH 6.5) infused for 5 min and then by 300 ml of 4% paraformaldehyde in borate buffer (pH 11.0) infused for 20 min (8). The brains were removed and postfixed in the high pH fixative for 2–3 h and then were cryoprotected by being placed in 0.01 M phosphate buffer

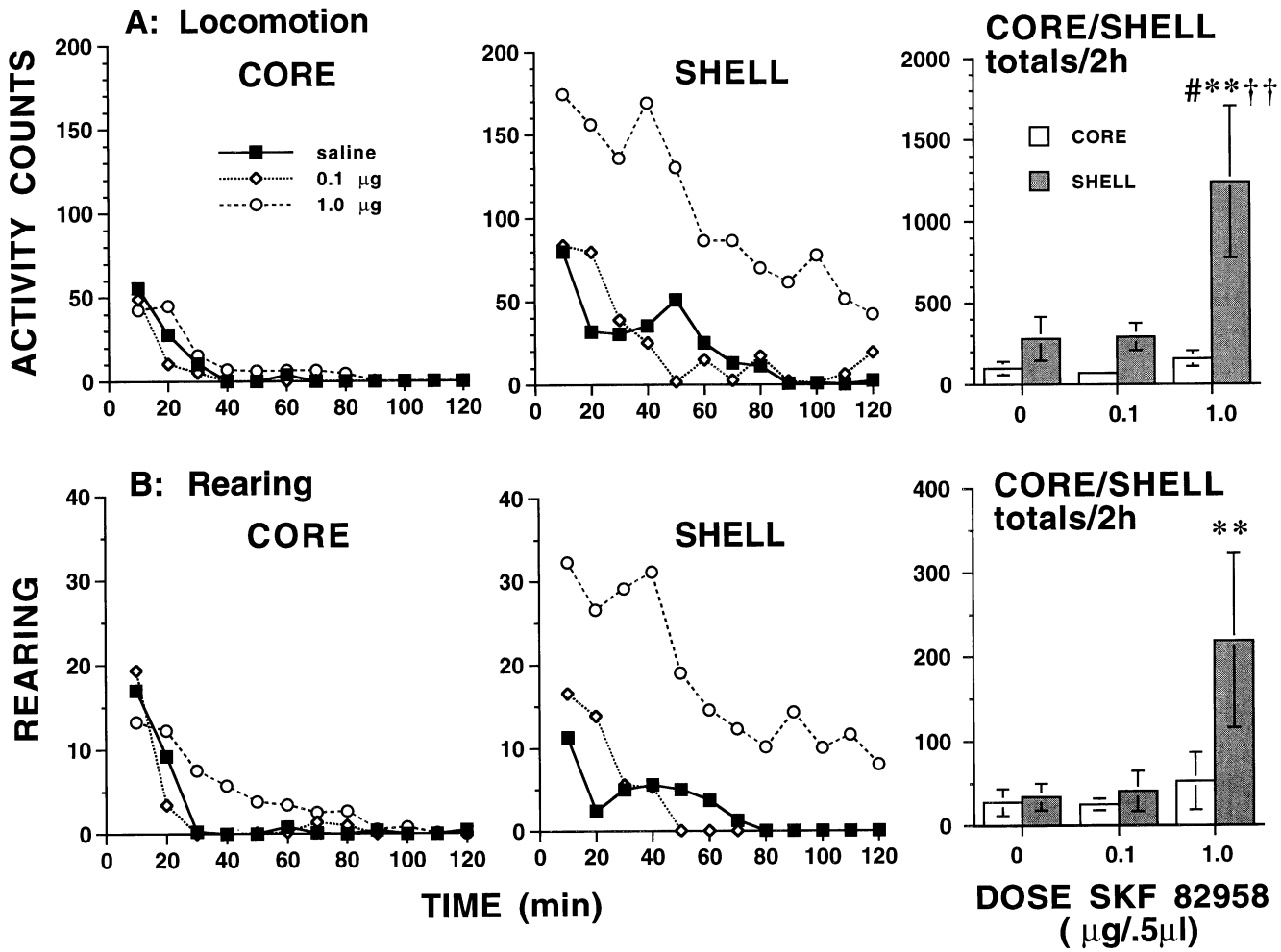

FIG. 2. Locomotor and rearing scores, in the photocell activity cage test, in response to SKF-82958 infusion into core ($n = 14$) and shell ($n = 8$) subregions of nucleus accumbens. Left and middle panels show time course of behavior (symbols indicate means); right panel shows mean totals ± SEM over the 2-h session. $^{**}p < 0.01$, dose effect; $\dagger\dagger p < 0.01$, dose × site interaction; $\#p < 0.05$, site effect.

containing 30% sucrose for approximately 42 h at 4°C. Frozen 30-μm-thick coronal sections throughout the extent of the nucleus accumbens were taken. Alternate sections were placed in a blocking solution composed of 0.01 M phosphate buffered saline (PBS; pH 7.4) containing 10% normal goat serum (NGS; Vector Laboratories, Burlingame, CA) and 0.2% Triton X-100 (Fischer Scientific, Pittsburgh, PA) for 30 min. The sections were rinsed in PBS and were incubated for 18 h at 8°C in a polyclonal rabbit anti-SP antibody (Incstar, Stillwater, MN; Lot 415206) diluted 1:5000 with PBS containing 4% NGS. After multiple rinses in PBS, the tissue was processed at room temperature using a Vectastain Elite ABC kit (Vector Laboratories). The sections were incubated in the biotinylated goat anti-rabbit secondary antibody (diluted 1:200 with PBS containing 4% NGS) for 60 min, rinsed in several changes of PBS and placed in the aviden-biotin complex solution (diluted 1:50 in PBS) for 60 min. After rinsing the sections for 18 h at 4°C with several changes of PBS, the peroxidase was visualized using a vector 3,3′-diminobenzidine substrate kit with nickel chloride enhancement. The sections were then mounted onto chrome-alum coated slides, air dried, dehydrated through graded alcohols, cleared in xylene and coverslipped with Permount.

Data Analysis

Statistical analyses were carried out using the Super ANOVA software package (Abacus). Activity data were analyzed by using a three-factor statistical analysis of variance (ANOVA) with dose and time as within-subjects (repeated measures) factors and with site as the between-subjects factor. Observation data were analyzed with dose or treatment as the within-subjects factor and with site as the between-subjects factor. Each behavioral parameter (locomotion and rearing for experiment 1; locomotion, rearing, feeding duration, feeding bouts, food intake, drinking duration and water intake for experiment 2) was analyzed separately.

RESULTS

Experiment 1: Photocell Activity Cages

Dopamine infused into both the core and shell regions of nucleus accumbens elicited an increase in general motor activity. This increase was reflected in both locomotion (Fig. 1A) and rearing (Fig. 1B). For locomotion, analysis of variance indicated a significant effect of dose [$F(3, 57) = 7.47, p < 0.001$] and a dose × time interaction [$F(15, 285) = 3.08, p < 0.001$].

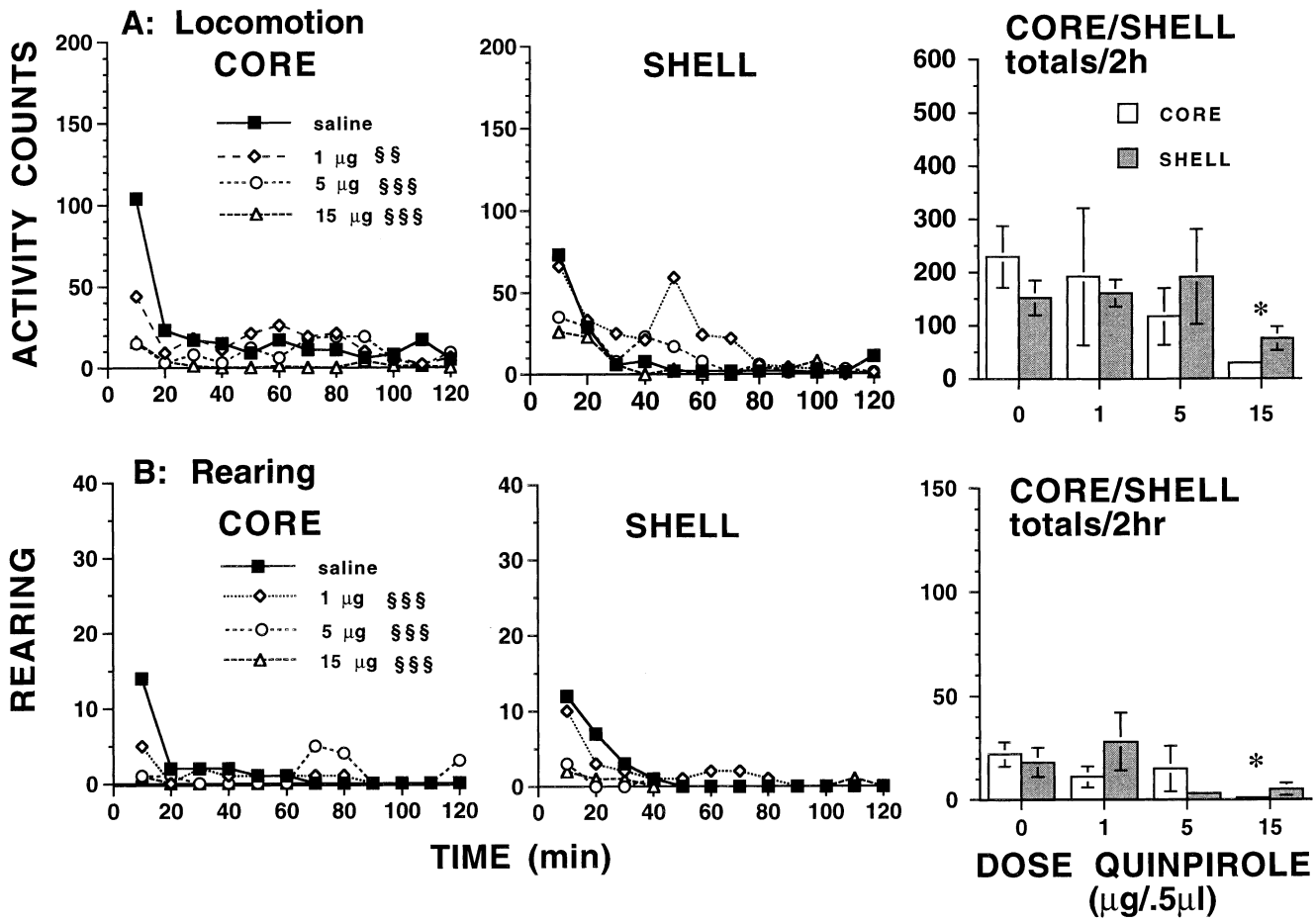

FIG. 3. Locomotor and rearing scores, in the phototcell activity cage test, in response to quinpirole infusion into core ($n = 8$) and shell ($n = 7$) subregions of nucleus accumbens. Left and middle panels show time course of behavior (symbols indicate means); right panel shows mean totals ± SEM over the 2-h session. *$p < 0.05$, dose effect; §$p < 0.05$, dose × time × site interaction.

For rearing, there was also a significant effect of dose [$F(3, 57) = 7.46, p < 0.001$], a dose × time interaction [$F(15, 285) = 4.18, p < 0.001$] and a dose × site interaction [$F(3, 57) = 3.48, p < 0.05$]. In general, animals infused with the higher dose of DA remained active throughout the first hour. Figure 1B shows that this dose also caused more rearing when infused into the shell than into the core.

Infusion of the D-1 agonist SKF-82958 into the accumbens subregions also caused differential effects on activity depending on site. For locomotion (Fig. 2A), there was a significant effect of dose [$F(2, 32) = 6.3, p < 0.01$], site [$F(1, 16) = 16.13, p < 0.001$] and a dose × site interaction [$F(2, 32) = 4.99, p < 0.05$]. A similar profile was observed for rearing (Fig. 2B), although the site effects just missed statistical significance [site, $F(1, 16) = 3.86, p < 0.06$; dose × site interaction, $F(2, 32) = 2.53, p < 0.09$]. There was an overall effect of dose for rearing, due to an enhancement by the highest dose of the D-1 agonist [$F(2, 32) = 4.49, p < 0.02$]. It can be observed from Fig. 2 that SKF-82958 caused marked activation when infused into the shell but did not affect motor activity following infusion into the core at the doses tested.

Quinpirole administration to the accumbens resulted in a significant decrease in motor activity for both subregions (Fig 3A,B). For locomotion, there were no overall significant site effects or dose × site interactions. However, when the scores of vehicle-infused rats were compared with those infused with the low dose (1 μg), a significant dose × time × site interaction was found [$F(11, 143) = 2.37, p < 0.01$]. Figure 3A shows that, in the beginning of the session, this low dose had a suppressive effect on behavior in the core but not in the shell. There were also significant dose × time interactions for the vehicle vs. 5-μg dose [$F(11, 143) = 1.54, p < 0.001$] and vehicle vs. 15-μg dose [$F(11, 143) = 8.49, p < 0.001$]. For the high dose, there also was an overall effect of dose [$F(1, 13) = 15.08, p < 0.001$]. It is clear from Fig. 3A that the medium and high doses of quinpirole had suppressive effects on locomotion at the beginning of the session, when control activity was relatively high. The profile for rearing was very similar. Comparison of the vehicle score with the low dose revealed a significant dose × time × site interaction [$F(11, 143) = 3.29, p < 0.001$]. As for locomotion, rearing in the beginning of the session was suppressed by quinpirole in the core but not in the

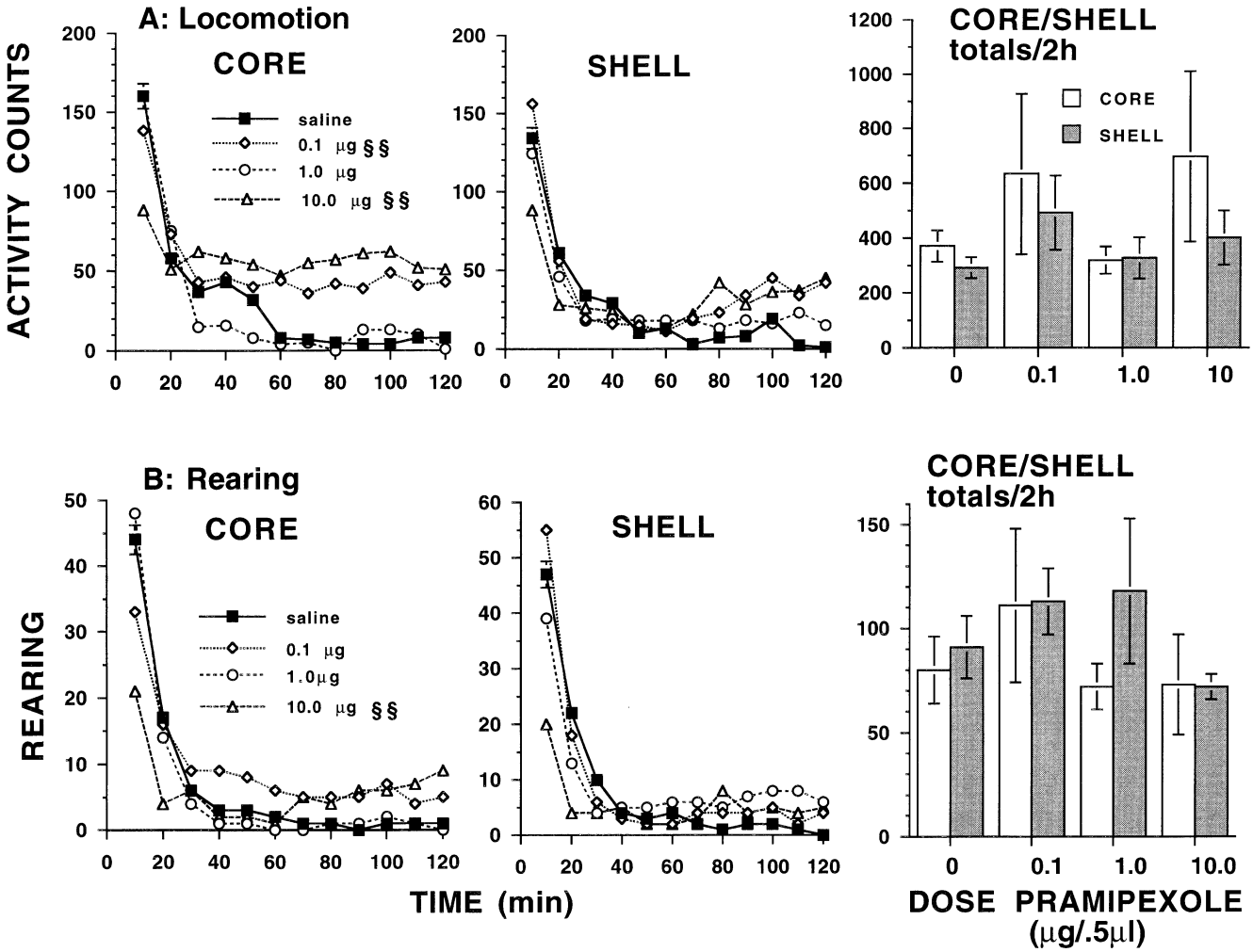

FIG. 4. Locomotor and rearing scores, in the photocell activity cage test, in response to pramipexole infusion into core ($n = 12$) and shell ($n = 14$) subregions of nucleus accumbens. Left and middle panels show time course of behavior (symbols indicate means); right panel shows mean totals ± SEM over the 2-h session. §§§$p < 0.001$, dose × time interaction (for both site groups).

shell. Comparison of vehicle with with the medium dose produced a significant dose × time interaction [$F(11, 143) = 4.6$, $p < 0.001$], as was true for the high dose [$F(11, 143) = 8.3$, $p < 0.001$]. These doses strongly suppressed rearing in both groups (Fig. 3B).

Pramipexole had complex effects on motor behavior, depending on dose and time course. The number of subjects was higher in this experiment because results were so variable with initial tests (also see error bars in Fig. 4A, right panels). There were no overall treatment or site effects of pramipexole on locomotion, as can be observed from the right hand graphs in Fig. 4A, although at some doses, some rats showed increased locomotion. However, there was an overall significant dose × time interaction [$F(33, 792) = 3.89$, $p < 0.001$]. Further analysis indicated that this interaction was due to significant dose × time interactions between vehicle and the low dose scores and between vehicle and the high dose scores ($p < 0.001$). The time course in Fig. 4A shows that rats treated

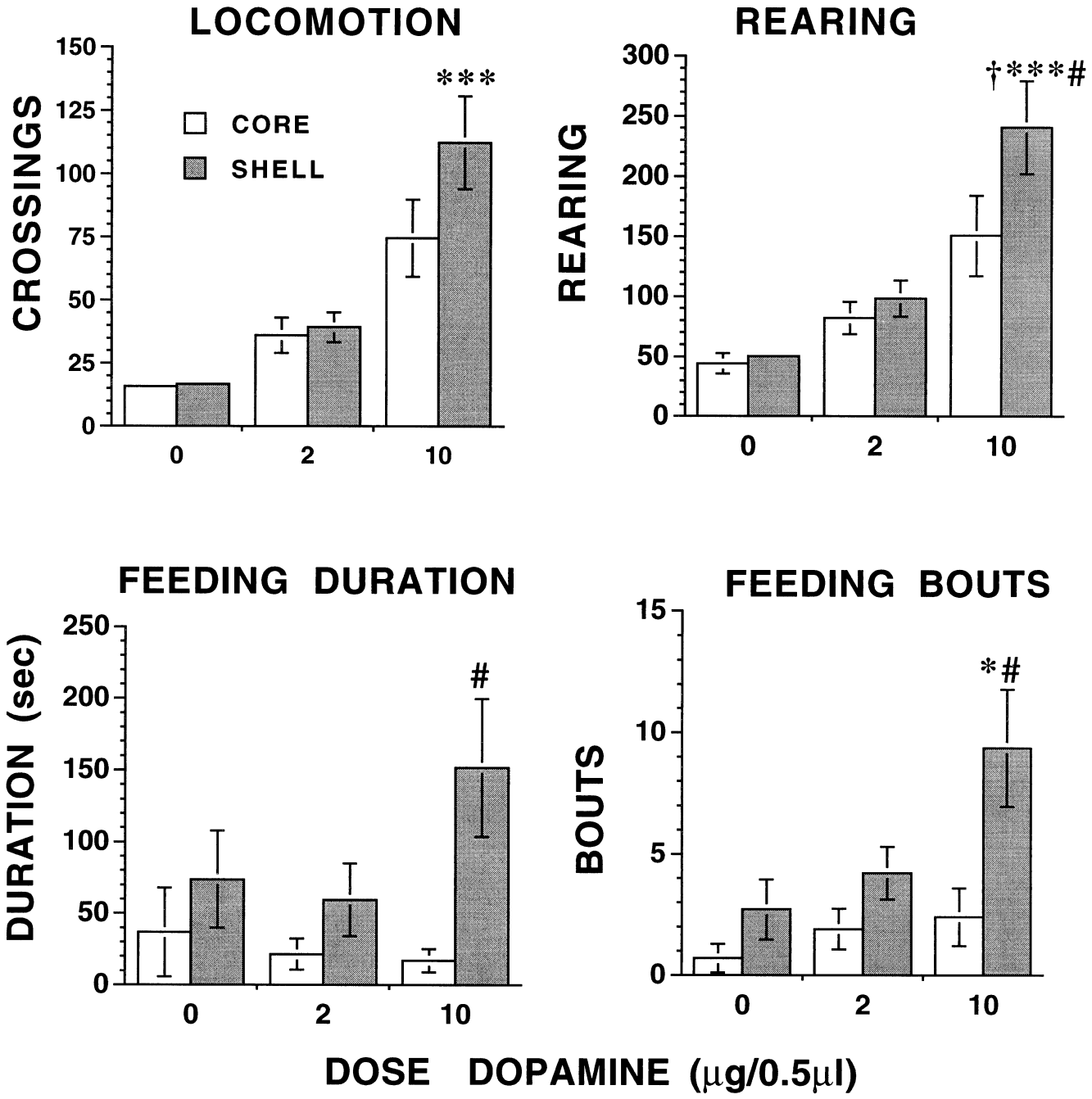

FIG. 5. Behavioral effects of dopamine infusion into core ($n = 14$) and shell ($n = 10$) subregions of accumbens in the behavioral observation test. *$p < 0.05$, ***$p < 0.001$, dose effect; †dose × site interaction, #$p < 0.05$, site effect.

TABLE 1
FOOD INTAKE IN GRAMS FOLLOWING INJECTIONS OF DOPAMINE INTO CORE AND SHELL SUBREGIONS

	Food Intake		
	Dose (μg DA)		
Site	0	2	10
Accumbens core	0.28 ± 0.2	0.22 ± 0.13	0.21 ± 0.13
Accumbens shell	0.46 ± 0.21	0.42 ± 0.17	1.16 ± 0.36*

*$p < 0.03$, site effect.

with the high dose of pramipexole were initially less active than were the control rats and then more active during the remainder of the session. Animals also were more active later in the session following infusion of the low dose of pramipexole. This profile appeared more pronounced in the core group than in the shell group, although there were no site effects or site × treatment interactions. For rearing, there were no site or overall treatment effects, but there was a significant dose × time interaction [$F(33, 792) = 5.2, p < 0.001$]. Further analyes indicated that this effect was due to a significant dose × time interaction between vehicle and the high dose scores ($p < 0.001$). Inspection of Fig. 4B reveals that, similar to locomotion, animals treated with the higher dose of pramipexole showed initial inhibition followed by activation.

Experiment 2: Behavioral Observation

Figure 5 shows the behavioral effects of DA infusion into the core and shell subregions in the observation test. For locomotion, there was a strong effect of dose [$F(2, 44) = 29.2, p < 0.001$] and no significant site effects, although the response tended to be higher in the shell group. For rearing, there was a significant site effect [$F(1, 22) = 4.4, p < 0.05$], a dose effect [$F(2, 44) = 22.5, p < 0.001$] and a dose × site interaction [$F(2, 44) = 3.66, p < 0.05$]. It can be observed from Fig. 5 that rearing was enhanced in the shell relative to the core following the

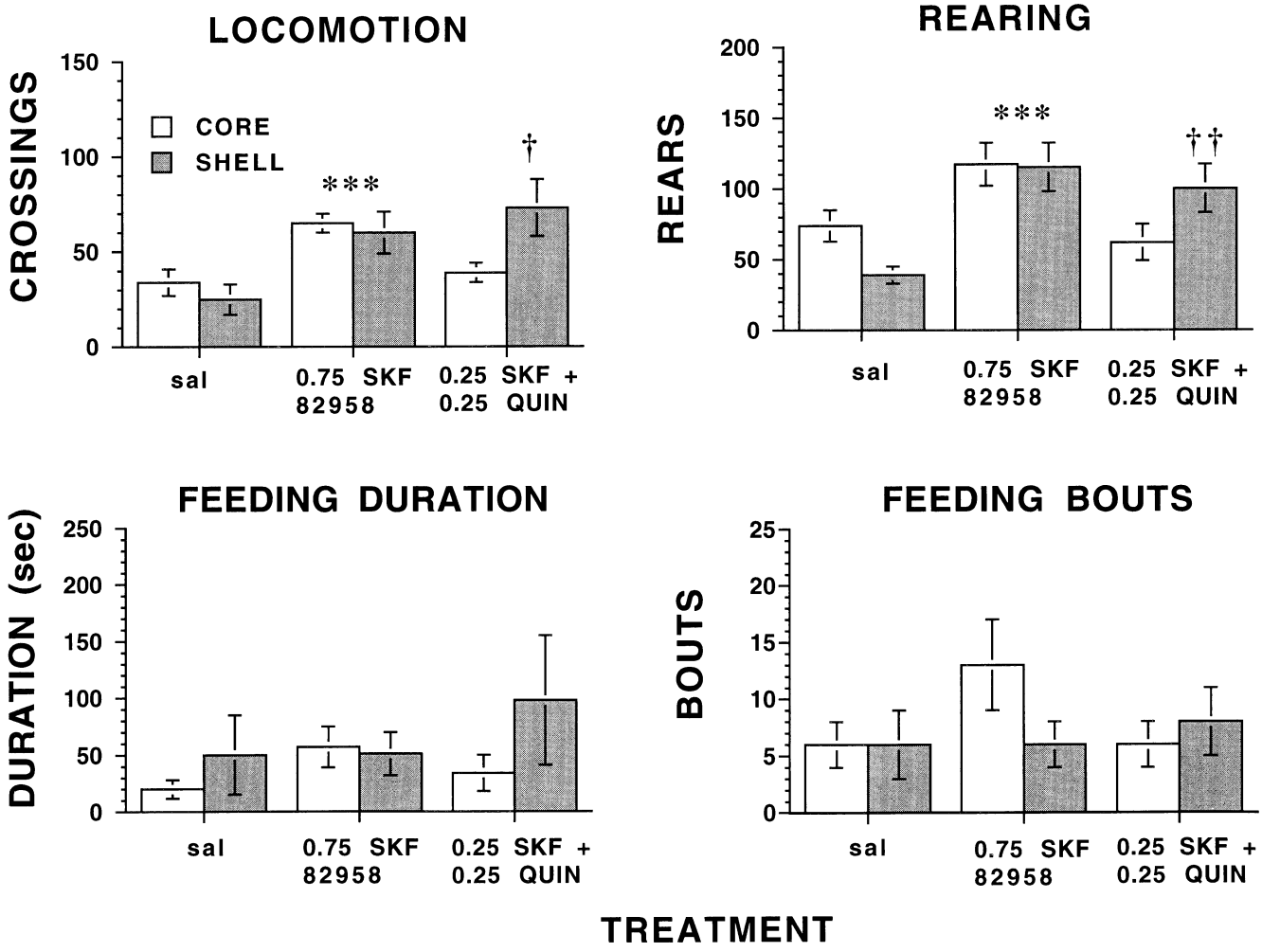

FIG. 6. Behavioral effects of infusion of SKF-82958 or SKF-82958/quinpirole mixture into core ($n = 8$) and shell ($n = 8$) subregions of accumbens in the behavioral observation test. ***$p < 0.001$, treatment effect; †$p < 0.05$, ††$p < 0.01$, treatment × site interaction. Doses are in micrograms.

highest dose of DA. Rats treated with DA in the shell also tended to spend more time feeding; for duration of feeding, there was an effect of site [$F(1, 22) = 0.8$, $p < 0.05$], and for number of feeding bouts there was an effect of site [$F(1, 22) = 7.3$, $p < 0.05$] and of dose [$F(2, 44) = 4.5$, $p < 0.05$]. In addition, food intake was slightly but significantly increased in the shell group; for this measure, there was a significant site effect [$F(1, 22) = 5.72$, $p < 0.03$]. Because baseline intake tended to be higher in the shell than in the core group, dose and dose × site interactions did not reach significance for this parameter. The intake values are shown in Table 1.

Figure 6 shows that SKF-82958 produced a marked potentiation of locomotion [$F(1, 12) = 24.8$, $p < 0.001$] as compared with saline controls. Rearing was also enhanced by the D-1 agonist [$F(1, 12) = 9.7$, $p < 0.001$]. For rearing, there was a tendency toward a treatment × site interaction that did not quite reach significance [$F(1, 12) = 3.6$, $p < 0.08$], suggesting that the magnitude of increase in rears was greater in the shell group than in the core group. SKF-82958 had no effect on feeding behavior or intake. The effects of combined administration of a low dose of SKF-82958 and quinpirole were compared statistically with the saline control. This analysis revealed dose × site

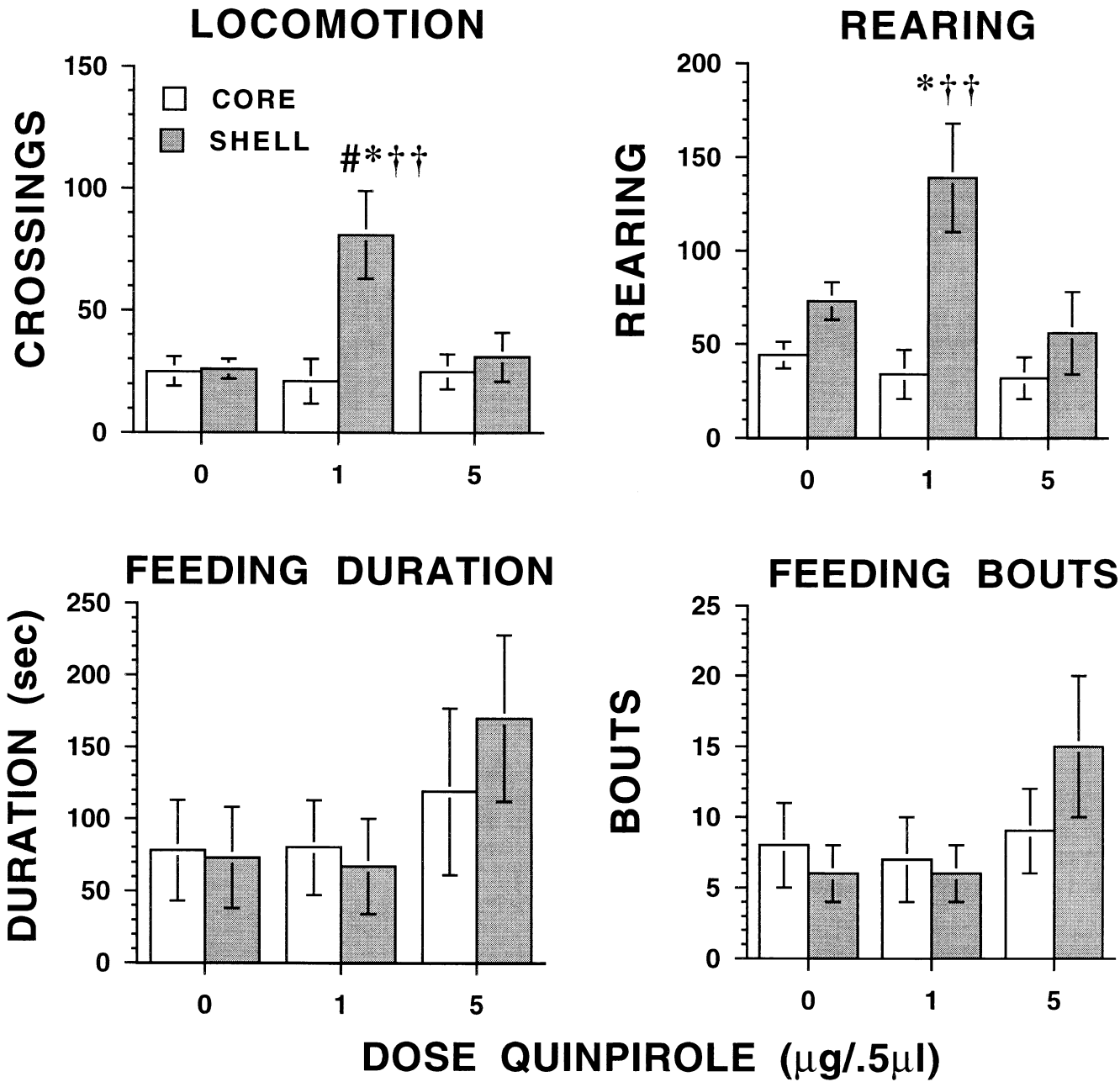

FIG. 7. Behavioral effects of infusion of quinpirole into core ($n = 9$) and shell ($n = 10$) subregions of accumbens in the behavioral observation test. *$p < 0.05$, dose effect; ††$p < 0.01$ dose × site interaction; #$p < 0.05$, site effect.

interactions for both locomotion [$F(1, 12) = 7.28, p < 0.05$] and rearing [$F(1, 12) = 10.6, p < 0.01$]. There were no significant effects on feeding duration, feeding bouts or intake following combined treatment.

Quinpirole infusion resulted in differential effects dependent on site in this behavioral test. For locomotion, there were significant effects of site [$F(1, 17) = 5.68, p < 0.05$], dose [$F(2, 34) = 3.98, p < 0.05$] and a dose × site interaction [$F(2, 34) = 5.57, p < 0.01$]. Rearing also was differentially affected depending on site of infusion. There was a significant effect of site [$F(1, 17) = 8.03, p < 0.01$], dose [$F(2, 34) = 4.86, p < 0.05$] and a dose × site interaction [$F(2, 34) = 5.27, p < 0.01$]. Figure 7 shows that the lower dose of the D-2 agonist selectively increased behaviors following infusion in the shell but not in the core. The higher dose of quinpirole did not appear to alter motor behaviors. Feeding behaviors were not altered by quinpirole treatment in either site.

There were no effects on duration of drinking or water intake after any of the treatments.

Histological Analysis

The results of the histological analysis are presented in Fig. 8. Figure 8A–D shows Nissl-stained material revealing the injector tracks and injection location. Figure 8E–H shows estimations of representative placements superimposed on sections stained for SP immunoreactivity, which clearly reveals core and shell compartments within the accumbens.

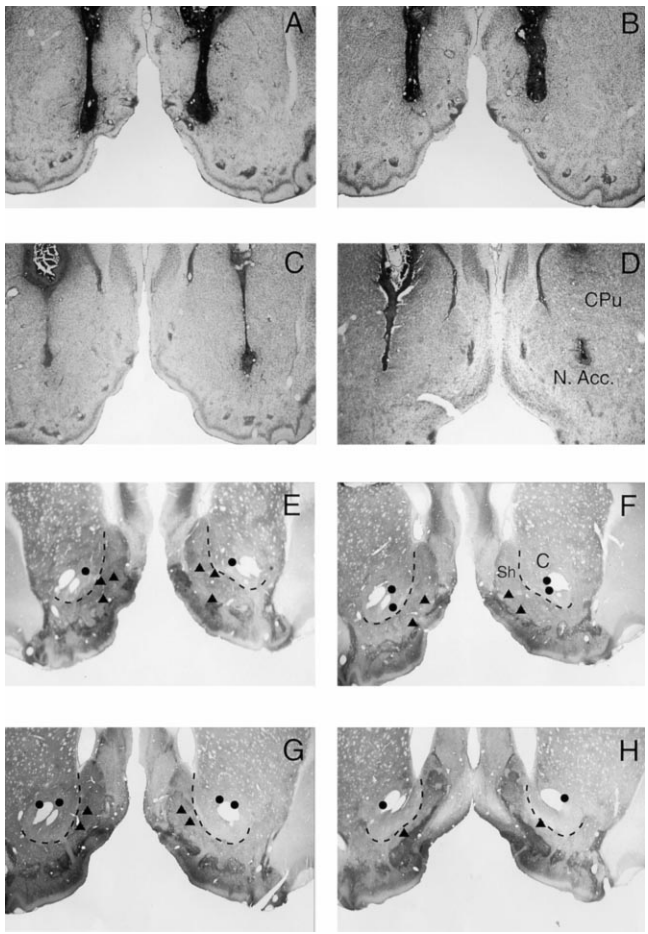

FIG. 8. Histological representation of injection sites. Placements from two representative animals from a shell group (A,B) and from a core group (C,D) are shown. Examples of the approximate placements in the core (dots) and shell (triangles) from several animals are shown superimposed on sections stained for SP immunoreactivity at intervals of 120 μm through the accumbens (magnification 20×).

DISCUSSION

The present study suggests that the behavioral responses to certain DA agonists infused into the nucleus accumbens may be differentiated according to site. Specifically, the shell subregion appears to be relatively more sensitive that the core subregion to the activating effects of DA, D-1 and D-2 agonists and their combination. Evidence in support of this hypothesis is reflected in the generally higher magnitude of responses observed in the shell than in the core. However, evidence was not found for behavioral differentiation following infusion of the D-3 preferring agonist. In addition, a small but significant feeding response was elicited by DA in the shell subregion of accumbens. These results support the notion that core and shell subregions of accumbens can be behaviorally differentiated (19,26,37,38,82).

Although both core and shell subregions support dose-dependent increases in behavioral responses, increases in certain behaviors were more apparent in the shell than in the core. For example, DA microinjections into the shell potentiated rearing more than locomotion in the activity test and the observation test, indicated by significant dose × site interactions for rearing but not for locomotion. It is not clear why this may be the case, but rearing is a behavior highly sensitive to dopaminergic drug effects and may reflect exploratory tendencies. It is interesting that the largest site difference was observed following D-1 stimulation in the activity test. In that case, the shell was much more sensitive than the core to SKF-82958. Thus, the shell may be a primary site for the motor activating effects of D-1 agonists, described previously following systemic injections (42). This core–shell difference for the D-1 agonist was absent, however, in the observation test. This discrepancy between tests could be due to several reasons. First, the dose was slightly different between the two paradigms, and the core–shell differences may be seen only above a certain dose (as was true for DA). Second, the evaluation period was different between the two tests (2 h vs. 30 min), food was present in one test and not in the other and baseline responses are also different. Therefore, results could differ between the tests for a number of reasons.

The results with the D-2 agonist quinpirole also were complex and appeared to depend on site, dose and method of behavioral testing. In the activity cages, the higher doses of quinpirole induced a clear suppression of motor behaviors in both accumbens regions. This is at first glance somewhat surprising because DA agonists are generally considered to produce stimulatory effects on behavior. However, the literature provides ample evidence for suppressive effects of D-2 agonists when injected either systemically (32) or directly into accumbens (1,57,70). Other studies have reported either no effect of quinpirole injected into the accumbens in this dose range or a slight delayed increase in activity (10,22,54). It is not certain why suppression occurs, but it may be due to either stimulation of presynaptic autoreceptors (1) or the requirement for concurrent D-1 postsynaptic stimulation for motor activation (32). In contrast, D-1 agonists are reported to consistently activate behavior when infused into the accumbens (22,41). This general profile is in agreement with our findings, at least for

relatively high doses of quinpirole. However, for lower doses of quinpirole in the shell, there was no suppressive effect in the activity cage test and a clear activating effect in the observation test. Figure 7 shows that infusion of the lower dose into the shell, but not inot the core, induced a marked increase in motor behavior.

Concurrent stimulation with low doses of both the D-1 and D-2 agonists effectively elicited motor stimulation only in the shell. This result is in agreement with a recent study by Essman et al. (23). That work did not specifically compare core and shell subregions, but close examination of their histological analysis indicates that the most effective sites for motor stimulation elicited by a low-dose D-1/D-2 agonist combination were in the caudal, medial accumbens. Therefore, the present results suggest that the shell subregion of accumbens is preferentially sensitive to the D-1/D-2 synergism required for full expression of DA-like locomotor effects, as previously established in studies with systemic drugs (10). How this differential sensitivity relates to receptor distribution is uncertain; one study found that D-1 density was similar in core and shell regions and that D-2 density was less in the shell than in the core (7).

Although the shell region has relatively higher D-3 density than the core (21), pramipexole, which was only tested in the activity cage test, did not appear to differentiate between core and shell subregions, and the motor responses were very variable. The binding profile for this compound indicates a stronger preference for D-3 rather than for D-2 or D-4 receptors (14,42,43,61). The inhibition observed in the first part of the session was similar to that observed for quinpirole and could be due to autoreceptor stimulation. The activating effects observed later in the session, although small in magnitude, may reflect postsynaptic D-3 stimulation. However, other studies that have examined behavioral effects of pramipexole or other D-3 preferring agonists report only inhibitory effects (2,42). Because pramipexole was not tested in the observation test, conclusions cannot yet be made concerning the role of D-3 receptors in feeding.

The small but significant feeding response observed following DA stimulation of the shell is noteworthy. The literature on the role of DA in ingestive behavior is extensive and complex and will not be reviewed here. However, this result suggests that the shell may play a more important role than the core in the mediation of feeding behavior. Strong supportive evidence for this notion is provided by work showing that blockade of glutamate receptors in the shell, but not in the core, induces a powerful feeding response (38). In that study, DA antagonists partially inhibited the feeding response, and it was hypothesized that DA in the shell may have a modulatory influence on ingestive behavior. However, the feeding response reported here is much smaller in magnitude than that elicited by either AMPA antagonists (38) or GABA agonists (unpublished results) infused into the shell. In the latter cases, up to 8 g were ingested and animals fed continuously for most of the 30-min session.

These data add to a growing body of literature indicating anatomical and functional specialization within subregions of the nucleus accumbens. Although there may be site differences with regard to a number of neurotransmitter systems, of relevance to the present findings are possible differences in dopaminergic transmission. Deutch and Cameron (19) found that DA utilization is preferentially increased in the shell following exposure to stress. Denser DA innervation in the shell also is suggested by immunohistochemical studies (25,73), and the shell is less sensitive than the core to the neurotoxic effects of 6-OHDA (81). There are fewer DA uptake sites in the shell than in the core (39), which could account for greater levels of DA found in this region. Electrophysiological studies have shown that the shell neurons are more sensitive to the inhibitory effects of applied DA than are core neurons, and these studies further suggest that shell neurons are more excitable than those of the core (49). Another study showed that the action of DA on postsynaptic potentials in the shell is exclusively D-1 mediated (50), suggesting a unique role for D-1 receptors in this region.

Intriguing differences between the core and the shell with respect to the DA system also have been suggested in relation to psychostimulant dependence. For example, the augmentation in extracellular DA concentrations associated with cocaine is greater in the shell than in the core (51), and acute cocaine administration augments glutamic acid decarboxylase mRNA only in shell neurons (64). Moreover, Pilotte et al. (53) showed that the decrease in DA transporters observed during cocaine withdrawal is confined to the shell subregion. Consideration of these findings with data suggesting a critical role for D-1 receptors in both the rewarding properties (6,13,47,56,57) and neuroadaptive effects (27,69) of stimulants suggests that D-1 receptors in the shell may play a critical role in behavioral activation and reward. The shell and its associated circuits, which preferentially involve limbic structures, may be involved not only in appetitive but also in aversive motivation because the shell may also play a prominent role in the response to stress (19,30). Further investigation of accumbens subregions may confirm this hypothesis and is likely to contribute to knowledge about neural mechanisms underlying drug abuse.

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