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Opiate Antagonists Stereoselectively Attenuate the Consumption of Food But Not of Water by Pigeons

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DEVICHE, P. AND A. WOHLAND. *Opiate antagonists stereoselectively attenuate the consumption of food but not of water by pigeons.* PHARMACOL BIOCHEM BEHAV 21(4) 507–512, 1984.—Three experiments were performed to evaluate the influence of the two opiate antagonists, naloxone HCl (NAL) and Mr 2266, on the ingestive behavior of domestic pigeons. In the first and second experiments, these drugs were administered at 3 doses (0.25, 1 and 4 mg) to non-deprived and to 24 hr-fasted pigeons, respectively. Measure of the food and water consumption of the birds for up to 6 hrs post-injection revealed that as compared to control values, administration of both antagonists attenuated feeding without reducing drinking. Administration of both drugs produced a rather similar anorexic effect, with the difference that Mr 2266 tended to decrease the food intake for a longer period of time than did NAL. In the third experiment, the food consumption of fasted pigeons was reduced by the injection of Mr 2266, but not of its (+) stereoisomer Mr 2267, showing that the behavioral influence of Mr 2266 is stereoselective. Confronted with other studies, these results suggest that in pigeons, opiate receptors participate in the regulation of the food consumption without playing a major role in the control of the water intake.

Drinking Feeding Ingestive behavior Mr 2266 Naloxone Opiate antagonists Stereoselectivity Pigeons

MUCH evidence has now been collected suggesting that endogenous opiates participate in the regulation of ingestive behavior (for reviews, see [21, 23, 26, 30]. Studies performed with opiate antagonists like naloxone (NAL) are consistent with this hypothesis. Given in a wide variety of experimental situations, these substances attenuate the consumption of food and of water [3, 4, 17, 28, 29]. This reduction is considered to arise from a central effect of these drugs [2, 6, 7, 33] and to result from a specific interaction with opioid receptors. For example, the potency of various opiate antagonists to attenuate drinking correlates with their relative binding affinity for the brain opioid receptors [1]. Furthermore, the decreased consumption of food and of water which is produced by opiate antagonists is stereoselective [18, 25, 32]. Finally, treatment of satiated animals with either opiate agonists [16, 31, 34] or with opioid peptides [11, 15, 19, 20] can induce changes in the opposite direction, that is stimulate ingestive behavior.

We recently started to examine the possible involvement of opiate substances in the control of food and water intake in domestic pigeons. In this species, peripheral as well as central administration of NAL reduced feeding [8,10] whereas intracerebral injection of β-endorphin enhanced the consumption of food [9]. By contrast, treatment with NAL at doses which quite efficiently reduced feeding failed to alter the water intake of pigeons placed in several experimental situations [5,8], leading to propose that contrary to mammals, pigeons may lack an endorphinergic regulation of drinking.

The present study was initiated to obtain additional information concerning the opioid control of ingestive behavior in pigeons. To this aim, we first compared the effects of the administration of NAL with that of the other opiate antagonist, Mr 2266, on the ingestive behavior of either satiated or fasted pigeons. In rats, Mr 2266 binds with a relatively higher affinity than NAL to the brain kappa opioid receptors [12,27]; this receptor subtype appears to be involved in the regulation of the water [14] as well as the food [22] intake of these animals. We reasoned that if the same is true in pigeons, it might then be that although no effect of NAL injection on drinking has been hitherto detected, administration of Mr 2266 may nonetheless influence this behavior. Furthermore, if kappa opioid receptors play a role in the food ingestion of pigeons, injections of Mr 2266 should attenuate feeding as or more efficiently than does the treatment with equivalent amounts of NAL.

In this investigation, we also investigated whether the anorexic influence of Mr 2266 administration to pigeons is stereoselective. The results obtained show that this is the case, and they support the view that in this species, opiate antagonists reduce feeding by specifically interacting with opiate receptors.

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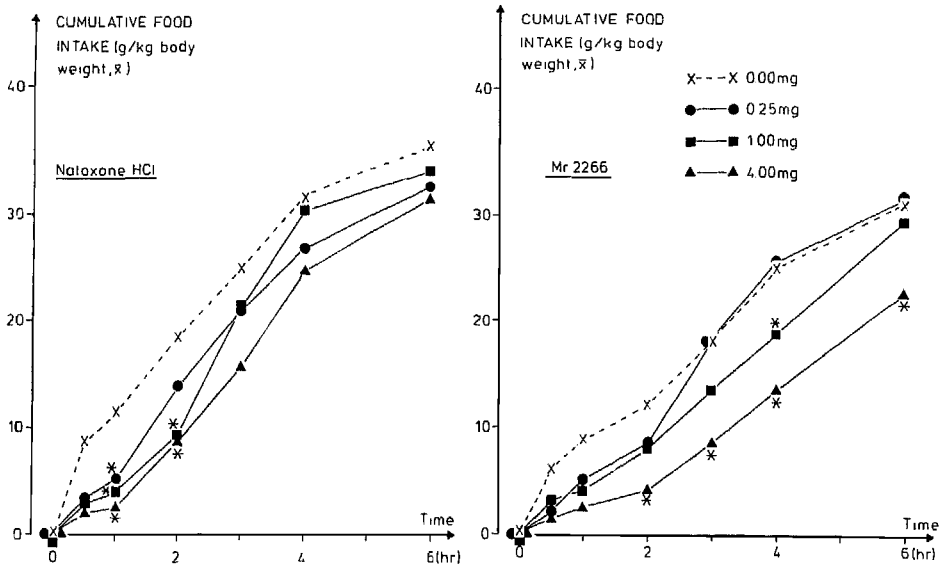

FIG. 1. Cumulative food intake of non-deprived domestic pigeons (n=9) as a function of time after the intramuscular injection of either naloxone HCl or Mr 2266 at 3 doses, or the corresponding control solutions (for naloxone HCl:0.5 ml of isotonic saline; for Mr 2266:0.8 ml of 0.1 N HCl); *2-tailed probability ≤ 0.05, comparison with corresponding control values, Student's *t*-test. Standard errors have been omitted to clarify the picture.

METHOD

Birds

The subjects were 9 adult drug naive domestic pigeons (*Columba livia L.*) of undetermined sex, weighing 440±20 g (mean±SE) and obtained from local breeders. During the experiments, the birds were kept in individual wire mesh cages, which were all situated in the same room but visually isolated from adjacent cages. The room temperature was maintained to about 18°C, and lighting was provided by fluorescent strip lights from 0700 hr to 2000 hr. Except during the testing sessions (see below), standard food (mixed grain) and grit were continuously available. Tap water was always provided ad lib.

Treatments

The same birds were used for 3 consecutive experiments, which were separated from each other by a minimal interval of 7 days.

The *first experiment* examined the influence of either NAL or (−)-2-(3-furylmethyl)-noretazocine (Mr 2266) injection on the consumption of food and water by freely feeding and drinking pigeons. Each antagonist was given at 3 doses, which were 0.25, 1 and 4 mg; NAL was dissolved in 0.9% saline, to reach a final volume of 0.5 ml/injection, whereas Mr 2266 was dissolved in 0.1 N HCl, to reach a final volume of 0.8 ml/injection. As controls, the birds received an injection of 0.5 ml saline, and another one consisting of 0.8 ml of 0.1 N HCl.

In the *second experiment*, the same treatments were administered as in the first experiment, but the birds were 24 hr food-deprived at the time of the injections.

The *third experiment* aimed at determining whether the effects of Mr 2266 injection which were observed in the other experiments were stereoselective. For this, each pigeon received 3 injections of Mr 2266 at the same concentrations as before (0.25, 1 and 4 mg), and identical quantities of the (+) stereoisomer of this drug, that is Mr 2267. Both compounds were dissolved in 0.1 N HCl to reach a final volume of 0.8 ml/injection; this quantity of the vehicle was also given as control.

Injections were administered into the pectoral muscles, in an individually randomized order, and in the afternoon. Each pigeon received each treatment, and it therefore served as its own control. A minimal interval of 2 days separated consecutive injections to a same individual.

Procedure

Before administering the solutions, the food and water containers were removed from the cages, emptied when necessary, and replenished with a precisely measured quantity of either standard food or tap water. The food containers were sufficiently large and deep to prevent any significant spillage when the birds ate. The pigeons were then weighed to the nearest 5 g, injected, and immediately released into their home cage. Meanwhile, their food and water containers had been returned. The amounts left in them was measured to the nearest 0.1 g after 30, 60, 120, 180, 240 and 360 min; approximately 10 sec were required to perform any single measure. Data were transformed into cumulative amounts of food and water ingested per kg of body weight as a function of time post-injection.

Data Analysis

The data were submitted to two-way analyses of the variance (ANOVAs) for repeated measures (BMDP2V program, Los Angeles, CA), which enabled to detect differences between various treatments, effects across the time, and inter-

TABLE 1

CUMULATIVE WATER INTAKE (MEAN ± SE) OF EITHER NON-DEPRIVED (UPPER PANEL) OR 24 HR-FASTED (LOWER PANEL) PIGEONS (N=9) AS A FUNCTION OF TIME AFTER THE INTRAMUSCULAR INJECTION OF EITHER NALOXONE HCl OR MR 2266 AT 3 DOSES, OR THE CORRESPONDING CONTROL SOLUTIONS (FOR NALOXONE HCl: C1=0.5 ml OF ISOTONIC SALINE; FOR MR 2266:C2=0.8 ml OF 0.1 N HCl)

Non-Deprived Pigeons

Time After Injection (min)	Naloxone HCl				Mr 2266			
	C1	0.25 mg	1 mg	4 mg	C2	0.25 mg	1 mg	4 mg
30	2.5±1.7	4.4±1.8	3.9±1.4	3.6±1.5	4.1±1.6	4.4±2.3	2.7±1.1	1.9±1.6
60	4.0±1.7	6.4±1.8	5.1±1.6	6.4±1.9	5.4±1.7	5.6±2.5	3.9±1.5	7.0±2.2
120	10.8±2.8	11.5±3.0	7.2±1.3	12.1±2.8	9.0±2.5	7.6±2.4	6.6±1.7	10.5±2.4
180	15.7±3.0	17.1±3.7	17.1±2.2	18.6±5.0	17.6±3.2	14.5±2.4	14.9±4.2	18.9±3.2
240	26.8±3.5	28.5±3.7	30.5±2.5	27.5±5.9	26.8±4.1	28.7±3.6	22.3±3.6	27.9±2.7
360	44.6±3.3	45.9±4.9	44.8±3.8	44.0±5.3	43.8±5.0	43.5±4.6	37.8±3.6	44.9±4.7

24 Hour Food-Deprived Pigeons

Time After Injection (min)	Naloxone HCl				Mr 2266			
	C1	0.25 mg	1 mg	4 mg	C2	0.25 mg	1 mg	4 mg
30	7.2±1.9	7.0±1.7	5.8±1.8	8.8±1.9	6.4±2.3	7.7±1.8	6.0±2.4	4.1±2.0
60	12.6±3.0	11.4±2.4	6.5±1.7	11.0±1.7	8.3±2.4	11.7±2.1	9.1±2.7	6.3±2.4
120	20.4±2.1	21.5±3.5	11.0±3.0*	19.1±2.1	15.7±2.7	14.3±1.8	13.2±2.2	10.8±2.6
180	25.0±2.2	27.8±4.1	20.4±2.7	24.7±3.6	21.7±3.3	22.5±3.6	21.4±3.6	22.3±3.4
240	37.0±4.2	37.0±5.0	31.1±4.1	36.0±4.1	31.5±4.2	34.3±3.5	33.7±4.7	30.5±5.2
360	54.2±5.7	55.1±5.7	51.8±5.2	56.3±6.8	51.5±5.6	50.8±4.7	50.6±6.1	52.3±7.1

*2-Tailed probability ≤0.05, comparison with corresponding control values, Student's *t*-test.

actions between these 2 factors. Due to the very nature of the data which were collected (cumulative measures), these ANOVAs always yielded a reliable influence across the time (p always <0.001), which will therefore not be considered further. Student's *t*-tests for paired data were also employed. Results were considered significant when they corresponded to a two-tailed probability <0.05 and approaching significance when this probability was comprised between 0.05 and 0.10.

RESULTS

Injection of NAL and of Mr 2266 to Non-Deprived Pigeons

Results obtained for the food intake are depicted in Fig. 1. The data pertaining to the 3 treatments with either NAL or with Mr 2266 and the corresponding controls were submitted to two separate 4 treatments × 6 times ANOVAs, revealing reliable differences between the doses, $F(3,24)>4.00$, $p<0.01$ in both cases, as well as treatment × time interactions, (NAL: $F(15,120)=1.68$, $p\leq 0.06$; Mr 2266: $F(15,120)=2.19$, $p\leq 0.01$). Injection of each dose of NAL reduced feeding as compared with control values (2 treatments × 6 times ANOVAs: 0.25 and 4 mg, $F(1,8)>6.00$, $p<0.04$; 1 mg, $F(1,8)=4.29$, $p\leq 0.07$). This decrease was relatively short-lasting, since it was not observed for longer than 2 hrs post-injection (see Fig. 1). There was no difference whether the birds received 0.25 or 1 mg of NAL, or whether they were administered 1 or 4 mg of the antagonist.

Injection of 0.25 mg or of 1 mg of Mr 2266 did not reliably influence the food intake, whereas 4 mg of the drug attenuated it, $F(1,8)=13.16$, $p\leq 0.007$. With this dose, the consumption of food was decreased for up to 6 hrs post-injection (see Fig. 1), that is for a longer period of time than when the birds received the same amount of NAL.

An additional feature of this experiment is that the reduction of feeding which was produced by the 2 opiate antagonists was not accompanied by any reliable alteration of the water intake (see Table 1).

Injection of NAL and of Mr 2266 to Fasted Pigeons

Like it was done before, the data obtained for the food intake were submitted to 4 treatments (3 doses of either NAL or Mr 2266 + one corresponding control injection) × 6 times ANOVAs, showing significant differences between the various treatments, $F(3,24)> 11.50$, $p<0.001$ in both cases, and in the case of NAL, also a reliable treatment × time interaction, $F(15,120)=3.25$, $p\leq 0.0002$. The administration of each dose of NAL as well as of Mr 2266 reduced the food intake of the pigeons as compared with the corresponding control values (six 2 treatments × 6 times ANOVAs: $F(1,8)$ always >7.00, $p<0.03$; see Fig. 2).

When the birds received 0.25 or 4 mg of NAL, or 0.25 mg of Mr 2266, treatment × time interactions were also detected, $F(5,40)$ always ≥ 2.70, $p\leq 0.03$. The effect produced by 0.25 mg and 1 mg of NAL were equal to each other, and no difference was found between the influence of 1 mg and 4 mg of the antagonist either. Similarly, 0.25 mg and 1 mg of Mr 2266 equally decreased feeding. At the latter dose, this drug tended to reduce feeding to a larger extent than when given at the dose of 4 mg, $F(1,8)=3.84$, $p\leq 0.09$. Finally, and as it was observed in the first experiment, injection of Mr

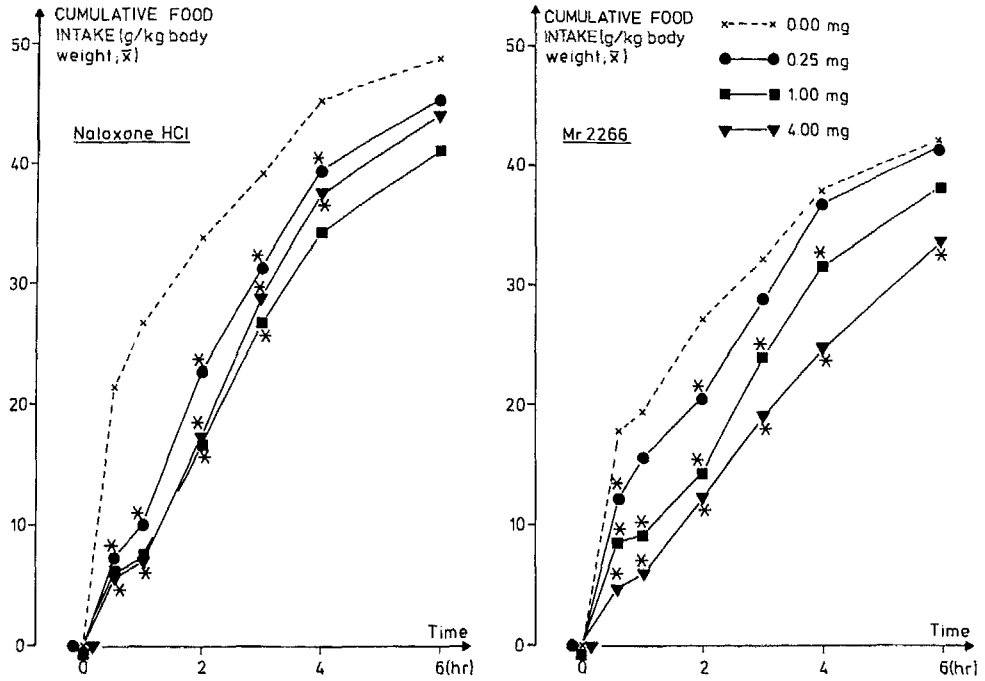

FIG. 2. Cumulative food intake of 24 hr-fasted pigeons (n=9) as a function of time after the intramuscular injection of either naloxone HCl or Mr 2266 at 3 doses, or the corresponding control solutions. See Fig. 1 for further comments.

2266 (4 mg) induced a longer-lasting anorexia (6 hr post-injection) than did the administration of NAL, the effect of which was not observed for more than 4 hr post-injection.

As was the case in the first experiment, the various treatments failed to modify the water intake of the birds in a general fashion (see Table 1) except that at the dose of 1 mg, NAL attenuated drinking as compared with control values, $F(1,8)=5.17$, $p\leq0.05$, with a reliable treatment × time interaction, $F(5,40)=2.87$, $p\leq0.03$, see Table 1. This result, however, is difficult to interpret, since no such difference appeared when the pigeons received either 0.25 mg or 4 mg of the opiate antagonist.

Injection of Mr 2266 and of Mr 2267 to Fasted Birds

A 4 treatment × 6 times ANOVA indicated that there was no general difference in the amount of food eaten when the birds received either the control solution of the 3 doses of Mr 2266, $F(3,24)=2.19$, $p\leq0.11$. There was, however, a highly significant treatment × time interaction, $F(15,120)=3.00$, $p\leq0.0004$. A similar analysis performed with the data obtained for the injection of the control solution and of Mr 2267 provided the same result (dose effect, $p\leq 0.29$; treatment × time interaction, $p\leq0.008$).

As compared with the control situation, 0.25 mg of Mr 2266 did not reliably influence feeding, whereas either 1 or 4 mg of this antagonist reduced it (see Fig. 3; 1 mg, $F(1,8)=5.43$, $p\leq0.05$; 4 mg, $F(1,8)=3.35$, $p\leq0.10$ with a treatment × time interaction, $F(5,40)=2.74$, $p\leq0.03$). Such a reduction was not observed when the pigeons were administered Mr 2267. At the dose of 4 mg, this substance actually enhanced feeding as compared with the control situation, $F(1,8)=5.37$, $p\leq0.05$, with a reliable treatment × time interaction, $F(5,40)=2.96$, $p\leq0.02$; this difference occurred at 60 min and 120 min after the injection, see Fig. 3.

In this experiment, the amount of water drunk by the pigeons as a function of time post-injection was very similar with that measured in the previous experiment, and it was not reliably affected by the administration of either Mr 2266 or its stereoisomer.

DISCUSSION

In the present study, the injection of NAL to pigeons attenuated their food consumption. This response presented several interesting characteristics. On the one hand, it was obtained not only in fasted, but also in non-deprived pigeons, showing that NAL can interfere with the normal control of ingestive behavior in birds having non-limited access to food. On the other hand, the anorexia which followed NAL treatment was only partial and transitory, since it lasted for no more than 2 hr in freely-feeding pigeons and 4 hr in fasted birds. From these points of view, our results compare well with those obtained previously in the same species [5,8]. Furthermore, NAL reliably attenuated the food intake of either non-deprived or fasted pigeons already at the minimum dose of 0.25 mg, which again conforms with data showing that as low a dose as 25 μg can reduce feeding by 24 hr food-deprived birds [10].

One aim of this investigation was to gather information supporting the hypothesis that in pigeons, opiate antagonists reduce feeding by specifically interacting with opiate receptors. We think that the data which are presented here

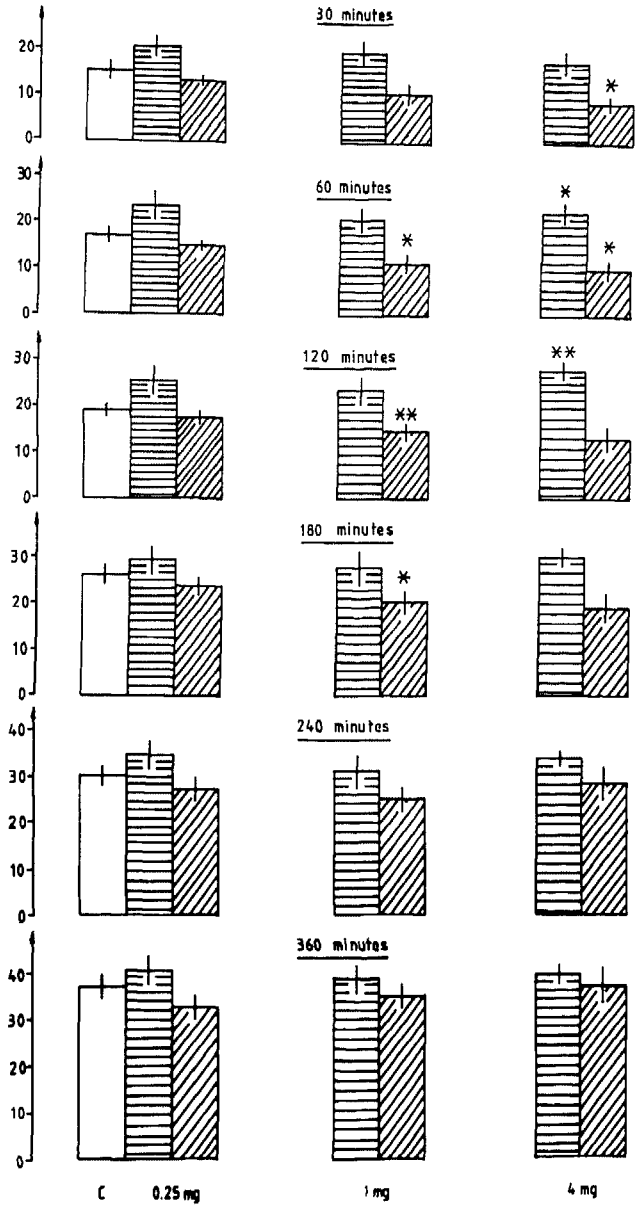

FIG. 3. Food intake (g/kg body weight; mean±SE) of 24 hr food-deprived pigeons (n=9) at 6 different times after the intramuscular injection of either a control solution (C; 0.8 ml of 0.1 N HCl) or of 3 doses of either Mr 2266 (oblique lines) or its (+) stereoisomer, Mr 2267 (horizontal lines) dissolved in the same vehicle. Comparison with corresponding control values are expressed as follows (Student's *t*-test, 2-paired probabilities): $*p \leq 0.05$; $**p \leq 0.02$.

strongly favor this hypothesis. Indeed, they establish that the anorexic influence of opiate antagonists has some generality, in the sense that it is produced not only by the treatment with NAL, but also with Mr 2266, another opiate antagonist possessing a very different chemical structure. More importantly, the consumption of food was decreased by the administration of Mr 2266, but not of its (+) stereoisomer, Mr 2267. The behavioral effect of Mr 2266 was therefore stereoselective, a major argument favoring the view that it followed the actual binding of this drug to opiate receptors.

In the two first experiments, the various experimental treatments were administered in a random order, providing the opportunity to directly compare the relative behavioral influence of NAL with that of Mr 2266 injection. Both antagonists decreased the food consumption. A close scrutiny of the results obtained in experiments 1 and 2 also shows that Mr 2266 was behaviorally longer-acting than identical doses of NAL, since it decreased the food intake of the birds for up to 6 hr post-injection, whereas in the same experiments, the anorexic effect of NAL did not last for more than 2 hr (first experiment) or 4 hr (2nd experiment) after the treatment. These observations raise the question of the mechanism of action of these drugs on the food intake of pigeons.

Previous investigations showed that pigeons possess functionally differentiated kappa and mu opioid receptors subtypes [13]. It has also been recognized that Mr 2266 is a more selective kappa antagonist than NAL, which has a higher affinity to the mu than to the kappa opioid receptors [12, 24, 27]. Furthermore, it has been proposed that kappa opioid receptors play an important role in initiating feeding in rats [22]. It is therefore possible that kappa opioid receptors play a role in the endorphinergic regulation of the food intake of pigeons as well, and that in this study, Mr 2266 treatment attenuated feeding by specifically interacting with this receptor subtype. Confirmation of this hypothesis will of course require additional investigations, and namely the detailed examination of the behavioral effect of selective kappa as compared with other opioid receptors agonists.

A last point of interest concerns the regulation of drinking in pigeons. In two different experimental conditions (experiment 1, non-deprived birds; experiments 2 and 3, fasted birds), the administration of the opiate antagonists produced an anorexia which was not concurrent with a hypodipsia, indicating that feeding was not attenuated consequently to a general motor impairement or non-specific debilitation of the subjects. Though the results obtained for drinking in fasted birds are difficult to interpret, it nevertheless appears that in freely fed and watered pigeons, the administration of NAL or of Mr 2266 is able to reduce feeding without affecting the fluid intake. This finding extents previously obtained results, where as much as 5 mg NAL/bird did not reduce drinking when given to either water-deprived or hypertonic saline-loaded pigeons [8]. Interestingly, the reductions of the food and of the water intake which are induced by NAL treatments to rats are dissociable from each other (e.g., [4]), suggesting that they may depend on at least partly distinct endorphinergic mechanisms. In pigeons, such a mechanism appears to operate on the food intake, but there is so far no evidence that opioid receptors are involved in the regulation of the water intake. Pigeons may therefore represent an extremely interesting species for selectively investigating the endorphinergic control of the food ingestion.

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