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Behavioral Responses of Restricted-Fed Fowls to Pharmacological Manipulation of 5-HT and GABA Receptor Subtypes

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KOSTAL, L. AND C. J. SAVORY. *Behavioral responses of restricted-fed fowls to pharmacological manipulation of 5-HT and GABA receptor subtypes.* PHARMACOL BIOCHEM BEHAV **53**(4) 995–1004, 1996.—Effects on environmentally induced oral stereotypies (object pecking and drinker-directed activity) and other behavior (sitting, standing, pacing, preening), of preferential antagonists and agonists of central 5-HT and GABA receptor subtypes, were examined in individually caged broiler breeder fowls subjected to chronic food restriction. All drugs were injected intravenously at three doses, and their effects compared with a saline control treatment. The only significant ($p < 0.05$) effect of 5-HT antagonists [NAN-190 (5-HT_{1A}), ketanserin (5-HT_2), MDL-72222 (5-HT_3)] was an increase in pacing with ketanserin (0.8 mg/kg). With 5-HT agonists, 8-OH-DPAT (5-HT_{1A}) suppressed the two oral stereotypies and increased standing (all 1.0 mg/kg) and preening (0.2 mg/kg), α-methylserotonin (5-HT_2) suppressed the oral stereotypies and increased sitting (all 1.0 mg/kg), and *m*-CPBG (5-HT_3) suppressed drinker-directed activity (1.0 mg/kg). The GABA antagonists (bicuculline ($GABA_A$), 5-aminovaleric acid ($GABA_B$) had no effect, and of the GABA agonists [muscimol ($GABA_A$), baclofen ($GABA_B$)], muscimol suppressed preening and increased sitting, standing (all 1.0 mg/kg), and pacing (0.2 mg/kg). Most of the significant effects of serotonergic and GABAergic agents on behavior here appeared to reflect at least some degree of sedation, and there was no real evidence of any specific influence of these compounds on the oral stereotypies within the range of doses tested.

5-HT (5-hydroxytryptamine, serotonin) GABA (γ-aminobutyric acid) Receptor subtypes Antagonists Agonists Behavior Oral stereotypies Food restriction Fowls

GROWING parent stock (breeders) of meat-type chickens (broilers) are routinely fed on restricted rations to limit body weight at sexual maturity and thereby improve health and reproductive performance (23). Birds fed on these 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 (49). They are 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 (29,48).

Such abnormal behavior caused by chronic food restriction has features in common with the behavioral syndrome seen after pharmacological stimulation of central dopamine receptors. Thus, in rats, pigs, pigeons, and chickens, hyperactivity and stereotyped movements of limb, head, and mouth occur during food restriction (18,29,40,47) and after treatment with the dopamine receptor agonists amphetamine and apomorphine (7,19,21,39,57,63). These similarities suggest that dopaminergic processes may underlie at least some environmentally induced abnormal behavior, and this view is supported by evidence that the oral stereotypies of restricted-fed pigs, pigeons, and chickens are suppressed by treatment with the dopamine receptor antagonist haloperidol (20,30,62).

From this and related work with broiler breeders it was concluded that their oral stereotypies are mainly under dopaminergic control, but that adrenergic and opioid peptide mechanisms play a contributory role (30,50). The involvement of noradrenaline and opioids may be due, at least partly, to their known interactions with dopamine (2,8,12,14,36).

Another specific behavioral syndrome is induced by stimulation of central serotonin 5-HT receptors (11,13,25). It, too, includes stereotyped limb and head movements that resemble components of environmentally induced behavior. Moreover,

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like amphetamine, the 5-HT receptor agonist 8-OH-DPAT causes increased locomotion at low doses, and behavioral stereotypies that arise as its dose is increased do so at lower doses in food-restricted rats (5). Such apparent analogies with the dopamine syndrome suggest that serotonergic mechanisms may also underlie expression of environmentally induced abnormal behavior, and particularly that associated with food restriction. In support of this proposal, hyperactivity (wheel running) in rats induced by chronic food restriction was found to be associated with increased serotonin turnover, and suppressed by treatment with 5-HT receptor agonists (44). Schedule-induced polydipsia in rats was also suppressed and enhanced by 5-HT agonist and antagonist treatments, respectively (34).

There are various ways in which serotonin interacts with the dopaminergic system (6,7,9,42,60), and components of the 5-HT behavior syndrome are influenced by manipulation of dopamine (5,11,13). Hence, 5-HT receptors could be involved in expression of environmentally induced abnormal behavior through activation of dopaminergic mechanisms.

The inhibitory neurotransmitter GABA (γ-aminobutyric acid) could also be implicated in control of abnormal behavior for the same reason, because it, too, interacts functionally with dopamine. One hypothesis proposes that it regulates activity of dopamine cell bodies in the substantia nigra via a striatonigral feedback loop (41). Another hypothesis suggests that dopamine controls the activity of the striatonigral GABAergic pathway, and hence, GABA-mediated inhibition of nondopaminergic efferent neurons in the substantia nigra, zona reticulata (51). In fowls, central treatment with an inhibitor of GABA-transaminase activity, at doses that increase GABA content, antagonized apomorphine-induced stereotyped behavior, while drugs that inhibit GABAergic neurotransmission produced an intense pattern of stereotyped movements (37). On the other hand, local injection of specific GABA agonists into the substantia nigra (or its avian analogue) has been found to cause locomotor and stereotyped head movements in rats and pigeons that resemble the behavior syndrome induced by dopamine agonists (1,3,46,52,53). In rats, central administration of the GABA agonist muscimol stimulated chewing in the absence of food (32), and food deprivation resulted in a decrease in cerebellar GABA receptors (65).

There appears to have been no previous study of serotonergic and GABAergic involvement in avian environmentally induced abnormal behavior. In a series of experiments reported here we investigated the role of 5-HT and GABA receptor subtypes in expression of the oral stereotypies shown by individually caged restricted-fed broiler breeders. This was done by measuring birds' behavioral responses after intravenous injection of centrally acting preferential antagonists and agonists of the respective receptors. The 5-HT antagonists tested were NAN-190 (5-HT_{1A}), ketanserin tartrate (5-HT_2), and MDL-72222 (5-HT_3), while the 5-HT agonists were 8-OH-DPAT (5-HT_{1A}), α-methylserotonin maleate (5-HT_2), and *m*-CPBG (5-HT_3). The GABA antagonists were bicuculline ($GABA_A$) and 5-aminovaleric acid ($GABA_B$), and the GABA agonists were muscimol ($GABA_A$) and baclofen ($GABA_B$).

METHODS

Animals and Husbandry

In each experiment, there were either 10 (Experiments 1 and 2) or 8 (Experiments 3 and 4) immature female broiler breeders (Ross 1, Ross Breeders Ltd., Midlothian, UK), which were 11 to 16 weeks old and weighed 1.23 to 1.54 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 at least 4 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 standard commercial 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 liter 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 four experiments were done two at a time, 5-HT antagonists [1] and agonists [2] together, and then GABA antagonists [3] and agonists [4]. Birds in one experiment were in alternate cages in the battery, separated by birds in the other concurrent experiment. Experiments 1 and 2 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). Experiments 3 and 4 lasted 16 days, each being conducted on alternate days, and birds being weighed once a week. Within each experiment, the eight birds received eight injection treatments (two drugs at three doses and two 0.9% saline controls). In all the experiments, each bird received a different injection 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 published information (see below) 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 periods, commencing at the start, by noting each injected bird's behavior in every minute from a single "on the dot" observation (56), 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 (33)]. The last two activities (but not pacing or preening) were stereotyped in form, according to the usual definition of stereotypies (38). From these observations were calculated proportions of time spent by each bird in each activity in each time period. The computer software used for the analysis was written by LK in Turbo Pascal (Borland International, Scotts Valley, CA).

Statistical Analysis

In the 10 × 10 (Experiments 1 and 2) and 8 × 8 (Experiments 3 and 4) Latin square designs, each injection treatment 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 (26). Latin square designs must have even numbers of rows and columns to balance such

residual effects; this was why there were two saline control treatments in Experiments 3 and 4. 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. Two birds died at different times in Experiment 1, and one became lame in Experiment 3. As data obtained from these were incomplete, they were excluded from the analysis.

With each of the six activities, responses over the 3 h after injection were analyzed on an hourly basis, using mean proportions of time calculated from the two alternate 15-min sampling periods in each hour. A (Latin square) ANOVA, assessing effects of injection treatment and carryover from the preceding treatment, and allowing for differences between birds and days, was used to calculate the error variance. This value was then used for comparing each of the experimental treatments (drug and dose) with the corresponding saline control treatment, by Dunnett's (16,17) multiple comparison test. In Experiments 3 and 4, data from the two saline controls were averaged for this purpose.

No statistical comparisons between drugs were made because equivalent doses (low, medium, high) of different drugs were not equimolar.

Experiment 1, 5-HT Receptor Antagonists

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

NAN-190(1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl]-piperazine hydrobromide) (5-HT_{1A}) was dissolved in a minimal amount of 0.1% ascorbic acid and diluted to required concentrations with distilled water; the doses injected were 0.02, 0.1, and 0.5 mg/kg (22). Ketanserin tartrate (5-HT_2) was dissolved in distilled water and doses were 0.16, 0.8, and 4.0 mg/kg (31). MDL-72222 (3-tropanyl-3,5-dichlorobenzoate) (5-HT_3) was dissolved in a minimal amount of 1 M acetic acid and diluted to required concentrations with distilled water; doses were 0.16, 0.8, and 4.0 mg/kg (4). Acidic solutions were adjusted to pH 5.5–6.5 by titration with 1 M sodium hydroxide.

Experiment 2, 5-HT Receptor Agonists

8-OH-DPAT [(±)-2-dipropylamino-8-hydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide] (5-HT_{1A}) was dissolved in distilled water and doses were 0.04, 0.2, and 1.0 mg/kg (61). α-Methylserotonin maleate (5-HT_2) and *m*-CPBG [1-(*m*-chlorophenyl)-biguanide hydrochloride] (5-HT_3) were dissolved in 0.9% saline and injected in doses 0.04, 0.2, and 1.0 mg/kg (24,28).

Experiment 3, GABA Receptor Antagonists

All GABA receptor antagonists and agonists were dissolved in 0.9% saline. (−)-Bicuculline methiodide ($GABA_A$) was injected in doses 0.08, 0.4, and 2.0 mg/kg (59), and 5-aminovaleric acid hydrochloride ($GABA_B$) in doses 0.8, 4.0, and 20.0 mg/kg (59).

Experiment 4, GABA Receptor Agonists

Muscimol hydrobromide ($GABA_A$) was injected in doses 0.04, 0.2, and 1.0 mg/kg (53), and (±)-baclofen ($GABA_B$) in doses 0.08, 0.4, and 2.0 mg/kg (54).

RESULTS

Experiment 1, 5-HT Receptor Antagonists

With the saline control treatment, overall mean proportions of time spent in different activities in Experiment 1 were 0.0% sitting, 43.6% standing, 0.7% pacing, 7.2% preening, 32.5% object pecking, and 16.0% drinker-directed activity. From the Dunnett's tests, the only significant ($p < 0.05$) effect of experimental treatment on behavior was with the medium dose of ketanserin, which stimulated pacing in the first hour after injection (Fig. 1).

Experiment 2, 5-HT Receptor Agonists

With the saline treatment, overall mean proportions of time spent in different activities in Experiment 2 were 2.2% sitting, 45.6% standing, 0.4% pacing, 7.9% preening, 30.2% object pecking, and 13.8% drinker-directed activity. Compared with the antagonists in Experiment 1, effects of the 5-HT receptor agonists on behavior were more pronounced. Thus, in the first hour after injection, the high doses of all three agonists and the medium dose of α-methylserotonin suppressed drinker-directed activity, and the high doses of 8-OH-DPAT and α-methylserotonin suppressed object pecking (Fig. 2). Also in the first hour, standing and preening were stimulated by the high and medium doses of 8-OH-DPAT, respectively, and sitting was stimulated by the high dose of α-methylserotonin.

Experiment 3, GABA Receptor Antagonists

With the saline treatment, overall mean proportions of time spent in different activities in Experiment 3 were 0.0% sitting, 48.8% standing, 1.2% pacing, 12.1% preening, 27.7% object pecking, and 10.2% drinker-directed activity. Neither GABA receptor antagonist had any significant effect on behavior (Fig. 3).

Experiment 4, GABA Receptor Agonists

With the saline treatment, overall mean proportions of time spent in different activities in Experiment 4 were 0.2% sitting, 42.1% standing, 0.7% pacing, 14.7% preening, 25.6% object pecking, and 16.7% drinker-directed activity. The only significant effects on behavior were with muscimol, which suppressed preening and stimulated sitting and standing in the first hour with the high dose, and stimulated pacing in the third hour with the medium dose (Fig. 4).

DISCUSSION

The purpose of these experiments was to investigate the role of 5-HT and GABA receptor subtypes in expression of oral stereotypies shown by caged restricted-fed broiler breeders; i.e., object pecking and drinker-directed activity. The results indicate that these activities were influenced only by the 5-HT receptor agonist treatments, and not by the 5-HT antagonists or GABAergic agents.

In previous related work (30,50) it was proposed that the increased sitting (an activity not normally seen) and standing observed after treatment with some dopaminergic and adrenergic compounds reflected varying degrees of sedation. The increases in those activities here in the first hour after injection of the high dose (1.0 mg/kg) of all three 5-HT receptor agonists (Fig. 2) and the $GABA_A$ receptor agonist muscimol (Fig. 4) can be similarly interpreted, and hence, this apparent sedation may have been responsible for concomitant suppression of the oral stereotypies (Fig. 2) or preening (Fig. 4).

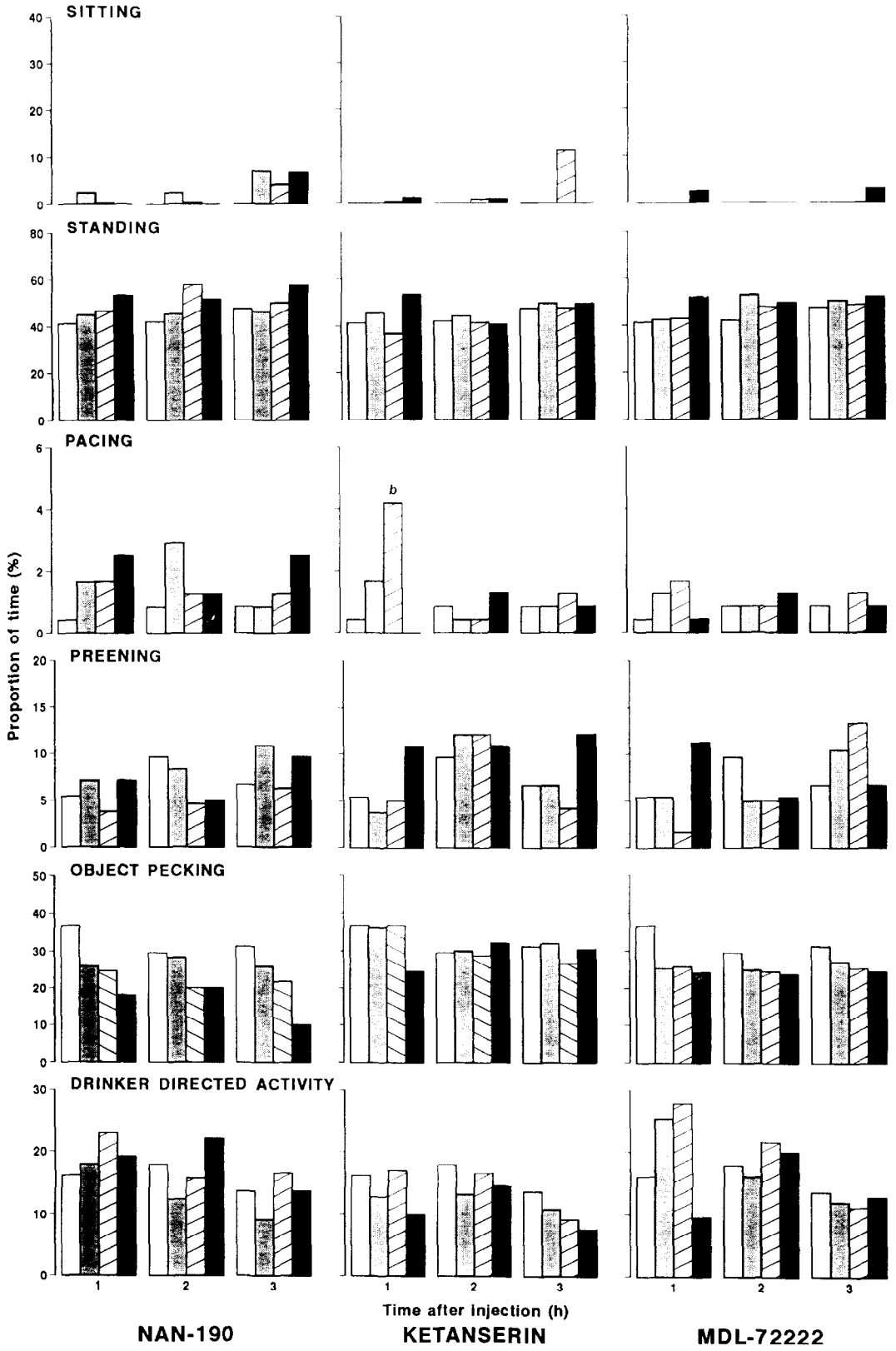

FIG. 1. Mean (n = 8) proportions of time spent per bird in different activities in three hours (from two alternate 15-min periods per hour) after intravenous injection (1 ml/kg) of either saline (open columns) or low (dotted columns), medium (slanted rule columns), or high (filled columns) doses of three 5-HT receptor antagonists (see the Method section for actual doses) in Experiment 1. The superscript above a column represents a significant difference from the saline treatment in that hour; $^{b}p < 0.01$.

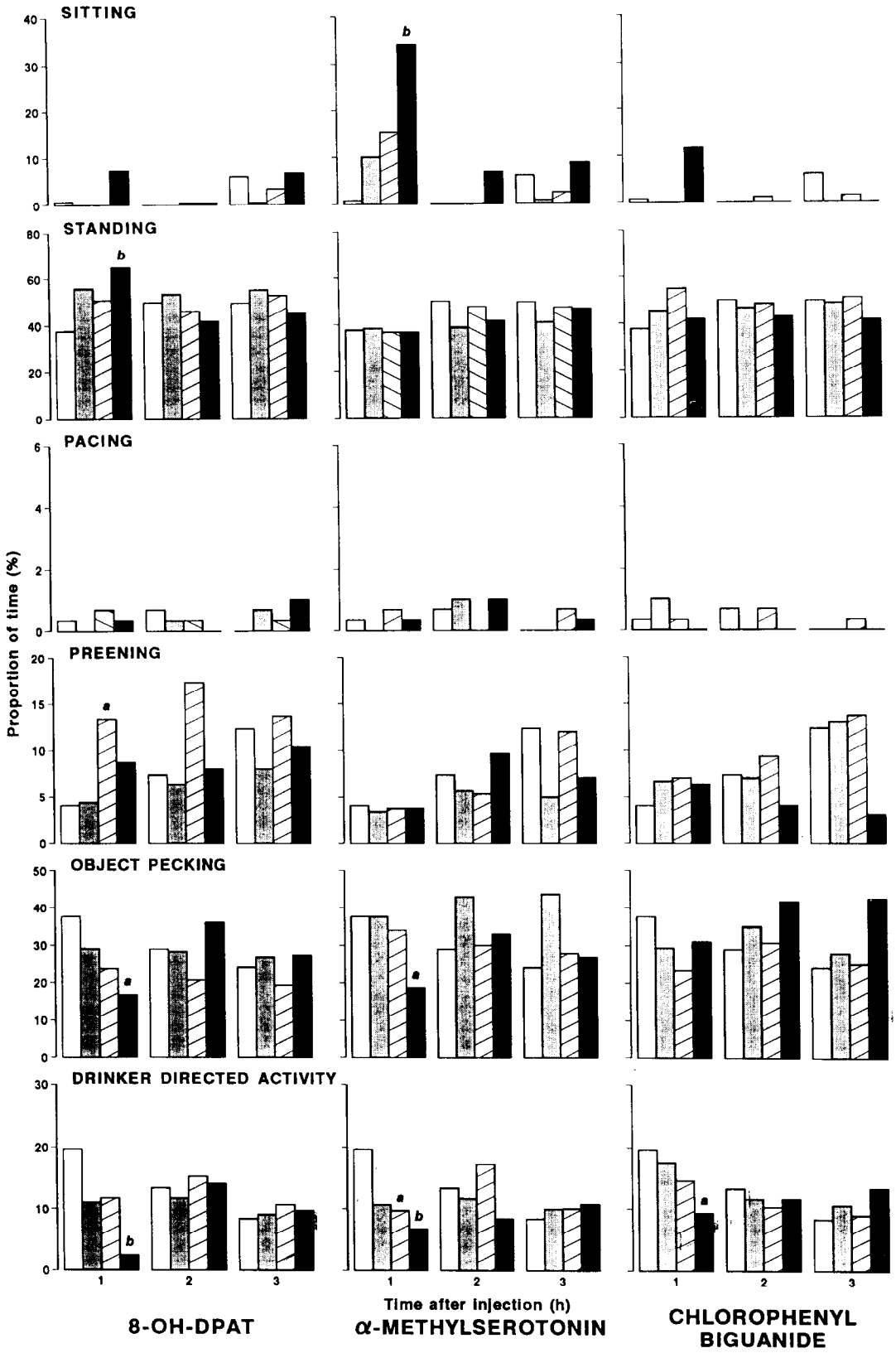

FIG. 2. Mean (n = 10) proportions of time spent per bird in different activities in 3 h (from two alternate 15-min periods per hour) after intravenous injection (1 ml/kg) of either saline (open columns) or low (dotted columns), medium (slanted rule columns), or high (filled columns) doses of three 5-HT receptor agonists (see the Method section for actual doses) in Experiment 2. Superscripts above columns represent significant differences from the saline treatment in that hour; $^{a}p < 0.05$, $^{b}p < 0.01$.

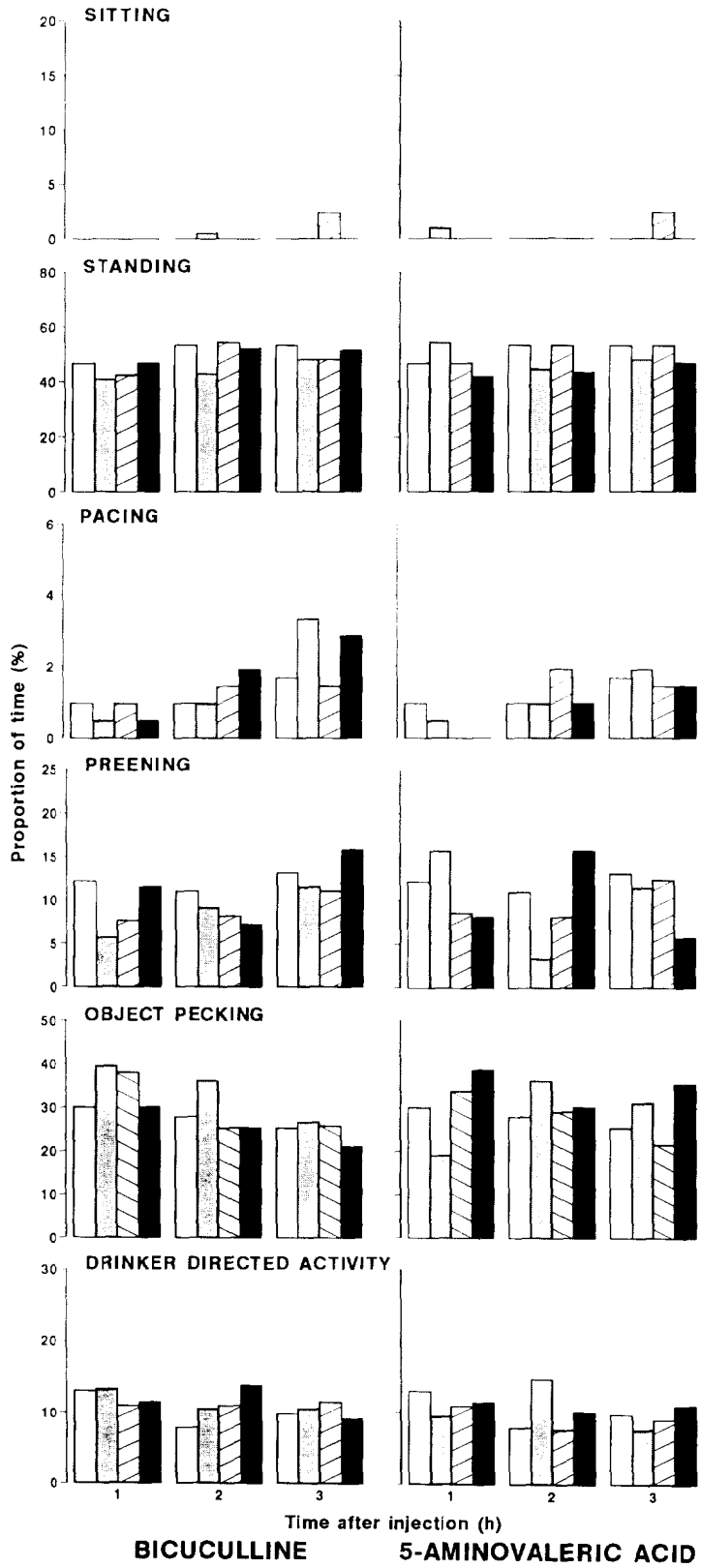

FIG. 3. Mean (n = 7) proportions of time spent per bird in different activities in 3 h (from two alternate 15-min periods per hour) after intravenous injection (1 ml/kg) of either saline (open columns) or low (dotted columns), medium (slanted rule columns), or high (filled columns) doses of two GABA receptor antagonists (see the Method section for actual doses) in Experiment 3.

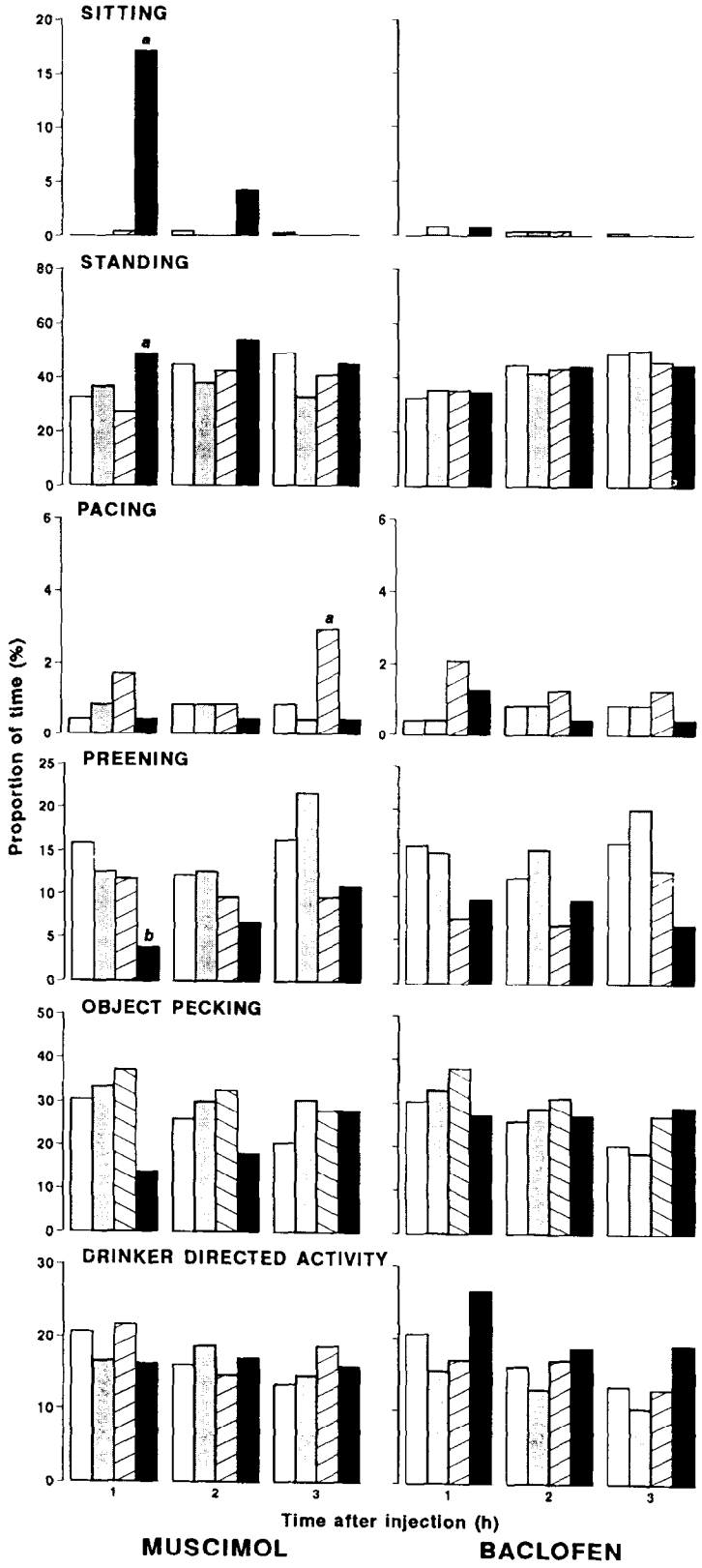

FIG. 4. Mean (n = 8) proportions of time spent per bird in different activities in 3 h (from two alternate 15-min periods per hour) after intravenous injection (1 ml/kg) of either saline (open columns) or low (dotted columns), medium (slanted rule columns), or high (filled columns) doses of two GABA receptor agonists (see the Method section for actual doses) in Experiment 4. Superscripts above columns represent significant differences from the saline treatment in that hour; $^{a}p < 0.05$, $^{b}p < 0.01$.

When there were no significant increases in sitting or standing to indicate sedation, the medium dose (0.2 mg/kg) of the 5-HT_{1A} agonist 8-OH-DPAT caused increased preening in the first hour after injection. It also caused consistent vocalization and scratching behavior immediately after injection (not seen with other treatments), but this was not recorded systematically. The scratching response may correspond to the treading component of the 5-HT behavior syndrome described in rodents and pigeons (11,13,25). Increased preening (or grooming) has not been referred to as part of the 5-HT syndrome, and in restricted-fed broiler breeders it may in some contexts be causally and functionally equivalent to object pecking and drinking (48). Displacement preening has been identified as a response to frustration of feeding in fowls (15). However, neither preening nor the two oral stereotypies were influenced here by the 5-HT_{1A} antagonist NAN-190 (Fig. 1).

In rats, schedule-induced polydipsia and hunger-induced wheel running were attenuated by treatment with a 5-HT_2 agonist, and the former activity was enhanced by a 5-HT_2 antagonist (34,44). Neither of these reports (34,44) provided information about other behavioral responses, so it cannot be judged whether the inhibitory effects of 5-HT agonists reported there were associated with any evidence of sedation. In the present study, attenuation of the two oral stereotypies with medium (0.2 mg/kg) and high (1.0 mg/kg) doses of the 5-HT_2 agonist α-methylserotonin was associated with such evidence (see above); and the medium (0.8 mg/kg) dose of the 5-HT_2 antagonist ketanserin stimulated pacing but not oral activity.

The response to *m*-CPBG (Fig. 2), which has high affinity for 5-HT_3 receptors (28), provides evidence of 5-HT_3 binding sites in the fowl. This was in doubt because Peroutka (43) found no significant specific binding of [^{3}H]-quipazine, another selective 5-HT_3 agonist, in chicken brain membranes, although quipazine itself was behaviorally active in chicks (64). The high (1.0 mg/kg) dose of *m*-CPBG had a nonsignificant biphasic effect on object pecking (Fig. 2) that resembled that of a high (8.0 mg/kg) dose of bromocriptine, a D_2 dopamine receptor agonist, on the same activity in a previous experiment (30). This analogy may be no coincidence because there is evidence of interaction between 5-HT_3 receptors and dopaminergic systems (60). Thus, in vitro activation of 5-HT_3 receptors stimulated dopamine release from rat striatum (6), which is part of a mechanism controlling expression of amphetamine-induced stereotypies (27). Blockade of 5-HT_3 receptors did not antagonize such stereotypies (10), but did suppress amphetamine-induced locomotion through inhibition of dopamine activity in the mesolimbic system (9). In the present study, blockade of 5-HT_3 receptors with MDL-72222 had no significant effect on behavior (Fig. 1).

The $GABA_A$ receptor agonist muscimol was the only GABAergic agent to influence behavior here. It caused increased sitting and standing and reduced preening with the high (1.0 mg/kg) dose, and a delayed increase in pacing with the medium (0.2 mg/kg) dose (Fig. 4). This is similar to its biphasic action on locomotor activity described in mice (53,58). Typically, locomotion and spontaneous motility, in species including ducks, geese, and chick embryos, are stimulated by GABA antagonists and suppressed by GABA agonists when treatments are administered either systemically or centrally (35,41,45,55). In the present study there was no such effect of GABA antagonists on locomotor activity (Fig. 3). Also, in contrast to the reported effects of centrally administered GABA antagonist and agonist treatments on stereotyped behaviors in fowls (37), there was no indication that such treatments influenced the oral stereotypies of restricted-fed broiler breeders when administered systemically.

In conclusion, most of the significant effects of serotonergic and GABAergic agents on behavior in the present study appeared to reflect at least some degree of sedation, and there was no real evidence of any specific influence of these compounds on the oral stereotypies within the range of doses tested.

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REFERENCES

1. Anderson, K. D.; Reiner, A. Striatonigral projection neurons: A retrograde labelling study of the percentages that contain substance P or enkephalin in pigeons. J. Comp. Neurol. 303:658–673; 1991.
2. Antelman, S. M.; Caggiula, A. R. Norepinephrine-dopamine interactions and behavior. Science 195:646–653; 1977.
3. Arnt, J.; Scheel-Kruger, J. Behavioral differences induced by muscimol selectively injected into pars compacta and pars reticulata of substantia nigra. Naunyn Schmiedebergs Arch. Pharmacol. 310:43–51; 1979.
4. Aulakh, C. S.; Hill, J. L.; Yoney, H. T.; Murphy, D. L. Evidence for involvement of 5-HT_{1C} and 5-HT_2 receptors in the food intake suppressant effects of 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI). Psychopharmacology (Berlin) 109:444–448; 1992.
5. Bendotti, C.; Samanin, R. The role of putative 5-HT_{1A} and 5-HT_{1B} receptors in the control of feeding in rats. Life Sci. 41:635–642; 1987.
6. Blandina, P.; Goldfarb, J.; Green, J. P. Activation of a 5-HT_3 receptor releases dopamine from rat striatal slice. Eur. J. Pharmacol. 155:349–350; 1988.
7. Cheng, H. C.; Long, J. P. Dopaminergic nature of apomorphine-induced pecking in pigeons. Eur. J. Pharmacol. 26:313–320; 1974.
8. Cooper, S. J. Interactions between endogenous opioids and dopamine: Implications for reward and aversion. In: Willner, P.; Scheel-Kruger, J., eds. The mesolimbic dopamine system: From motivation to action. New York: Wiley; 1991:331–366.
9. Costall, B.; Domeney, A. M.; Kelley, M. E.; Naylor, R. J.; Tyers, M. B. The antipsychotic potential of GR38032F, a selective antagonist of 5-HT_3 receptors in the central nervous system. Br. J. Pharmacol. 90:89P; 1987.
10. Costall, B.; Domeney, A. M.; Naylor, R. J.; Tyers, M. B. Effects of the 5-HT_3 receptor antagonist, GR38032F, on raised dopaminergic activity in the mesolimbic system of the rat and marmoset brain. Br. J. Pharmacol. 92:881–894; 1987.
11. Curzon, G. Stereotyped and other motor responses to 5-hydroxytryptamine receptor activation. In: Cooper, S. J.; Dourish, C. T., eds. Neurobiology of stereotyped behaviour. Oxford: Clarendon Press; 1990:142–168.
12. Di Chiara, G.; Imperato, A. Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats. J. Pharmacol. Exp. Ther. 244:1067–1080; 1988.
13. Dickinson, S. L.; Curzon, G. Roles of dopamine and 5-hydroxytryptamine in stereotyped and nonstereotyped behaviour. Neuropharmacology 22:805–812; 1983.
14. Dickinson, S. L.; Gadie, B.; Tulloch, I. F. α_1- and α_2-Adrenoreceptor antagonists differentially influence locomotor and stereotyped behaviour induced by *d*-amphetamine and apo-

morphine in the rat. Psychopharmacology (Berlin) 96:521-527; 1988.
15. Duncan, I. J. H.; Wood-Gush, D. G. M. Thwarting of feeding behaviour in the domestic fowl. Anim. Behav. 20:444-451; 1972.
16. Dunnett, C. W. New tables for multiple comparisons with a control. Biometrics 20:482-491; 1964.
17. Dunnett, C. W. Multiple comparisons. In: McArthur, J. W.; Colton, T., eds. Statistics in endocrinology. Cambridge: The MIT Press; 1970:79-103.
18. Falk, J. L. The nature and determinants of adjunctive behavior. Physiol. Behav. 6:577-588; 1971.
19. Goodman, I. J. Amphetamine and apomorphine induced behavior in adult pigeons. Pharmacol. Biochem. Behav. 15:701-704; 1981.
20. Goodman, I.; Zacny, J.; Osman, A.; Azzaro, A.; Donovan, C. Dopaminergic nature of feeding-induced behavioral stereotypies in stressed pigeons. Pharmacol. Biochem. Behav. 18:153-158; 1983.
21. Hine, B.; Wallach, M. B.; Gershon, S. Involvement of biogenic amines in drug-induced aggressive pecking in chicks. Psychopharmacologia 43:215-221; 1975.
22. Hjorth, S.; Sharp, T. Mixed agonist/antagonist properties of NAN-190 at 5-HT_{1A} receptors: Behavioural and in vivo brain microdialysis studies. Life Sci. 46:955-963; 1990.
23. Hocking, P. M.; Waddington, D.; Walker, M. A.; Gilbert, A. B. Control of the development of the ovarian follicular hierarchy in broiler breeder pullets by food restriction during rearing. Br. Poult. Sci. 30:161-174; 1989.
24. Ismaiel, A. M.; Titeler, M.; Miller, K. J.; Smith, T. S.; Glennon, R. A. 5-HT_1 and 5-HT_2 binding profiles of the serotonergic agents alpha-methylserotonin and 2-methylserotonin. J. Med. Chem. 33: 755-758; 1990.
25. Jacobs, B. L. An animal behavior model for studying central serotonergic synapses. Life Sci. 19:777-786; 1976.
26. John, P. W. M. Statistical design and analysis of experiments. New York: Macmillan; 1971.
27. Joyce, E. M.; Iversen, S. D. Dissociable effects of 6-OHDA-induced lesions of neostriatum on anorexia, locomotor activity and stereotypy: The role of behavioural competition. Psychopharmacology (Berlin) 83:363-366; 1984.
28. Kilpatrick, G. J.; Butler, A.; Burridge, J.; Oxford, A. W. 1-(*m*-Chlorophenyl)-biguanide, a potent high affinity 5-HT_3 receptor agonist. Eur. J. Pharmacol. 182:193-197; 1990.
29. Kostal, L.; Savory, C. J.; Hughes, B. O. Diurnal and individual variation in behaviour of restricted-fed broiler breeders. Appl. Anim. Behav. Sci. 32:361-374; 1992.
30. Kostal, L.; Savory, C. J. Influence of pharmacological manipulation of dopamine and opioid receptor subtypes on stereotyped behaviour of restricted-fed fowls. Pharmacol. Biochem. Behav. 48:241-252; 1994.
31. Lacosta, S.; Roberts, D. C. S. MDL-72222, ketanserin, and methysergide pretreatments fail to alter breaking points on a progressive ratio schedule reinforced by intravenous cocaine. Pharmacol. Biochem. Behav. 44:161-165; 1993.
32. Levine, A. S.; Kuskowski, M. A.; Grace, M.; Billington, C. J. Food deprivation-induced vs. drug-induced feeding: A behavioral evaluation. Am. J. Physiol. 260:R546-R552; 1991.
33. Lintern-Moore, S. The relationship between water intake and the production of "wet" droppings in the domestic fowl. Br. Poult. Sci. 13:237-242; 1972.
34. Lu, C. C.; Tseng, C. J.; Wan, F. J.; Yin, T. H.; Tung, C. S. Role of locus coeruleus and serotonergic drug actions on schedule-induced polydipsia. Pharmacol. Biochem. Behav. 43:255-261; 1992.
35. Maderdrut, J. L.; Reitzel, J. L.; Oppenheim, R. W. Further behavioral analysis of GABA-mediated inhibition in the early chick embryo. Dev. Brain Res. 25:157-160; 1986.
36. Mavridis, M.; Colpaert, F. C.; Millan, M. J. Differential modulation of (+)-amphetamine-induced rotation in unilateral substantia nigra-lesioned rats by α_1 as compared to α_2 agonists and antagonists. Brain Res. 562:216-224; 1991.
37. Nistico, G. Relations between dopaminergic and GABAergic mechanisms in avian brain. Pharmacol. Res. Commun. 12:507-514; 1980.
38. Odberg, F. O. Abnormal behaviours: Stereotypies. In: Proceedings of the 1st world congress on ethology applied to zootechnics. Madrid; 1978:475-480.
39. Osuide, G.; Adejoh, P. O. Effects of apomorphine and its interaction with other drugs in the domestic fowl. Eur. J. Pharmacol. 23:56-66; 1973.
40. Palya, W. L.; Zacny, J. P. Stereotyped adjunctive pecking by caged pigeons. Anim. Learn. Behav. 8:293-303; 1980.
41. Paredes, R. G.; Agmo, A. GABA and behavior: The role of receptor subtypes. Neurosci. Biobehav. Rev. 16:145-170; 1992.
42. Parsons, L. H.; Justice, J. B. Perfusate serotonin increases extracellular dopamine in the nucleus accumbens as measured by in vivo microdialysis. Brain Res. 606:195-199; 1993.
43. Peroutka, S. J. Species variations in 5-HT_3 recognition sites labelled by [^{3}H]-quipazine in the central nervous system. Naunyn Schmiedbergs Arch. Pharmacol. 338:472-475; 1988.
44. Pirke, K. M.; Broocks, A.; Wilckens, T.; Marquard, R.; Schweiger, U. Starvation-induced hyperactivity in the rat: The role of endocrine and neurotransmitter changes. Neurosci. Biobehav. Rev. 17:287-294; 1993.
45. Reitzel, J. L.; Maderdrut, J. L.; Oppenheim, R. W. Behavioral and biochemical analysis of GABA-mediated inhibition in the early chick embryo. Brain Res. 172:487-504; 1979.
46. Rieke, G. K. The TPc, the avian substantia nigra: Pharmacology and behavior. Physiol. Behav. 28:755-763; 1982.
47. Rushen, J. P. Stereotypies, aggression and the feeding schedules of tethered sows. Appl. Anim. Behav. Sci. 14:137-147; 1985.
48. Savory, C. J.; Maros, K. Influence of degree of food restriction, age and time of day on behaviour of broiler breeder chickens. Behav. Proc. 29:179-190; 1993.
49. Savory, C. J.; Maros, K.; Rutter, S. M. Assessment of hunger in growing broiler breeders in relation to a commercial restricted feeding programme. Anim. Welfare 2:131-152; 1993.
50. Savory, C. J.; Kostal, L. The role of adrenoreceptors in control of oral stereotyped behaviour in restricted-fed fowls. Pharmacol. Biochem. Behav. 49:295-302; 1994.
51. Scheel-Kruger, J. Dopamine-GABA interactions: Evidence that GABA transmits, modulates and mediates dopaminergic functions in the basal ganglia and the limbic system. Acta Neurol. Scand. 73(Suppl. 107):9-54; 1986.
52. Scheel-Kruger, J.; Arnt, J.; Magelund, G. Behavioural stimulation induced by muscimol and other GABA agonists injected into the substantia nigra. Neurosci. Lett. 4:351-356; 1977.
53. Scheel-Kruger, J.; Christensen, A. V.; Arnt, J. Muscimol differentially facilitates stereotypy but antagonizes motility induced by dopaminergic drugs: A complex GABA-dopamine interaction. Life Sci. 22:75-84; 1978.
54. Shephard, R. A.; Wedlock, P.; Wilson, N. E. Direct evidence for mediation of an anticonflict effect of baclofen by $GABA_b$ receptors. Pharmacol. Biochem. Behav. 41:651-653; 1992.
55. Sholomenko, G. N.; Funk, G. D.; Steeves, J. D. Avian locomotion activated by brainstem infusion of neurotransmitter agonists and antagonists. II. γ-Aminobutyric acid. Exp. Brain Res. 85: 674-681; 1991.
56. Slater, P. J. B. Data collection. In: Colgan, P. W., ed. Quantitative ethology. New York: Wiley; 1978:7-24.
57. Terlouw, E. M. C.; De Rosa, G.; Lawrence, A. B.; Illius, A. W.; Ladewig, J. Behavioural responses to amphetamine and apomorphine in pigs. Pharmacol. Biochem. Behav. 43:329-340; 1992.
58. Tirelli, E.; Jodogne, C.; Perikel, J. J. Adult-like biphasic neurobehavioural changes induced by a $GABA_A$ agonist in infant and weanling mice. Dev. Brain Res. 61:207-215; 1991.
59. Toal, L.; Leslie, J. C.; Shephard, R. A. Effects of chlordiazepoxide and putative anxiogenics on conditioned suppression in rats. Pharmacol. Biochem. Behav. 49:1085-1090; 1991.
60. Tricklebank, M. D. Interactions between dopamine and 5-HT_3 receptors suggest new treatments for psychosis and drug addiction. Trends Pharmacol. Sci. 10:127-129; 1989.
61. Tricklebank, M. D.; Forler, C.; Fozard, J. The involvement of subtypes of 5-HT_1 receptor and of catecholaminergic systems in

the behavioral response to 8-hydroxy-2-(di-*n*-propylamino)tetralin in the rat. Eur. J. Pharmacol. 106:271–282, 1984.
62. Von Borell, E.; Hurnik, J. F. The effect of haloperidol on the performance of stereotyped behavior in sows. Life Sci. 49:309–314; 1991.
63. Waddington, J. L.; Molloy, A. G.; O'Boyle, K. M.; Pugh, M. T. Aspects of stereotyped and nonstereotyped behaviour in relation to dopamine receptor subtypes. In: Cooper, S. J.; Dourish, C. T., eds. Neurobiology of stereotyped behaviour. Oxford: Clarendon Press; 1990:64–90.
64. Wallnau, L. B. The effects of quipazine, fenfluramine and apomorphine on the morphine potentiation of tonic immobility. Pharmacol. Biochem. Behav. 15:895–901; 1981.
65. Wiezman, A.; Bidder, M.; Fares, F.; Gavish, M. Food deprivation modulates γ-aminobutyric acid receptors and peripheral benzodiazepine binding sites in rats. Brain Res. 535:96–100; 1990.