The Effects of Opioid Antagonists on Ingestive Behavior in the Domestic Fowl

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McCORMACK, J. F. AND D. M. DENBOW. The effects of opioid antagonists on ingestive behavior in the domestic fowl. PHARMACOL BIOCHEM BEHAV 27(1) 25-33, 1987.—The effects of opioid antagonists on food and water intake in commercial stocks of chickens were investigated. Four experiments were conducted to examine the effects of naloxone (N-allylnoroxymorphone) and naltrexone (N-cyclopropylnoroxymorphone) in broiler and Single-Comb White Leghorn cockerels. Birds were injected intramuscularly with either naloxone HCl or naltrexone HCl at doses from 2.5 to 10 mg/kg. Food and water were offered ad lib 15 min post-injection. In broilers, naloxone dose-dependently attenuated food and water consumption for 300 min, while in Leghorns naloxone attenuated food and water intake for 240 and 300 min, respectively. Naltrexone dose-dependently reduced food and water consumption for 300 min in both broilers and Leghorns. Neither naloxone nor naltrexone significantly altered food or water intake at 24 hr. A fifth experiment was conducted to verify the specificity of opioid antagonism for water intake. Broiler cockerels received an intraperitoneal injection of either isotonic saline (0.15 M NaCl) or hypertonic saline (2.5 M NaCl) followed by an intramuscular injection of either isotonic saline or naloxone HCl (5 mg/kg). Food was withheld for the entire experiment while water was offered ad lib 15 min following the second injection. Naloxone significantly attenuated drinking in normally hydrated and osmotically challenged birds for 150 min. The results suggest a role for endogenous opioid peptides in the regulation of food and water intake in meat and egg-laying stocks of chickens.

Food intake	Water intake	Broilers	Leghorns	Naloxone	Naltrexone	Opioids
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SINCE the discovery of brain opioid receptors in 1973 and the isolation of their endogenous ligands later in the decade (for review, see [1, 23, 41]) there has been considerable investigation into the role of these compounds in physiological and behavioral processes. Endogenous opioid peptides have been implicated as regulators or modulators of a myriad of processes, including thermoregulation, cardiovascular and pulmonary function, learning, and ingestive, social and sexual behavior [34].

Since the initial studies of Grandison and Guidotti [18] who demonstrated that injection of β -endorphin into the ventromedial hypothalamus (VMH) facilitated feeding in the rat, much attention has focused on ingestive behavior. Subsequent investigations, using either opioid agonists or antagonists, have provided corroborative evidence for the role of opioid peptides in the regulation of food and water intake [26].

Opioid antagonists are generally believed to act physiologically, altering ingestive behavior by the blockade of opioid receptors with a resultant attenuation of the actions of endogenous opioid peptides [26,34]. Opioid antagonists, such as naloxone and naltrexone, demonstrate high affinity for opioid receptors [43] and have been shown to decrease the ingestive stimulation induced by central administration of dynorphin-(1-13) [31] and β -endorphin [25].

Holtzman [19] first demonstrated an attenuation of food intake when the opioid antagonist naloxone was administered to rats. Additional investigations using mammalian species showed that antagonists were capable of suppressing food intake under a variety of conditions, e.g., satiated [21], deprived [5, 17, 44], 2-deoxy-D-glucose [36], stress-induced [30], and insulin-induced hypoglycemia [36]. While both food and water consumption were affected, water intake appeared to be particularly sensitive to the effects of antagonists and is possibly the primary behavior affected [5]. Opioid antagonists have been effective in attenuating water intake induced by deprivation [5, 20, 46], angiotensin II [36], hypertonic saline [7], and hypervolemia [36].

Endogenous opioid peptides whose effects may be blocked by antagonists have been isolated from Aves. Peptides isolated from the turkey (Meleagris gallopavo) [9] and the ostrich (Struthio camelus) [32] have been sequenced [9,33] and demonstrate high affinity for opioid receptors in binding assays [48,49]. There have been relatively few studies examining the affects of opioid antagonists in Aves. Cooper and Turkish [11] and Deviche and Schepers [15] observed a decrease in food intake when naloxone was administered to pigeons. In contrast to findings with mammals, there was no effect on water intake, indicating that the regulation of water intake in pigeons is independent of opioid regulation.

The present study was conducted to evaluate the effect of endogenous opioids on ingestive behavior in the domestic fowl. Opioid antagonists were used to determine the exist-

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ence and characterize the nature of opioid regulation in Leghorn and commercial broiler-type chickens.

METHOD

Animals

Commercial broiler and Single-Comb White Leghorns (SCWL) cockerels were reared in heated batteries until three and six weeks of age, respectively, and then transferred to individual cages. The chicks were provided starter mash [20% protein, 2864 kcal/kg metabolizable energy (ME)] and water ad lib, and were exposed to continuous light.

Experiments 1 and 2

These experiments were conducted to determine the effects of peripheral (intramuscular, IM) injections of naloxone HCl on food and water intake in 6-week-old broilers (Experiment 1) and 8-week-old SCWL (Experiment 2). A replicated completely randomized design was used with 20 chicks (10/replicate) assigned at random to four treatment groups consisting of 0, 2.5, 5, or 10 mg/kg naloxone HCl (Endo Laboratories, Inc., Garden City, NY) injected IM in a volume of 1 ml. Physiological saline (0.9% NaCl) served as a control solution. Immediately prior to initiating the experiment, feeders and waterers were removed and the chicks were weighed to the nearest 1 g. Injections were administered in random order into the pectoral muscle 15 min prior to the return of food and water. Food and water intake was measured to the nearest 1 g and 5 ml, respectively, with measurements being made at 30 min intervals for 300 min and again at 24 hr.

Experiments 3 and 4

These experiments were similar to Experiments 1 and 2, except naltrexone HCl (Endo Laboratories, Inc., Garden City, NY) was substituted for naloxone HCl and in Experiment 3 only one replicate (10 birds) was performed. Naltrexone is a congener of naloxone which exhibits greater potency and a longer period of efficacy [4]. The purpose of these experiments was to demonstrate that alterations in ingestive behavior induced by opioid receptor blockade are not unique to naloxone and may be elicited by related antagonists.

Experiment 5

This experiment was conducted to determine if naloxone HCl was capable of specifically attenuating water intake independent of effects on food intake. The experiment was conducted as a replicated completely randomized design with ten 6-week-old commercial broiler chicks (5 birds/replicate) assigned at random to one of four treatment groups. Treatments were as described in Table 1; the first and second injections were separated by a 45 minute interval. Immediately prior to the first injection feed and water was withdrawn and the chicks weighed to the nearest 1 g. Chicks were then administered their respective treatments in random order. Water was returned 15 minutes after the second injection and measurements made at 30 min intervals for 300 min. Food was withheld for the 300 min measurement period.

Statistical Analysis

In Experiments 1 through 4, cumulative food and water

 TABLE1

 EXPERIMENTAL PROCEDURE FOR EXPERIMENT 5

Treatment	First Injection*	Second Injection†		
Α	isotonic saline	isotonic saline		
В	isotonic saline	naloxone HCl		
С	hypertonic saline	isotonic saline		
D	hypertonic saline	naloxone HCl		

*Intraperitoneal injections of isotonic saline (0.15 M NaCl) and hypertonic saline (2.5 M NaCl) were delivered in a volume of 2 ml/kg, resulting in a 5 mM NaCl load for animals receiving hypertonic saline.

 \dagger Intramuscular injections of isotonic saline and naloxone HCl (5 mg/kg) were administered into the pectoral muscle in a volume of 1 ml. This injection was given 45 min after first injection.

intake at each time period was analyzed using analysis of variance. Dose-response relationships within observation periods were evaluated using linear and quadratic contrasts [38]. In Experiment 5, data were transformed to $(\sqrt{Y + 0.5})$ to achieve homogeneity of variances and normality. Data were analyzed using analysis of variance and orthogonal contrasts were used within observation periods to evaluate treatment differences [38]. Reported values are the untransformed data. Significance implies p < 0.05.

RESULTS

Experiments 1 and 2

Administration of naloxone caused a significant dosedependent attenuation of food and water intake in broilers (Fig. 1). The dose relationship for the reduction in food intake within observation periods was quadratic through 180 min and linear from 210 through 300 min. The minimally effective dose tested was 2.5 mg/kg while 5.0 mg/kg produced the maximum response. Water consumption was attenuated in a quadratic manner through 300 min. The relative efficacy of the doses was similar to that observed for food intake with 5.0 mg/kg being most efficacious. Naloxone had no effect on either food or water intake at 24 hr.

As in broilers, the administration of naloxone to SCWL also resulted in a significant dose-dependent reduction in food and water intake (Fig. 2). Food intake was decreased linearly through 180 min and again at 240 min. Water intake was attenuated in a linear manner at 30 min, quadratically from 60 through 90 min and linearly from 120 through 300 min. No treatment effect was noted on either food or water consumption at 24 hr.

Experiments 3 and 4

The effects of intramuscular injection of naltrexone HCl on food and water intake in broilers and SCWL are shown in Figs. 3 and 4, respectively. Administration of naltrexone to broilers resulted in a significant dose-dependent attenuation of food and water intake. Food intake was decreased in a linear manner through 60 min and quadratically from 90 through 300 min. Water intake was decreased in a quadratic manner from 60 through 300 min. The minimally effective dose tested was 2.5 mg/kg for both food and water consump-

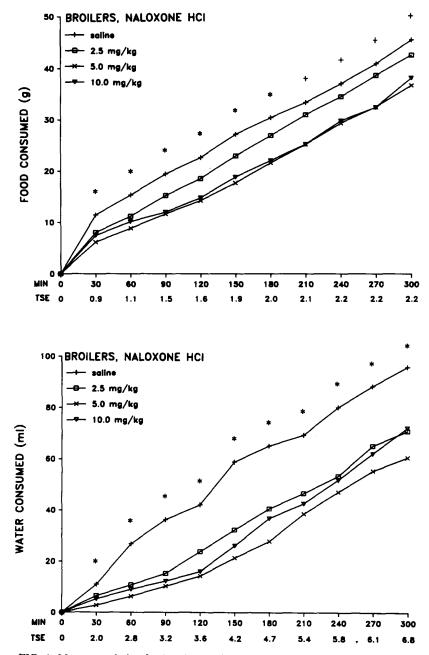


FIG. 1. Mean cumulative food and water intake of broiler cockerels in response to intramuscular injection of naloxone HCl. +, significant linear contrast (p < 0.05) within observation period. *, significant quadratic contrast (p < 0.05) within observation period. MIN, minutes; TSE, standard error of the treatment mean.

tion while the maximally effective dose was 5 mg/kg for food intake and 10 mg/kg for water intake. Naltrexone had no effect on either food or water consumption at 24 hr.

Naltrexone also produced a significant dose-dependent suppression of food and water consumption in SCWL. Food intake was attenuated in a quadratic manner from 60 through 300 min, with 2.5 mg/kg being the most effective dose prior to 180 min and 10 mg/kg the most effective at subsequent time periods. A quadratic dose relationship was observed for the depression in water intake through 240 min and a linear

Experiment 5

food or water consumption at 24 hr.

The results of experiment 5 are summarized in Table 2. Intracellular dehydration induced by a 5 mM saline load re-

relationship from 270 through 300 min. A similar suppression

in water intake was observed with the 2.5 mg/kg and 5 mg/kg

doses, while the 10 mg/kg dose attenuated water intake to the

greatest degree. No effect of treatment was noted on either

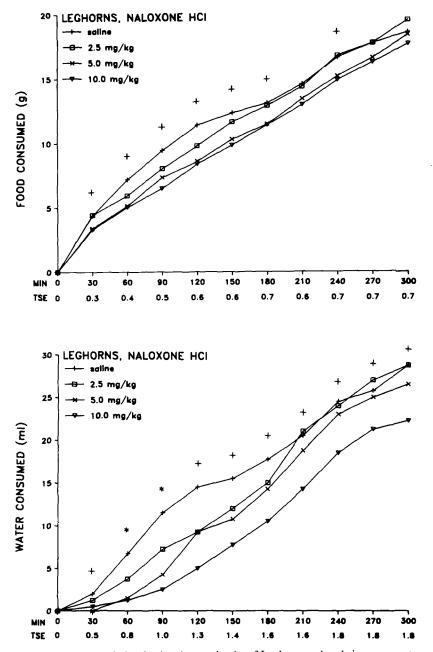


FIG. 2. Mean cumulative food and water intake of Leghorn cockerels in response to intramuscular injection of naloxone HCl. +, significant linear contrast (p<0.05) within observation period. *, significant quadratic contrast (p<0.05) within observation period. MIN, minutes; TSE, standard error of the treatment mean.

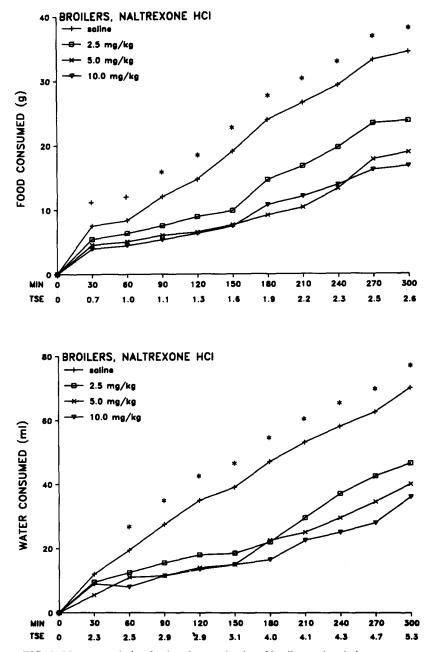


FIG. 3. Mean cumulative food and water intake of broiler cockerels in response to intramuscular injection of naltrexone HCl. +, significant linear contrast (p < 0.05) within observation period. *, significant quadratic contrast (p < 0.05) within observation period. MIN, minutes; TSE, standard error of the treatment mean.

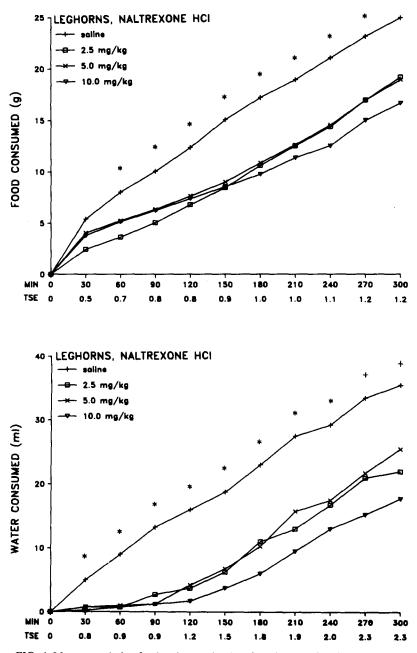


FIG. 4. Mean cumulative food and water intake of Leghorn cockerels in response to intramuscular injection of naloxone HCl. +, significant linear contrast (p < 0.05) within observation period. *, significant quadratic contrast (p < 0.05) within observation period. MIN, minutes; TSE, standard error of the treatment mean.

	TIME (min)									
Treatment	30	60	90	120	150	180	210	240	270	300
(A) Isotonic saline + isotonic saline‡	10	15	19	19	23	25	26	27	28	29
(B) Isotonic saline + naloxone HCl	3	4	4	4	5	5	14	22	24	26
(C) Hypertonic saline + isotonic saline	18	32	48	49	50	52	52	57	59	61
(D) Hypertonic saline + naloxone HCl	0	1	4	6	32	58	70	82	89	102
Standard Error of the Treatment Mean	1.8	2.1	2.1	2.3	5.4	8.5	8.8	9.2	9.2	9.1
F Value of Contrasts [†]										
A vs. B C vs. D AB vs. CD	1.80 15.50* 0.02	4.33* 30.31* 1.47	9.24* 58.90* 6.35*	10.09* 55.00* 6.04*	4.53* 9.88* 4.94*	3.53 2.36 6.37*	2.11 0.67 6.04*	1.08 0.06 7.44*	0.73 0.01 7.62*	0.68 0.53 12.20*

 TABLE 2

 THE EFFECT OF INTRAMUSCULAR INJECTIONS OF NALOXONE HCI ON MEAN CUMULATIVE WATER INTAKE (ml) OF BROILER

 COCKERELS WITH AND WITHOUT SALINE LOAD PRETREATMENT

*Critical F(1,35)=4.10, p<0.05; therefore, these contrasts are significant.

⁺F values reported are those obtained from analyses of transformed ($\sqrt{Y+0.5}$) data.

[‡]The birds received two injections 45 min apart. The first injection was either isotonic saline (0.15 M NaCl) or hypertonic saline (2.5 M NaCl), administered IP. The second injection was either isotonic saline or 5.0 mg/kg naloxone HCl administered IM.

sulted in a significant increase in water consumption relative to the isotonic saline injected treatments from 90 through 300 min. The response to saline load was significantly decreased for 150 min by the administration of naloxone. An attenuation in water consumption, relative to the isotonic saline control, was also observed from 60 to 150 min when naloxone was administered without saline load. Beyond 150 min the depressant effects of naloxone began to dissipate leading to rapid compensatory increases in water intake in naloxone-treated birds.

DISCUSSION

The results of this study demonstrate that the peripheral (IM) administration of opioid antagonists to broiler and SCWL chickens produced a dose-dependent attenuation of food and water consumption. The suppression of ingestive behaviors occured at doses from 2.5 to 10 mg/kg with maximum attenuation usually occurring at a dose of 5 mg/kg.

Broiler and SCWL chickens were utilized in order to evaluate the efficacy of opioid antagonists in altering ingestive behavior in the domestic fowl and to determine if the genetic selection for low and high body weight in eggproducing and meat-producing stocks, respectively, altered sensitivity to these compounds. Previous studies comparing meat and egg-laying stocks have shown that these stocks have different responses to putative regulators of ingestive behavior. Denbow et al. [12,14] have shown that broilers and SCWL respond differently to the central administration of biogenic amines. Epinephrine was effective in increasing food intake in broilers while having no effect in SCWL. On other central administration the hand, the of 5-hydroxytryptamine (5-HT) increased water intake of sated SCWL and decreased water intake of food-deprived SCWL [14] but produced no alteration in water intake in broilers [13]. Recently, Lacy *et al.* [24] found that intrahepatic infusions of lipids decreased feeding in SCWL but did not alter food intake in broilers. The attenuation of feeding and drinking observed in the present study demonstrates that opioid antagonists are effective in reducing ingestive behaviors in both stocks of chickens and that the genetic selection for egg-production and low body weight has not abolished the sensitivity to opioid antagonists. The possibility remains that the stocks differ in the degree of sensitivity to these substances.

Reductions in food intake have been observed in rats [21] and pigeons [11,15] in response to opioid antagonists. However, while opioid antagonists have consistently produced attenuation of water intake in mammals [2, 6, 20, 39] an effect on drinking behavior has not heretofore been observed in Aves [11,15].

Food and water consumption have been shown to be proportional in commercial stocks of chickens [28, 29, 37] which is suggestive of a common regulatory mechanism. Therefore, although naloxone and naltrexone reliably decreased water consumption in both broiler and SCWL chickens, the similarity in time course between the food intake and water intake responses and the incongruity with studies using pigeons necessitated further study to confirm that the attenuation of water intake was not simply an artifact of the effect on food intake.

Experiment 5 was conducted to evaluate the effect of naloxone on water intake independent from its effects on food intake. The results obtained in Experiment 5 demonstrated the ability of naloxone to attenuate drinking in normally hydrated chickens and in chickens induced to drink by hypertonic saline-induced intracellular dehydration. Furthermore, the decrease in water consumption occurred independently of any alterations in food consumption. Food and water intake, therefore, appear to be regulated by similar but independent opioid antagonist-sensitive regulatory systems. The genetic basis for such independent systems has been described by Marks [27]. It is plausable that a dissimilarity in the naoxone-sensitivity of water consumption exists between pigeons and commercial stocks of chickens.

The mechanisms by which opioid antagonists induce alterations in ingestive behavior still remain a matter of speculation. Two possible modes of action have been theorized. One mechanism is based on the central reward theory proposed by Belluzzi and Stein [3] and supported by the work of Carr and Simon [8]. The central reward theory hypothesizes that endogenous opioid peptides mediate drive-reduction reward and, therefore, enhance the reward value of ingestive acts. Accordingly, opioid antagonists would interrupt normal ingestive behaviors by interfering with this reward system rendering food and water consumption less satisfying.

A second mechanism, first proposed by Cooper [10], attributes antagonist-induced alterations in ingestive behavior to changes in the threshold of satiety. The satiety theory originated from the observation that naloxone served to further depress feeding behavior in animals already demonstrating reduced intake due to osmotic challenge. Therefore, opioid antagonists appeared to interrupt an opioid mediated mechanism which inhibited satiety. The satiety theory received support in subsequent studies by Siviy *et al.* [42] and Kirkam and Blundell [22] which have shown that naloxone hastens the termination of feeding and drinking by interfering with processes that serve to sustain consumption.

The possibility exists that opioid antagonists may act in a pharmacological manner by altering motor ability, or by inducing a non-specific malaise. This does not appear to be the case in the present study. No differences in motor activity, appearence of discomfort or overt behaviors were observed between control and experimental treatments. These observations are substantiated by other studies in which similar dosages were used and in which no malaise was observed [6,

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20, 21, 36]. Also, Segal *et al.* [40] found no alterations in the locomotor activity of rats at doses of naloxone as high as 20 mg/kg.

Further evidence against antagonists acting by means of a non-specific malaise is the fact that in both rats [6] and pigeons [16] the actions of opioid antagonists have been shown to be stereospecific. Also, opioid antagonists exhibit behavioral specificity for ingestive behaviors as has been demonstrated by the absence of any effect of naloxone on water intake in pigeons [11,15] and the dissociation of prey killing and prey eating in mouse killing rats [45].

High doses of naloxone have been found to produce varying degrees of conditioned taste aversion (CTA) in rats [17] but no reliable correlation has been found between the magnitude of the CTA and the suppression of water consumption [35,47]. In addition, Frenk and Rogers [17] were unable to suppress drinking with lithium chloride despite its ability to produce an extensive CTA. Therefore, there appears to be little evidence that naloxone exerts its effects by inducing a non-specific malaise.

Based on the results of this study it is possible to conclude that opioid antagonists produce an attenuation of food and water intake in meat and egg-laying stocks of chickens. The induction of this effect is most likely a manifestation of the interaction of these compounds with opioid receptors, resulting in the inhibition of the actions of endogenous opioid peptides. Therefore, it appears that endogenous opioid peptides play a significant role in the regulation of food and water intake in the domestic fowl.

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