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The Role of Adrenoreceptors in Control of Stereotyped Oral Behavior in Restricted-Fed Fowls

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SAVORY, C. J. AND L. KOSTAL. *The role of adrenoreceptors in control of stereotyped oral behavior in restricted-fed fowls.* PHARMACOL BIOCHEM BEHAV 49(2) 295–302, 1994.—Effects on environmentally induced oral stereotypies (object pecking and drinker-directed activity) of preferential antagonists and agonists of adrenoreceptor subtypes were examined in individually caged broiler breeder fowls subjected to chronic food restriction. Three drugs in each category were injected intravenously at three doses, and their effects compared with a saline control treatment. With the antagonists, object pecking was suppressed more by prazosin (α_1) and propranolol (β) than by yohimbine (α_2), while drinker-directed activity showed delayed stimulation with yohimbine and propranolol. With the agonists, drinker-directed activity was suppressed more by clonidine (α_2) than by isoproterenol (β) and phenylephrine (α_1), while object pecking was inhibited by the high doses of clonidine and isoproterenol but showed delayed stimulation with the low dose of clonidine and (nonsignificantly) the high dose of phenylephrine. Initial suppression of both oral stereotypies by the high doses of yohimbine and isoproterenol, and high and medium doses of clonidine, may have been due to sedation, because in those instances it coincided with increased sitting, an activity not normally seen. Increased standing with clonidine and the medium dose of yohimbine may also reflect sedation. When there were no significant increases in sitting or standing to indicate sedation, responses of both stereotypies were essentially the same with all three adrenoreceptor subtypes; i.e., object pecking was inhibited by the antagonist but not the agonist, while drinker-directed activity was inhibited by the agonist but not the antagonist. It is concluded that α_1, α_2, and β adrenoreceptors are all implicated in expression of these stereotypies, and that the two activities may be differentially controlled.

Adrenergic Receptor subtypes Antagonists Agonists Environmentally induced oral stereotypies Food restriction Fowls

PARENT stock (breeders) of meat-type chickens (broilers) are routinely fed on restricted rations during the growing period to limit body weight at sexual maturity and maximise subsequent fertility (21,24). Birds fed on recommended commercial rations eat only about a third as much as they would with free access to food, and are highly motivated to eat at all times (47). They are much more active than ad lib-fed control birds, and show increased pacing before feeding time and increased drinking and pecking at nonfood objects afterwards. Their expression of these activities is often stereotyped in form and is correlated positively with the level of food restriction imposed (27,45,46).

Recently it was shown that the stereotyped oral behavior of individually caged restricted-fed broiler breeders is sensitive to pharmacological manipulation of dopamine and opioid receptors. It was concluded that expression of object pecking, but not necessarily drinker-directed activity, depends more on activation of D_2 dopamine receptors than D_1 receptors, the role of D_3 and D_4 receptors is less clear, and activation of mu and possibly kappa opioid receptors may play a contributory role (28). Similar evidence of involvement of dopamine and/or opioid receptors in expression of environmentally induced stereotypies has also been obtained with other avian and mammalian species (10,13,14,16,25,51,57,60).

The role of adrenoreceptors in control of stereotypies is less clear. Some evidence indicates that they have little influ-

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ence. For example, stereotyped jumping in bank voles was suppressed by treatment with α-methyl-para-tyrosine, a tyrosine hydroxylase inhibitor, but not fusaric acid, a dopamine-β-hydroxylase inhibitor, thus implicating dopamine but not norepinephrine (38). Carazolol, a β-adrenoreceptor blocking agent used for prevention of stress syndromes in pigs (23), had no effect on behavior of tethered sows with oral stereotypies (50). Furthermore, it has been concluded (42) that amphetamine-induced stereotyped behavior is mediated through dopamine activity and not norepinephrine activity, both of which are potentiated by such indirectly acting sympathomimetic drugs.

On the other hand, there is evidence supporting a modulatory role for adrenergic neurotransmission in control of drug-induced stereotypies, reviewed by Antelman and Caggiula (3), who proposed that all stress-related behaviors may be mediated through interactions between brain norepinephrine and dopamine. This hypothesis was used to explain a positive correlation found in stressed pigeons between the incidence of feeding-induced stereotypies and the ratio of telencephalic dopamine to norepinephrine concentrations (16).

With drug-induced stereotypies, α adrenoreceptor subtypes have been implicated more closely than β receptors. In rodents, amphetamine- and apomorphine-induced gnawing have been potentiated by the α_2 receptor agonist clonidine, and inhibited by the α_2 antagonists yohimbine and idazoxan (12,17,35,36,56,66). Conversely, the α_1 antagonist prazosin enhanced apomorphine-induced gnawing, and effects of idazoxan and prazosin on locomotion and sniffing were opposite to those on gnawing (12). Based on these results, a differential regulatory role for norepinephrine was proposed, in which oral stereotypies thought to be mediated by striatal dopamine are facilitated by reduced and inhibited by increased norepinephrine activity, whereas locomotor activities thought to be mediated by mesolimbic dopamine are affected by norepinephrine activity in the opposite way (12). This proposal is supported by the finding that amphetamine-induced rotation in unilateral substantia nigra-lesioned rats was suppressed by α_1 antagonists and enhanced by α_2 antagonists, whereas respective agonists of these receptors had opposite effects (33). Excessive wheel running in semistarved rats was also suppressed selectively by α_2 receptor agonists (62).

Effects of β adrenoreceptor antagonists on amphetamine-induced stereotyped behavior have been less consistent, propranolol and pronethalol having been reported to be stimulatory in some studies (18,53,56), but inhibitory in others (11,29).

The aim of the two experiments described here was to assess possible involvement of α_1, α_2, and β adrenoreceptors in control of the oral stereotypies of individually caged restricted-fed broiler breeders referred to above. This was done by measuring birds' behavioral responses to treatment with centrally acting preferential antagonists and agonists of these receptor subtypes. The antagonists tested were prazosin (α_1), yohimbine (α_2), and propranolol (β), while the agonists were phenylephrine (α_1), clonidine (α_2) and isoproterenol (β).

METHOD

Animals and Husbandry

In each experiment, there were 10 immature female broiler breeder fowls (Ross 1, Ross Breeders Ltd., Midlothian, UK), which were 13 to 17 weeks old and weighed 1.39 to 1.64 kg (mean values) at the time of testing. They were tested in individual cages measuring 30 × 45 × 41 cm (w × d × h) in a three-tiered battery, where they had been housed for 5 weeks before testing commenced. They were fed ad lib for the first 2 weeks of life, and thereafter with weighed restricted rations provided daily at 0900 h, according to a program recommended in the Ross 1 Parent Stock Management Manual. At the time of testing, they received a grower diet (150 g/kg protein and 11.0 MJ/kg metabolizable energy) in pellet form from a food trough just outside the front of each cage, and they consumed all their daily ration in <15 min. Drinking water was available ad lib from a 1 l plastic container situated next to the feeder. Lights were on from 0600 to 2000 h, and ambient temperature was maintained at about 21°C.

Experimental Protocol

The two experiments, with adrenoreceptor antagonists [1] and agonists [2], were done simultaneously; birds in one experiment were in alternate cages in the battery, separated by birds in the other experiment. Each experiment lasted 5 weeks, one being conducted on Mondays and Thursdays and the other on Tuesdays and Fridays; birds were weighed on Wednesdays. Within each experiment, the 10 birds received 10 injection treatments (three drugs at three doses and a 0.9% saline control), each bird receiving a different treatment on each day, according to a Latin square arrangement. Low, medium, and high doses of each drug were in the proportions 1 : 5 : 25, and were based on results of previously published research and pilot trials. All birds were injected by wing vein with 1 ml/kg between 1010 and 1025 h (i.e., 1 h after feeding time), and their behavior was recorded on videotape for 3 h after the last injection.

Measurements were made from the 3-h videorecordings in six alternate 15-min time periods, commencing at the start, by noting each injected bird's behavior in every minute from a single "on the dot" observation (54), according to one of six categories. These were sitting (only), standing (only), pacing, preening (mainly while standing, occasionally while sitting), object pecking (at the empty feeder or parts of the cage), or drinker-directed activity (drinking was interspersed with, and indistinguishable from, pecking at the water or drinker without drinking; most birds produced wet fecal droppings indicating polydipsia (31)). The last two activities (but not pacing or preening) were stereotyped in form, according to the usual definition of stereotypies (37,61). From these observations were calculated proportions of time spent by each bird in each activity in each time period. The computer software used for this analysis was written by LK in Turbo Pascal (Borland International, Scotts Valley, CA).

In the Latin square experimental design, each of the 10 injection treatments was followed by each of the other treatments once on succeeding injection days, across all birds, thus balancing any carry-over effects of preceding treatments (22). Birds were injected in a different random order each day, so that, across all days, treatments were distributed evenly with respect to the time after injection (mean 8 min) when videorecording began. With each of the six activities and six time periods, a separate three-way ANOVA was carried out to determine the significance of effects of bird, injection day, injection treatment, and carry-over from the preceding treatment. These ANOVAs are not independent, because values in successive time periods may be correlated, and because activities were measured as proportions of time, so change in any activity is inevitably reflected by inverse change elsewhere. In addition, within each time period, each drug treatment was compared with the saline control treatment by *t*-test. No statistical

comparisons between drugs were made because equivalent doses (low, medium, high) of different drugs were not equimolar.

In both experiments, the drugs used came from Research Biochemicals Incorporated (Natick, MA).

Experiment 1, Adrenoreceptor Antagonists

Prazosin hydrochloride (α_1) was dissolved in a minimum amount of 1 M acetic acid and diluted to required concentrations with distilled water, and the doses injected were 0.1, 0.5, and 2.5 mg/kg. Yohimbine hydrochloride (α_2) was dissolved in distilled water and doses were 0.1, 0.5, and 2.5 mg/kg. (±)-Propranolol hydrochloride (β) was dissolved in 1 M acetic acid and diluted to required concentrations with 0.9% saline, and doses were 0.2, 1.0, and 5.0 mg/kg. Acidic solutions were adjusted to pH 5.5–6.5 by titration with 1 M sodium hydroxide.

Experiment 2, Adrenoreceptor Agonists

All adrenoreceptor agonists used were dissolved in saline. Phenylephrine hydrochloride (α_1) and clonidine hydrochloride (α_2) were injected in doses 0.02, 0.1, and 0.5 mg/kg. (±)-Isoproterenol hydrochloride (β) was injected in doses 0.1, 0.5, and 2.5 mg/kg.

RESULTS

Experiment 1, Adrenoreceptor Antagonists

Of the 36 ANOVAs with data from Experiment 1 (six activities and six time periods), there were significant ($p < 0.05$) effects of bird in 24, of injection day in four, of injection treatment in nine, and of carry-over from the preceding treatment in one (Table 1).

With the saline control treatment, overall mean proportions of time spent in different activities were 0.0% sitting, 39.3% standing, 0.7% pacing, 11.1% preening, 38.0% object pecking, and 10.9% drinker-directed activity. Object pecking was the activity affected most by treatment with the adrenoreceptor antagonists, and was suppressed by all of them (Fig. 1). The magnitude and duration of this effect appeared to be greater with prazosin (α_1) and propranolol (β) than yohimbine (α_2), although there was almost complete suppression in the first two time periods with the high dose of yohimbine which, judging from corresponding increases in sitting then, may have been due to sedation. Drinker-directed activity was also completely suppressed by the high dose of yohimbine in the first 15 min, but there was delayed stimulation with the medium dose. Propranolol also caused delayed stimulation of drinker-directed activity with the medium and low doses. Apart from the increased sitting with the high dose of yohimbine, each antagonist stimulated at least one nonstereotyped activity (sitting, standing, pacing, preening) in at least one time period, but these effects were not consistent.

Experiment 2, Adrenoreceptor Agonists

Of the 36 ANOVAs in Experiment 2, there were significant effects of bird in 12, of day in four, of treatment in 23, and of carry-over in two (Table 2).

With saline, overall mean proportions of time spent in different activities were 1.3% sitting, 45.1% standing, 0.5% pacing, 7.7% preening, 21.4% object pecking, and 24.0% drinker-directed activity. Unlike Experiment 1, drinker-directed activity was affected more than other activities by the adrenoreceptor agonists, and was suppressed by all of them (Fig. 2). The magnitude and duration of this effect were greatest with clonidine (α_2), intermediate with isoproterenol (β), and least and somewhat delayed with phenylephrine (α_1). Object pecking was also suppressed by clonidine and by the high dose of isoproterenol. This suppression by clonidine changed to delayed stimulation with the low dose injected, and the high dose of phenylephrine also facilitated object pecking in the last four time periods, although not significantly so. Suppression of both oral stereotypies by clonidine and isoproterenol in the first two periods may have been due to sedation, because sitting increased then, especially with the high doses. Standing also increased greatly with clonidine, and the decline in this effect with the low dose reflected the delayed increase in object pecking. Pacing was stimulated by the medium dose of isoproterenol in the first two periods, whereas preening showed early stimulation by low and high doses of phenylephrine, and later inhibition by medium and high doses of clonidine.

DISCUSSION

The purpose of these experiments was to identify the role of α_1, α_2, and β adrenoreceptor subtypes in control of oral

TABLE 1

SIGNIFICANCE OF EFFECTS OF BIRD, INJECTION DAY, INJECTION TREATMENT, AND CARRY-OVER FROM THE PRECEDING TREATMENT IN SIX TIME PERIODS AND SIX ACTIVITIES, IN EXPERIMENT 1 (ADRENORECEPTOR ANTAGONISTS)

Effect	Bird						Day						Treatment						Carry-over					
Time Period*	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
Activity																								
Sitting	–	–	–	–	a	–	–	–	–	–	–	–	c	c	–	–	–	–	–	–	–	–	–	–
Standing	c	c	a	–	a	–	–	b	–	–	–	–	b	–	a	–	–	–	–	–	–	–	–	–
Pacing	–	c	a	b	c	–	–	–	–	a	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Preening	b	–	b	c	c	–	–	–	–	–	–	–	–	–	–	a	–	–	–	–	–	–	–	–
Object pecking	c	–	b	c	c	c	–	–	–	–	–	–	c	c	–	–	–	–	–	–	–	–	–	–
Drinker directed	c	c	c	c	b	b	c	a	–	–	–	–	a	–	b	–	–	–	a	–	–	–	–	–

*Time periods refer to alternate 15 min in the 3 h after injections ended (see the Method section).
– not significant ($p > 0.05$); a $p < 0.05$; b $p < 0.01$; c $p < 0.001$.

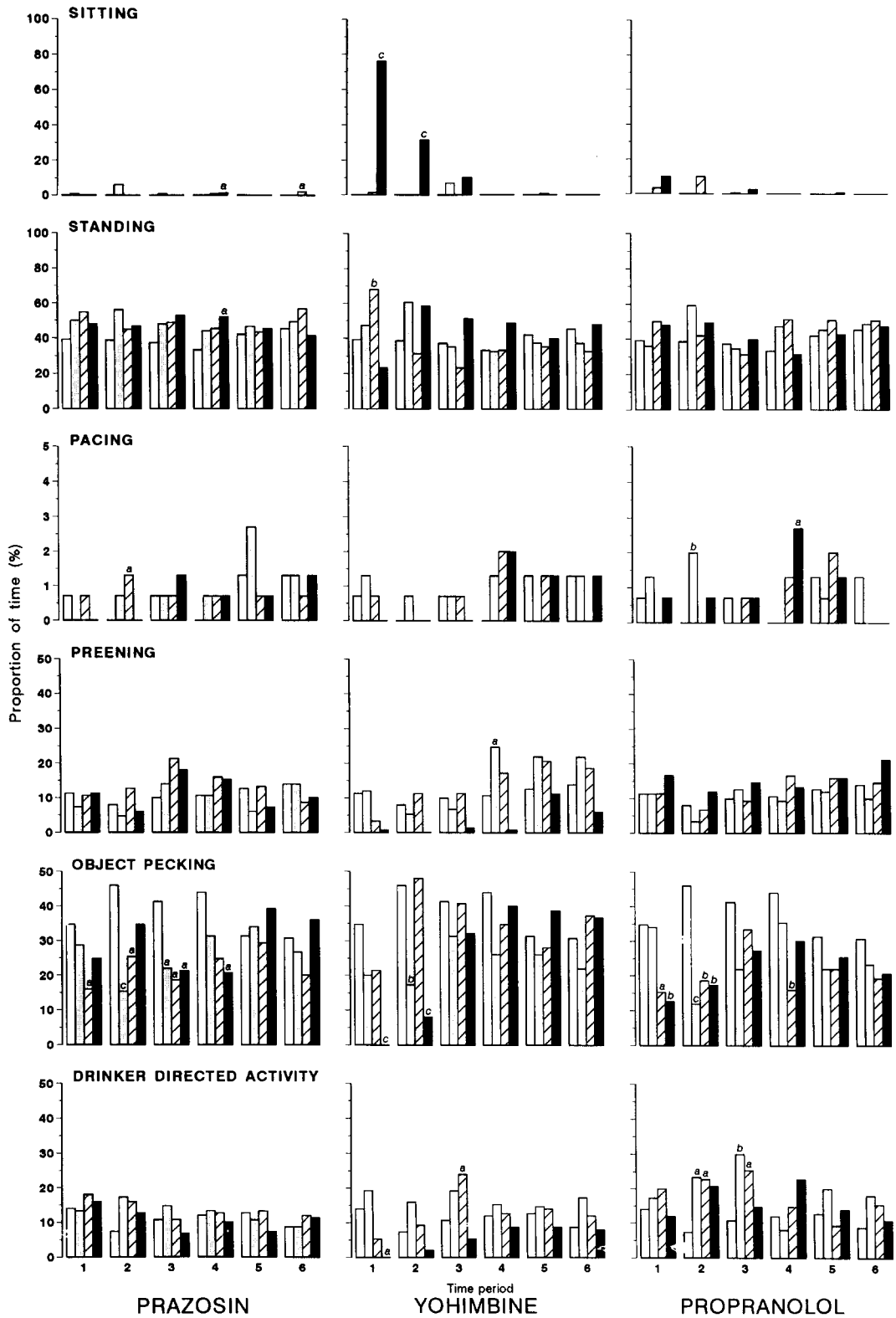

FIG. 1. Mean (n = 10) proportions of time spent per bird in different activities in six alternate 15-min periods, after intravenous injection (1 ml/kg) of either saline (□) or low (▨), medium (▨) or high (■) doses of three adrenoreceptor antagonists (see the Method section for actual doses) in Experiment 1. Superscripts above columns represent significant differences from the saline treatment in that time period: $^{a}p < 0.05$; $^{b}p < 0.01$; $^{c}p < 0.001$.

TABLE 2

SIGNIFICANCE OF EFFECTS OF BIRD, INJECTION DAY, INJECTION TREATMENT, AND CARRY-OVER FROM THE PRECEDING TREATMENT IN SIX TIME PERIODS AND SIX ACTIVITIES, IN EXPERIMENT 2 (ADRENORECEPTOR AGONISTS)

Effect	Bird						Day						Treatment						Carry-over					
Time Period*	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
Activity																								
Sitting	a	–	–	–	–	–	a	–	–	–	–	a	c	c	–	–	–	–	a	–	–	–	–	–
Standing	–	–	–	a	–	b	a	–	–	–	–	a	c	c	c	c	c	c	a	–	–	–	–	–
Pacing	–	–	–	a	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Preening	–	a	–	–	–	–	–	–	–	–	–	–	c	b	a	b	a	–	–	–	–	–	–	–
Object pecking	–	–	c	–	a	c	–	–	–	–	–	–	c	–	c	a	–	b	–	–	–	–	–	–
Drinker directed	–	b	b	c	c	–	–	–	–	–	–	–	c	c	b	b	a	b	–	–	–	–	–	–

Details as for Table 1.

stereotypies shown by caged restricted-fed broiler breeders, i.e., object pecking and drinker-directed activity. The results confirm that manipulation of adrenergic neurotransmission, with preferential antagonists and agonists of the receptors, does influence both of these activities markedly.

Whereas object pecking was suppressed by the α_1 antagonist prazosin, and showed delayed (nonsignificant) stimulation with the high dose of the α_1 agonist phenylephrine, drinker-directed activity was not affected by prazosin and was inhibited by low and medium doses of phenylephrine. Such apparent differential action of α_1 agents on object pecking and drinker-directed activity is not unlike the situation with apomorphine-induced activities in rats, where prazosin enhanced gnawing but inhibited sniffing and locomotion (12). In another study, prazosin was reported to have no effect on drug-induced behavior in rats, but the stereotypy score there combined sniffing, licking, and biting, and so would have obscured any differential action on particular activities (8).

Unlike rats, where α_1 and α_2 antagonists had opposite effects on apomorphine-induced oral behavior (12), here the effects of the α_2 antagonist yohimbine on object pecking and drinker-directed activity were broadly similar to those of prazosin. However, in the first two time periods, effects of the high dose of yohimbine, as well as those of high and medium doses of the α_2 agonist clonidine and β agonist isoproterenol, may well have been due to sedation; because in those instances there were marked increases in sitting, an activity not normally seen. The increased standing seen with clonidine and the medium dose of yohimbine may also reflect sedation.

Although the α_2 antagonists idazoxan and yohimbine enhanced drug-induced locomotor activity in rats (12,33), locomotion in the absence of stimulant drugs was inhibited by both these antagonists (7,9), perhaps reflecting sedation like that indicated here. Similarly, although the α_2 agonist clonidine enhanced drug-induced gnawing in rats and mice (35,36,56,66), it is known to cause sedation when administered on its own (19,65), and it suppressed hyperactivity in semistarved rats (62). Clonidine also has reinforcing properties, and has been shown to be self-administered and to produce a conditioned place preference in rats (4,52).

Nevertheless, in instances here when there were no significant increases in sitting or standing with the α_2 agents to indicate sedation, responses of the oral stereotypies to both the antagonist and the agonist were the same as with the corresponding α_1 agent; i.e., object pecking was inhibited by the antagonist and facilitated by the agonist, while drinker-directed activity was suppressed by the agonist but not the antagonist.

Similar responses were found with the mixed β_1 and β_2 antagonist propranolol and agonist isoproterenol. Thus, if we ignore the high dose of isoproterenol in the first three time periods, where increased sitting indicates sedation, object pecking was again inhibited by the antagonist but not the agonist, and drinker-directed activity was suppressed by the agonist but stimulated by the antagonist. The responses of drinker-directed activity are like those of dopamine receptor agonist-induced yawning in rats, amphetamine-induced gnawing in mice, and imipramine- (but not amphetamine)-induced pecking in chicks, which were all enhanced by propranolol (20,56,63,64).

The different responses of object pecking and drinker-directed activity to the adrenoreceptor agents tested here lend support to the proposal based on previous work (28) that, despite their apparent similarity and substitutability (46), these oral stereotypies of restricted-fed broiler breeders are controlled by distinct neural mechanisms. However, apart from the tendency of the two stereotypies to respond in opposite ways to the same agent, there is insufficient evidence to implicate either activity with any particular adrenoreceptor subtype(s). Unlike drug-induced stereotypies (see Introduction), these environmentally induced activities appear to be implicated just as closely with β receptors as α receptors. In semistarved rats, excessive wheel running was suppressed selectively by α_2 agonists rather than α_1 agonists, but the observed effects could have been due to sedation and β agonists were not tested (62).

In the previous study with dopamine and opioid receptor agents (28), it was suggested that one reason for different responses between object pecking and drinker-directed activity might have been because object pecking was always the dominant stereotypy with the saline control treatment. Here, object pecking was again dominant with saline in Experiment 1, but not in Experiment 2 when both stereotypies were roughly equivalent. Because of differences in potential for upward and downward change, behavioral suppression might be more likely with dominant activities and stimulation more likely with subordinate ones. If so, then this could explain at least some of the observed differences between stereotypies in the two experiments here. Any conclusion regarding different control mechanisms must, therefore, remain tentative.

Another consideration is the relative specificity of the agents tested here. In Experiment 1, prazosin has selective α_1

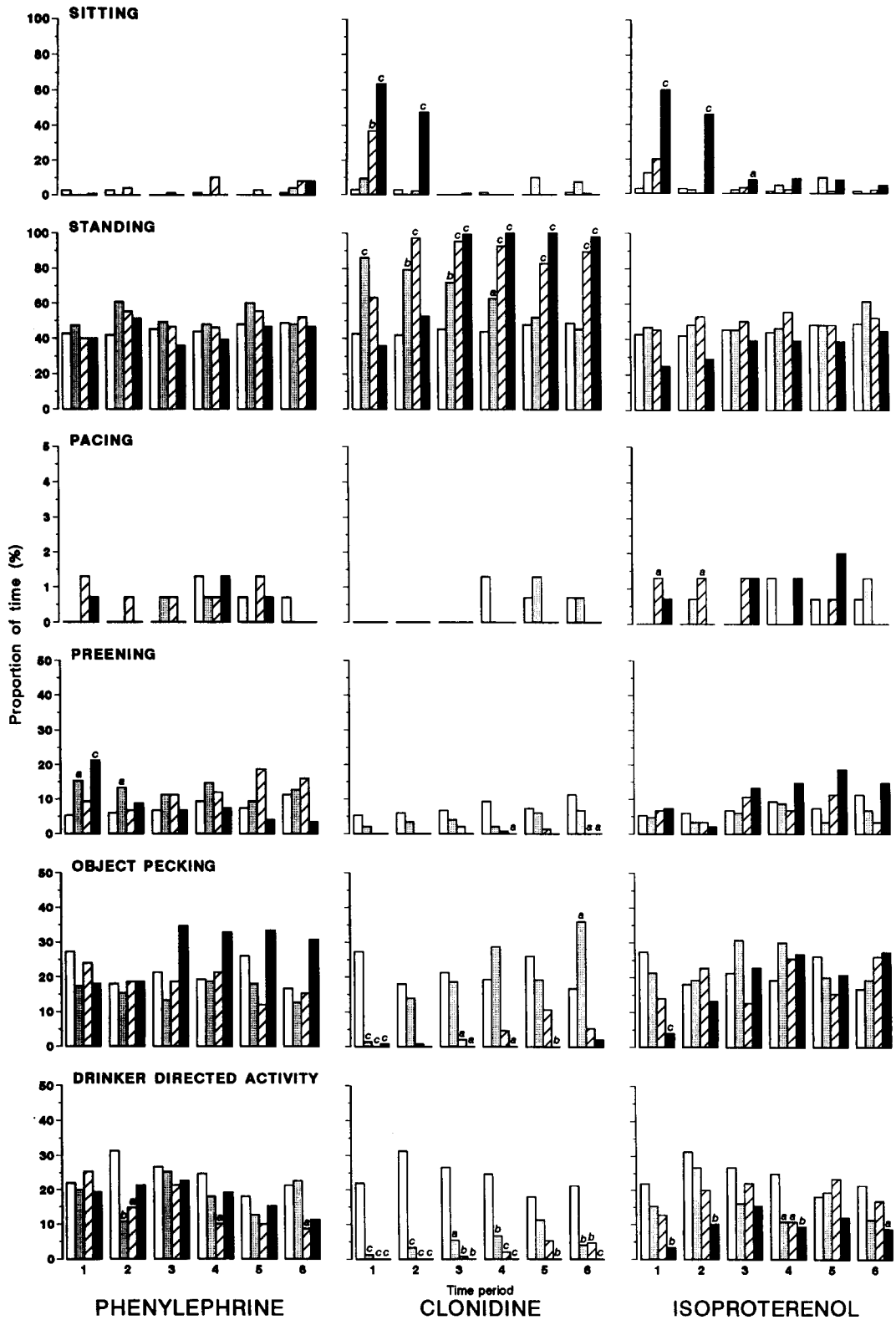

FIG. 2. Mean (n = 10) proportions of time spent per bird in different activities in six alternate 15-min periods, after intravenous injection (1 ml/kg) of either saline (□) or low (▨), medium (▨) or high (■) doses of three adrenoreceptor agonists (see the Method section for actual doses) in Experiment 2. Superscripts above columns represent signifcant differences from the saline treatment in that time period: ^{a}p 0.05; ^{b}p 0.01; $^{c}p < 0.001$.

receptor blocking activity (26) and low affinity for dopamine receptors (43), but can suppress dopamine turnover (2,59). Yohimbine, besides its α_2 receptor blocking activity (15,44), inhibits dopamine receptors and increases dopamine turnover (2,48,59), and also antagonises serotonin receptors (32,40) and benzodiazepine receptors (30). Propranolol is an antagonist of β_1 and β_2 receptors (5), but also interacts with serotonin receptors (34,39,41). In Experiment 2, phenylephrine and clonidine are agonists of α_1 and α_2 receptors, respectively (6,44,49), but clonidine also affects α_1 receptors at high doses (1). Isoproterenol, as well as antagonising β_1 and β_2 receptors (55), has been shown to facilitate dopamine release (58). Thus, apart perhaps from the high dose of clonidine, the effects of these agents on adrenoreceptor subtypes would appear to have been selective; but side effects of some of them on dopamine, serotonin, and/or benzodiazepine receptor activity cannot be excluded.

In conclusion, these results demonstrate that α_1, α_2, and β adrenoreceptor subtypes are all implicated in expression of stereotyped object pecking and drinker-directed activity by caged restricted-fed broiler breeder fowls, and that the two activities may be differentially controlled. However, the precise nature of mechanisms involved, in terms of whether the observed effects are mediated directly via particular adrenergic pathways, or indirectly via modulation of the dopaminergic system [cf. (3,12,33)], remains unclear.

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