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Serotonergic Modulation of Ingestive Behavior in Pigeons

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GÜNTÜRKÜN, O., A. GROTHUES, A. HAUTKAPPE, F. VISÉ, N. WAWRZYNIAK AND U. ZWILLING. *Serotonergic modulation of ingestive behavior in pigeons.* PHARMACOL BIOCHEM BEHAV 32(2) 415–420, 1989.—The effects of peripheral administration of the serotonin agonist zimeldine and the serotonin antagonist cyproheptadine on food and water consumption were evaluated in domestic pigeons. Injections of zimeldine reduced the amount of feeding and drinking dose-dependently in 24-hr fasted animals. Administration of cyproheptadine enhanced food and water consumption dose-dependently up to a dose of 160 μg per 100 g body weight in nondeprived pigeons. Higher doses reduced ingestion probably due to a general behavioral depression. The effect of zimeldine was antagonized by cyproheptadine. It is concluded that, as in mammals, serotonin participates as an inhibitor in the regulation of feeding in birds. Contrary to the situation in mammals it has no activating effect on drinking but leads to a reduction of water consumption in pigeons.

Feeding Drinking Serotonin Zimeldine Cyproheptadine Pigeons

SINCE the classical discovery of Grossman (18) that injections of norepinephrine into the hypothalamus induce feeding behavior in rats, the influence of different transmitter systems on ingestive behavior has been extensively studied. While it is generally accepted that dopamine and norepinephrine have a reliable effect on feeding, the role of serotonin (5-HT) has long been underestimated (20). Recent experiments have demonstrated that administration of serotonin antagonists such as cyproheptadine increases food intake in mammals (17,37), whereas serotonin agonists decrease feeding dose-dependently by a reduction of meal size and feeding bout duration (13, 14, 33). Lesions of the B8 raphe nuclei deplete 5-HT levels in the forebrain and lead to weight gains in rats (16), while intrahypothalamic injection of serotonin inhibits food intake (23). These studies suggest an inhibiting role of serotonin in the control of feeding behavior.

Experiments related to the influence of the serotonergic system on water intake in mammals have demonstrated that intrahypothalamic 5-HT injections produce a dipsogenic response while peripheral injections of serotonin or its precursor 5-hydroxytryptophan (5-HTP) lead to an enhancement of water consumption through an enhancement of the plasma renin concentration (22, 23, 25, 26, 40). Although the exact mechanisms with which the serotonergic system contributes centrally and peripherally to the regulation of drinking are only poorly understood, most studies indicate an activating role of serotonin in the regulation of water consumption [but see (17)].

Most of the research on the influence of different transmitter systems on ingestive behavior has been performed with mammals, while birds, also widely used for behavioral, physiological and anatomical experiments, have generally been less extensively studied. Denbow and co-workers (8–10) studied the effect of intraventricular 5-HT injections in chicks and turkeys and found a decrease in the amount of ingested food after administration of this transmitter. Although this resembles the results found in studies with mammals, the experiments with injections of 5-HT or its agonists are complicated by the fact that, beside their accepted role in the regulation of feeding, they often additionally induce a profound behavioral depression which could secondarily suppress feeding (1,2). One possibility to demonstrate that the effect of 5-HT on feeding is not a side effect of such a behavioral depression is to inject serotonin antagonists which should elicit food intake. The present experiments were therefore designed to determine the effect of administration of serotonin agonists and antagonists on food intake and water consumption in pigeons.

METHOD

Four experiments were conducted with 24 adult, drug naive domestic pigeons (*Columba livia*) of undetermined sex which were obtained from local breeders. Eight birds were used for the first two experiments, eight for the third and eight for the fourth experiment. During the study, these birds were kept in individual wire mesh cages, which were all situated in the same room.

The drugs used were the serotonin agonist zimeldine, $2HCl \cdot H_2O$ (Astra Läkemedel AB), an inhibitor of the neuronal reuptake of 5-HT (31), the serotonin antagonist cyproheptadine, HCl (Merck, Sharp and Dohme), a postsynaptic 5-HT receptor blocker (30), and pimozide (Janssen), a dopamine receptor blocker (30). Zimeldine and cyproheptamine were always dissolved in distilled water due to difficulties encountered in previous attempts to dissolve

cyproheptadine in saline. Pimozide was dissolved in 0.3% tartaric acid with a concentration of 0.3 mg/ml. Injections were given into the pectoral muscles and at least two days separated consecutive injections to the same individual. The order of injection of the various doses of the substances was counterbalanced.

The aim of the first experiment was to determine the effect of zimeldine injections on food intake and water consumption. In a pilot study zimeldine had reduced the amount of food and water ingested. To demonstrate this hypophagic and hypodipsic effect more clearly, the food and water containers of the pigeons were removed 24 hr before drug administration to induce a mild deprivation. Solutions consisted of 0.5 ml distilled water (control) or 5, 7.5, 10 or 20 mg zimeldine per 100 g body weight. Zimeldine was dissolved in the same vehicle. Directly after injections the animals were released into their home cages where their containers had been returned with 40 g of grain and 100 ml of water. The quantity of food left in the containers was weighed to the nearest 0.1 g at 30, 60, 90, 120, 150, 180, 210 and 240 minute postinjection. Within the same intervals the remaining water volumes were also measured to the nearest 0.5 ml. Approximately 15 sec were needed to perform a single food and water measurement. Data were converted into cumulative amounts of food and water ingested as a function of time after the injection. Since all treatments resulted in a nearly linear increase in the cumulative curves, only the 240 minute intakes were statistically analyzed with a Friedman ANOVA. When this test yielded a significant result ($p<0.05$), post hoc pairwise comparisons between the control and each of the experimental conditions were performed with the Wilcoxon test.

In the second experiment, using the same animals after an interval of 7 days, the effects of cyproheptadine injections on food and water ingestion were studied. The experiment was performed with satiated birds that had a grain mixture and tap water available continuously. The injected solutions consisted of 150, 155, 160, 165, 170, 180 and 190 μg cyproheptadine per 100 g body weight. The drug was dissolved in distilled water to a concentration of 1 mg/ml. Since even small alterations in the amount of cyproheptadine had markedly different effects, extreme care was taken to weigh the animals precisely before each treatment and to inject the calculated individual volume to the nearest 0.025 ml. The procedure and the time schedule of determining the amounts of food and water ingested as well as the data analysis were identical to that used in the first experiment.

The third experiment was a replication of a part of the second with eight new, drug-naive pigeons. As described in the Results section (see below), increases in the cyproheptadine doses up to 160 μg resulted in increasing food and water consumption. However, further increases in dosage lead to a reduction in ingestive behavior. Since it is difficult to test the resulting inverse U-shaped function with a conventional ANOVA, the aim of the third experiment was to replicate and to verify statistically the results of the second experiment for the control injection (0.5 ml distilled water) and the injection of 155 or 160 μg cyproheptadine per 100 g body weight. These two doses had yielded dose-dependent increases of feeding and drinking in the second experiment. Measurement of food and water intake were unchanged with respect to the previous experiment.

The fourth experiment was determined to test the interaction of the different drugs use. For this purpose cyproheptadine and zimeldine or cyproheptadine and pimozide were injected simultaneously. Pimozide is a dopamine receptor blocker which is known to exert a hypophagic effect (4,39).

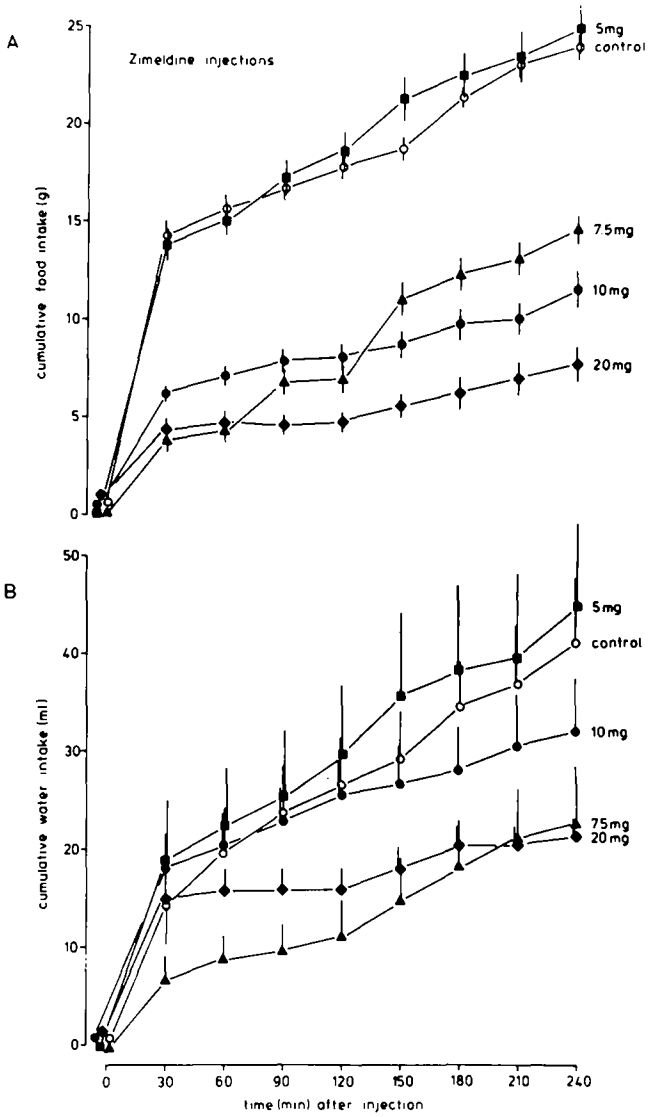

FIG. 1. Cumulative food and (B) water intake of 24-hr food- and water-deprived pigeons (n=8) as a function of time after the intramuscular injection of zimeldine at 4 doses, or of the control solution (0.5 ml distilled water). Bars indicate standard errors.

Eight new, drug-naive and satiated pigeons were used. The drugs were administered in the following dosages: cyproheptadine (160 μg per 100 g body weight), zimeldine (20 mg per 100 g body weight), pimozide (30 μg per 100 g body weight). In a pilot study it was shown that these dosages of pimozide and zimeldine both exert comparable hypophagic effects. With two-day intervals 0.5 ml distilled water (control), cyproheptadine, zimeldine, cyproheptadine + zimeldine, pimozide, and pimozide + cyproheptadine were injected. After 120 min the ingested amounts of food and water were determined as described for the first experiment.

RESULTS

Experiment I: Effects of Zimeldine

Results obtained for food intake after treatment with different zimeldine doses or the control injection are shown in Fig. 1A. The Friedman ANOVA reveals a significant effect of zimeldine on feeding ($p<0.001$). While injections with 5

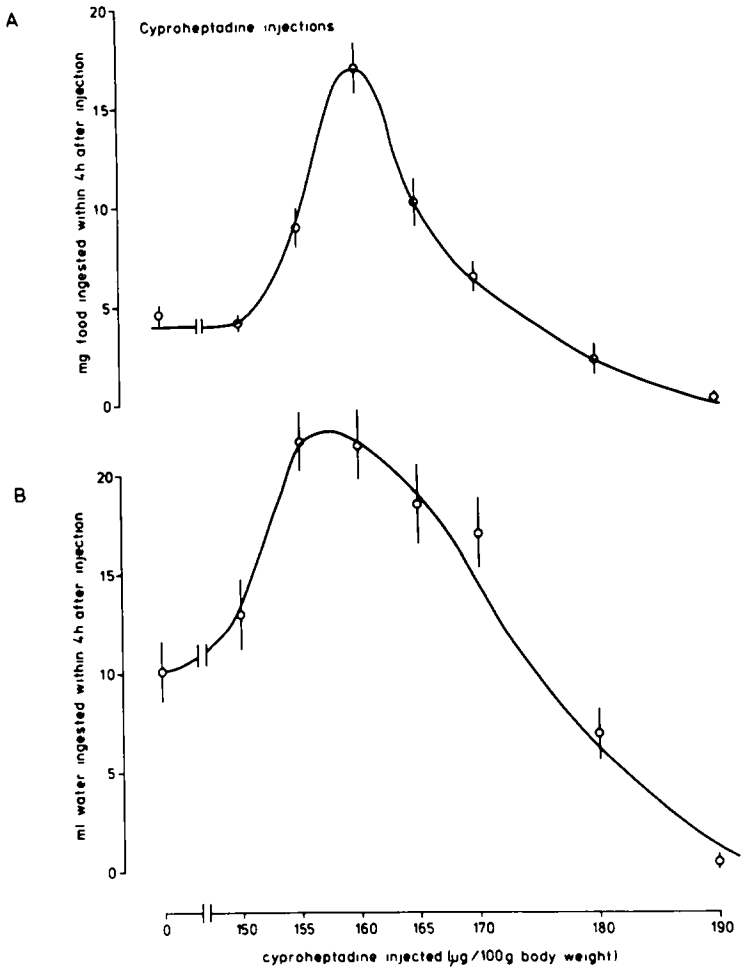

FIG. 2. (A) Amount of food and (B) water consumed by nondeprived pigeons (n=8) within 4 hr after injection of the 7 different cyproheptadine doses, or of the control solution (0.5 ml distilled water). Bars indicate standard errors.

mg per 100 g body weight of the drug had no effect on food consumption, administrations of 7.5, 10 and 20 mg zimeldine decreased feeding significantly and dose-dependently ($p<0.02$ for 7.5 mg, $p<0.01$ for 10 and 20 mg).

A similar result was obtained for water consumption (Fig. 1B). The Friedman ANOVA reveals a significant general effect of zimeldine on drinking ($p<0.001$). While injections of 5 mg again had no effect, all other doses reduced water intake significantly ($p<0.02$ for 10 mg, $p<0.01$ for 7.5 and 20 mg).

Experiment II and III: Effects of Cyproheptadine

Figure 2A shows the amount of food consumed within 4 hr after injection as a function of the different cyproheptadine doses used. As can be seen a dosage of 150 μg per 100 g body weight had no effect on food intake relative to the control injection. Higher doses of up to 160 μg increased feeding by up to four times the amount consumed after control injections. Even higher doses decreased food intake until the pigeons virtually stopped feeding after injections of 190 μg cyproheptadine per 100 g body weight. A similar effect was obtained for water ingestion (Fig. 2B). Although no quantitative behavioral measures were obtained, it was obvious during the experiment that the activity of the pigeons after injections with cyproheptadine doses higher than 170 μg was markedly reduced. After administration of 180 μg of the drug the animals sat motionless in their cages. After 190 μg they generally squatted with their eyes closed, even when gently prodded. These observations indicate that injections of 155 and 160 μg cyproheptadine lead to increases in ingestive behavior, but that administrations of higher doses induced a widespread behavioral depression during which the animals were unable to feed or drink. It is difficult to test the resulting inverse U-shaped function of feeding and drinking after increasing cyproheptadine doses with conventional statistical methods. A Friedman ANOVA with eight animals and eight different treatments applied to each of these animals gave no significant results ($p>0.1$ for feeding and drinking respectively). Therefore we decided to replicate this experiment with eight new pigeons. These drug-naive animals were injected at two-day intervals with 0.5 ml distilled water with 155 and 160 μg cyproheptadine. These doses had yielded a dose-dependent enhancement of ingestion.

The results of this third experiment are depicted in Fig. 3. Although the effects were slightly smaller, there was no marked difference with the results of the second experiment. Increasing cyproheptadine doses resulted in dose-dependent increases in food and water intake (Friedman ANOVA, each

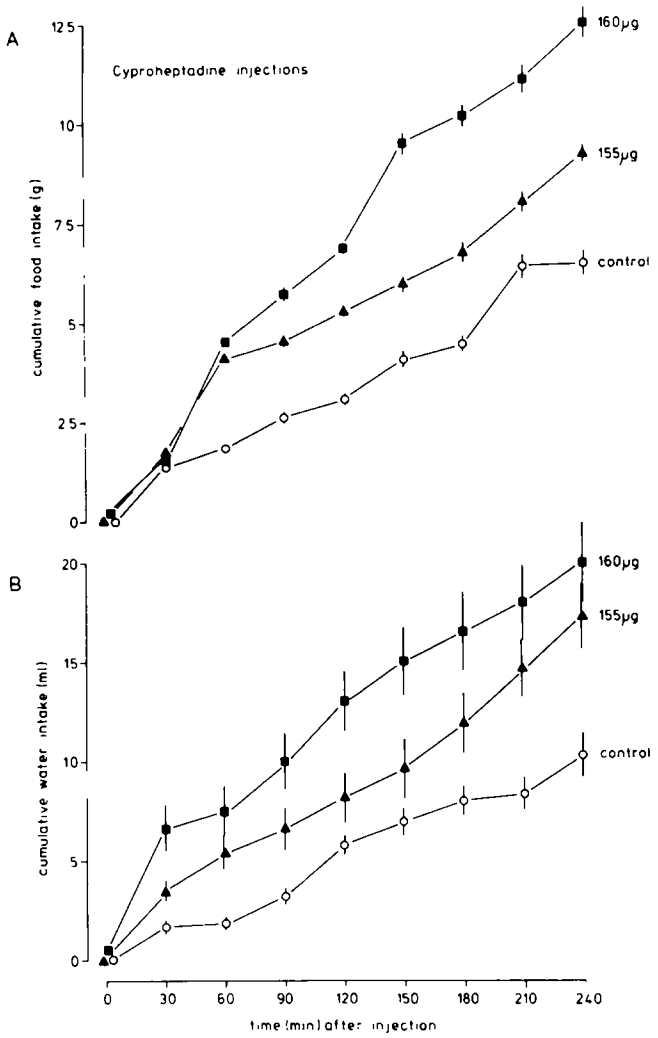

FIG. 3. (A) Cumulative food and (B) water intake of nondeprived pigeons (n=8) as a function of time after the intramuscular injection of cyproheptadine at 2 doses, or of the control solution (0.5 ml distilled water). Bars indicate standard errors.

$p<0.05$). Separate analysis with the Wilcoxon test revealed that both doses yielded significant enhancement of feeding ($p<0.05$ for 155 µg, $p<0.02$ for 160 µg cyproheptadine) and drinking ($p<0.05$ for both 155 and 160 µg cyproheptadine) in comparison with the control injections.

Experiment IV: Interaction of Cyproheptadine With Zimeldine and Pimozide

Results obtained for food and water intake after treatments with different combinations of cyproheptadine, zimeldine and pimozide are shown in Fig. 4A and B. The Friedman ANOVA reveals a significant effect of the injections both on feeding and drinking ($p<0.05$ each). As demonstrated in the previous experiments, cyproheptadine increased the ingested amounts of food and water, while zimeldine injections lead to a hypophagic and hypodipsic response. Both for food and water the amounts ingested were approximately ten times higher after cyproheptadine than after zimeldine injections (both $p<0.01$). Pimozide had

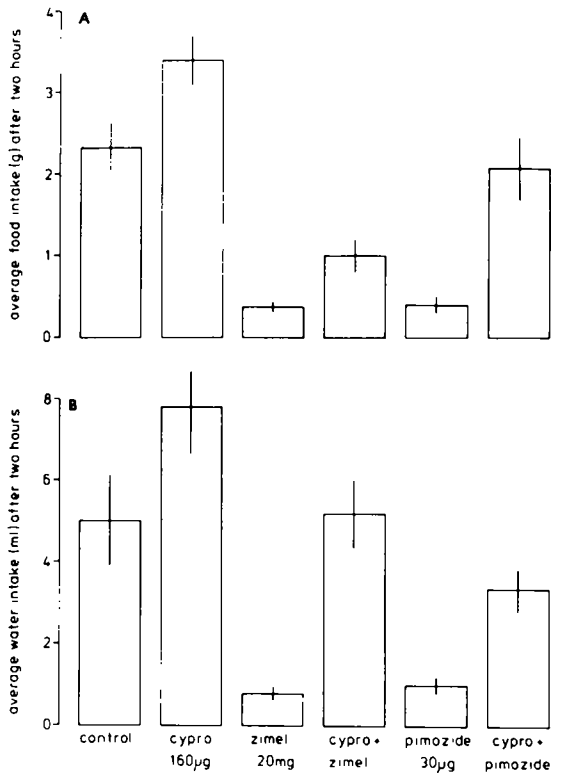

FIG. 4. Average food and water intake of nondeprived pigeons (n=8) two hours after injection of 0.5 ml distilled water (control), cyproheptadine, zimeldine, cyproheptadine + zimeldine, pimozide or pimozide + cyproheptadine. Bars indicate standard errors.

an effect similar to zimeldine. It decreased feeding and drinking significantly relative to the control injections ($p<0.01$).

The results of combined injections demonstrate that the effect of zimeldine was partly antagonized by cyproheptadine. This effect was more obvious for drinking for which the average amount of ingested water was approximately equal to the amount ingested after control injections. Pigeons with combined injections of cyproheptadine and zimeldine, ingested significantly more water than birds which were injected only with zimeldine ($p<0.01$). The results are not equally obvious for feeding. Combined cyproheptadine and zimeldine injections led to an amount of food ingested which was enhanced relative to the zimeldine administrations, but did not reach the amount consumed after control injections. As a consequence, the results of the combined injections for feeding did not significantly differ from the results after control and from the results after zimeldine injections ($p>0.05$ for each).

Combined injections of cyproheptadine and pimozide showed that both for feeding and drinking the hypophagic and hypodipsic effect of pimozide was abolished by cyproheptadine. The results of the combined injections did not differ from the control injections, but were significantly enhanced relative to the pimozide administrations (feeding and drinking, $p<0.05$ each).

DISCUSSION

The present study shows that the serotonin agonist zimeldine decreases feeding and drinking dose-dependently.

Injections of the serotonin antagonist cyproheptadine has the reverse effect and leads to an increase in the amount of food and water consumed. These results clearly demonstrate an inhibitory role of the serotonergic system in the control of ingestive behavior in birds.

The effect of serotonin on feeding in pigeons accords with studies in mammals which have yielded much evidence for a 5-HT contribution in the control of food intake. Peripheral injection of the 5-HT precursor 5-hydroxytryptophan (5-HTP) or of fenfluramine, which enhances the release and blocks the neuronal reuptake of endogenous 5-HT, has been shown to produce a dose-dependent suppression of feeding (3, 6, 32, 36). This effect of fenfluramine is antagonized by administration of postsynaptic 5-HT receptor blockers and by lesions of the median raphe nuclei, which synthesize 5-HT (16,34). Central 5-HT injections into the paraventricular nucleus of the rat lead to a dose-dependent suppression of feeding (24). Peripheral administration of 5-HT receptor blockers leads to the opposite effect and enhances food intake as demonstrated for pizotifen (38) and cyproheptadine (17,38). Serotonergic neurons in mammals seem to modulate feeding mainly by an activatory influence on the hypothalamic ventromedial and paraventricular nuclei (24,27). Since the distribution of monoamines in the hypothalamus of birds and mammals match (15,35), future studies will show whether the central mechanisms with which 5-HT neurons modulate feeding in pigeons also resemble those of mammals.

The present study demonstrates that the serotonergic system has an inhibitory influence on water consumption in birds. By contrast, experiments with rats demonstrated that 5-HT and 5-HTP are potent dipsogens which increase the consumption of water (22, 23, 26). Peripheral inhibition of the decarboxylation of 5-HTP with carbidopa abolished the 5-HTP-induced drinking response without affecting the dipsogenic response to serotonin (22). This finding suggests that conversion of 5-HTP to serotonin at a peripheral site contributes in rats to an induction of drinking. The serotonergic mediation of water consumption additionally seems to be centrally mediated in mammals, since blockade of central serotonergic receptors inhibited the 5-HTP-induced drinking response in the dog, while direct intrahypothalamic serotonin administrations produced a dipsogenic response in monkeys (28,41). These studies indicate that an increase in the centrally and peripherally available serotonin concentration leads to drinking in mammals. Since an incresae of the synaptic concentration and thus of receptor occupancy of 5-HT led to a decrease of water consumption in the pigeons of the present study, the drinking system of birds and mammals seems to differ with respect to its serotonergic subsystem. Deviche and Schepers (11,12) demonstrated that the drinking system of birds and mammals additionally differs with respect to the opioid system: while it is established that injections of opiate antagonists attenuate drinking in rats (7), the same treatment has no effect on water intake in pigeons. This indicates that, contrary to feeding, the drinking systems of birds and mammals demonstrate important differences, at least for the serotonergic and opioid systems.

From the present data it is not possible to reveal whether the effects of feeding and drinking take place independently and simultaneously or whether the effect on drinking is secondary to feeding. That both effects occur within the first 30 minutes indicates that they seem to be independent. This assumption is supported by the observation of pilot studies in which feeding and drinking were equally enhanced also within the first 15 minutes after injection.

The suppression of feeding and drinking after high doses of cyproheptadine seems to be due to a serotonergically mediated widespread behavioral depression as previously observed in studies with rats (1,2). Similar results with birds were obtained by Hingtgen and Aprison (19) who found a marked decline of operant pecking behavior in pigeons after peripheral injections of α-methyl-m-tyrosine, which depletes serotonin and norepinephrine levels in brain and peripheral tissue. The behavioral depression of the pigeons correlated with the time course of brain serotonin depletions but not with that of norepinephrine reduction.

The results of the experiment with combined injections demonstrate that the effect of zimeldine can at least partly be antagonized with cyproheptadine. This effect is more obvious for drinking than for feeding. This may be an evidence for an involvement of different 5-HT receptor types in the modulation of feeding and drinking. Slightly different affinities of zimeldine and cyproheptadine would then cause different effects with respect to food and water intake.

The effect of pimozide on feeding in pigeons accords with different previous studies which demonstrated a dopaminergic modulation of food intake in mammals (4,39). The fact that the hypophagic and hypodipsic effect of pimozide could be reduced by cyproheptadine could indicate that serotonin as well as dopamine act independently on neural substrates which control ingestion. Recent theoretical propositions have drawn attention to models of feeding embodying multiple neurochemical controls in which different transmitters interact in hypothalamic subnuclei (3,27). These ideas are in keeping with the notion that the microregulatory controls over feeding can be experimentally separated and it seems likely that afferent neurochemical systems may be involved in the control of distinct features of ingestion (4). This detailed information is completely lacking in birds. But further comparative studies with species of different classes could reveal important information on the general pattern of how transmitter systems interact in the control of feeding and drinking.

From the present data it is not possible to conclude whether the modification of the ingestive behavior may have arisen by direct action on brain 5-HT or indirectly by changes in the gut, where 90–98% of the total serotonin amount is located (21). In mammals it is known that the serotonergic modulation of ingestion is centrally as well as peripherally mediated (2, 3, 20, 24, 29). Preliminary data from our laboratory demonstrate that intraventricular administrations of small amounts of cyproheptadine, which are far below the effective dose for peripheral injections, significantly enhance the amount of ingested food and water in pigeons. This accords with other experiments in birds which demonstrated a hypophagic effect after intraventricular 5-HT injections (8–10). These studies suggest that the serotonergic system of birds may modulate feeding and drinking at least in part via central mechanisms.

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