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The Role of Opioid Mechanisms in the Anorectic Effects of Stimulants: U50,488H Enhances Amphetamine Inhibition of Free Feeding in Rats

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NENCINI, P. AND P. VALERI. *The role of opioid mechanisms in the anorectic effects of stimulants: U50,488H enhances amphetamine inhibition of free feeding in rats.* PHARMACOL BIOCHEM BEHAV **48**(1) 63–68, 1994.—The influences of the κ-opiate agonist U50,488H (U50; 4 mg/kg IP), the neuroleptic haloperidol (HAL; 0.3 mg/kg IP), and MK-801 (0.2 mg/kg IP), a noncompetitive antagonist for NMDA receptors, were compared on the effects of nine days of *d*-amphetamine (AMPH) treatment (3 mg/kg IP) on food and water intake and urine output. AMPH prevented feeding stimulation produced by U50 during the first 2 h, whereas U50 inhibited the hyperphagic phase that rats showed between 2 and 5 h after AMPH administration. Tolerance did not develop to the first 2-h suppression of feeding; in contrast, the late hyperphagic phase slowly recovered across the nine days of treatment. Combined administration of the two drugs barely affected water intake but considerably increased urine output. Unlike U50, HAL left the late hyperphagic response to AMPH unchanged and delayed the development of hyperdipsia. In our study MK-801 had one effect only: It significantly reduced amphetamine diuresis. These results suggest that by inhibiting the late hyperphagic response U50 enhances the anorectic effects of AMPH, but that dopamine probably has no direct role in this interaction.

Feeding Drinking Diuresis Amphetamine U50,488H Haloperidol MK-801

ALTHOUGH it is considered the prototypical anorexant, amphetamine (AMPH) also activates ingestive behavior, particularly under conditions of chronic administration. Within a few daily administrations, at moderate doses, AMPH shows a biphasic effect on ingestive behavior in the rat. An almost complete suppression of feeding and drinking that lasts no more than 2 h is followed by an overshoot of food and water intake, which more than compensates for the initial suppression (1,8,15,16). With few exceptions [see, e.g., (5,6,29)], analyses of pharmacological mechanisms involved in the effects of AMPH on ingestive behavior have focused mainly on the early anorectic phase (7,10,11). There are good reasons, however, for paying more attention to the late proingestive phase, not least because it compensates for the anorectic effects of AMPH. Thus, preventing the progressive augmentation of this phase may help in maintaining the efficacy of AMPH as an appetite suppressant.

U50,488H (U50) is a selective κ-opiate which produces prophagic effects that are enhanced by chronic administration of AMPH or cathinone (1,15,16,17). Although the effects of U50 on AMPH-induced feeding have never been studied, U50 would be expected to antagonize this response. This prediction is based on the evidence that in general U50 and the putative endogenous κ-opioid dynorphin inhibit the behavioral effects of psychomotor stimulants. For instance, U50 suppresses ipsilateral circling produced by methamphetamine in rats bearing nigrostriatal lesions (19) and attenuates the discriminative stimulus effects of cocaine in monkeys (21). Dynorphin A(1–13) inhibits rearing activated by both cocaine (24) and methamphetamine (25). The inhibition of these dopamine-

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mediated behaviors is consistent with the evidence that κ-opioids prevent firing of the dopamine cells of the substantia nigra (22,26) and prevent dopamine release from striata (14) and the nucleus accumbens (3,4).

In this study we gave 4 mg/kg of U50, a dose that fully activates feeding in satiated rats (15,18), daily in combination with AMPH (3 mg/kg) for nine days, a period that allows a clear differentiation between the two AMPH effects: the initial suppression and the late activation of ingestive behavior. Besides food and water intake, we also measured urine output, since the diuretic effect of AMPH remains unchanged throughout chronic administration (15).

Since U50 inhibits psychomotor stimulant effects and central dopaminergic activity, we compared the influence of U50 on AMPH ingestive responses with that exerted by MK-801 and haloperidol (HAL). Particularly interesting is the comparison with MK-801, a noncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors for glutamate, which inhibits dopamine release elicited by amphetamines (2,27). It has also been suggested, but not confirmed, that MK-801 prevents sensitization to the motor effects of amphetamines (9,23).

MATERIALS AND METHODS

Animals

Seventy-two male Sprague-Dawley rats (Charles River, Como, Italy) with weights ranging from 275 to 326 g at the beginning of the study were used for the experiments. The animals were housed singly in metabolic cages (Tecniplast Gazzada) at 23°C with a 12-h light-dark cycle (0700–1900). They had free access to water and food, the latter being available as a gross powder obtained by grinding lab pellets (Standard Diet 4RF21, Mucedola s.r.l.). To minimize spillage due to behaviors not related to food intake (i.e., stereotyped gnawing) we avoided dispensing lab pellets. During the first week, in which the rats were allowed to adapt to the new environment, manipulation was restricted to a daily handling for weight record. For the next three days before drug treatment began the animals were injected IP with water and independent measures were taken as described below.

Independent Measures

During the experimental procedure, food and water intake and urine output were measured by weighing (with an approximation of 0.1 g) food receptacles, water bottles, and urine cylinders before and 2 and 5 h after drug administration. To prevent evaporation, urine cylinders contained a layer of mineral oil.

Procedure

The same procedure was used in three distinct sets of experiments. In the first set, designed to study the influence of U50 on AMPH responses, 24 rats were assigned to four groups. The animals received IP water or U50 (4 mg/kg) 10 min before water or AMPH (3 mg/kg) according to a 2 × 2 design representing all treatment combinations. Treatment lasted nine days and independent measures were taken as described.

In the second set of experiments U50 was replaced by HAL (0.3 mg/kg), and in the third by MK-801 (0.2 mg/kg). The HAL and MK-801 doses were chosen because they do not disrupt unconditioned behaviors (12,30).

Data Analysis

Data were processed using an analysis of variance (ANOVA) with two between factors (AMPH: two levels; U50, HAL, or MK-801: two levels) and one within factor (days: nine levels). Tukey's test was used for subsequent comparisons within logical sets of means.

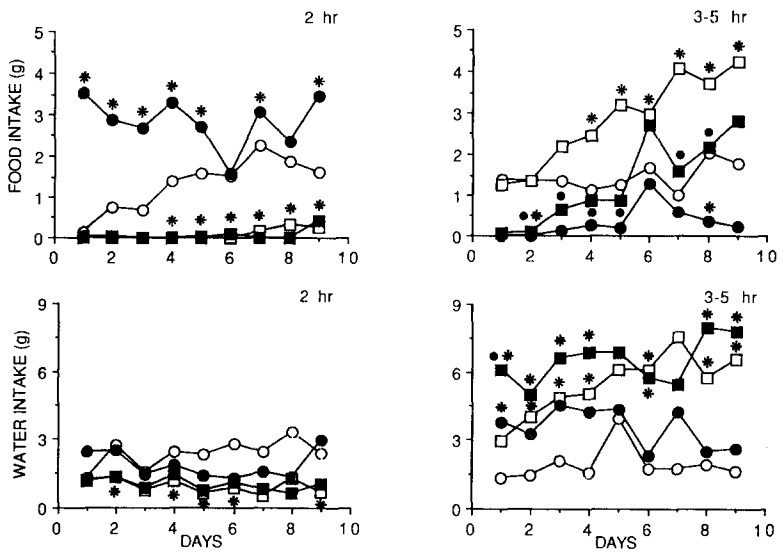

FIG. 1. Mean food and water intake at 2 and 5 h in groups treated with amphetamine (AMPH) alone (3 mg/kg IP, □) or in combination with U50 (4 mg/kg IP, ■). Groups treated with the solvent or with U50 alone are represented by ○ and by ●, respectively. *$p < 0.05$ vs. solvent group, Tukey's test. •$p < 0.05$ vs. AMPH group, Tukey's test.

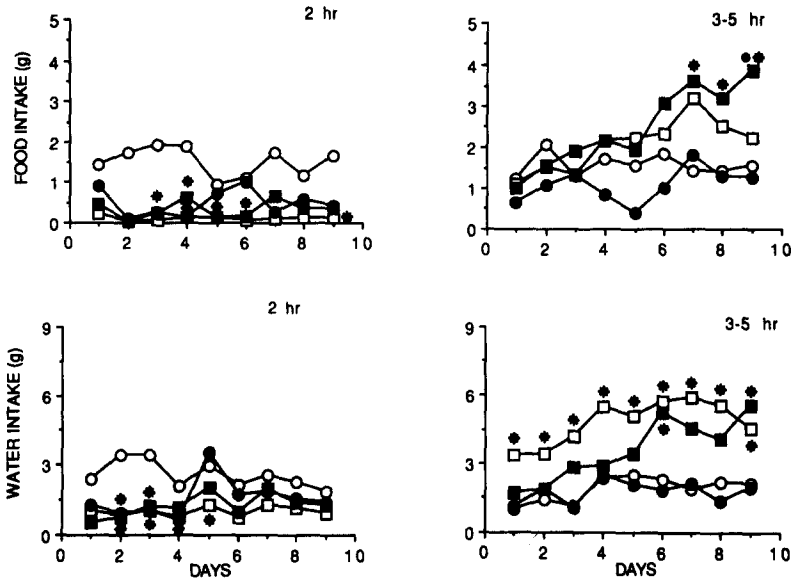

FIG. 2. Mean food and water intake at 2 and 5 h in groups treated with amphetamine (AMPH) alone (3 mg/kg IP, □) or in combination with HAL (0.3 mg/kg IP, ■). Groups treated with the solvent or with HAL alone are represented by ○ and by ●, respectively. *$p < 0.05$ vs. solvent group, Tukey's test. •$p < 0.05$ vs. AMPH group, Tukey's test.

Drugs

d-Amphetamine sulfate (Salars, Italy), *trans*-(±)-3,4-dichloro-*N*-methyl-*N*-(2-(*i*-pyrrolidinyl)cyclohexyl))-benzeneacetamide methane sulfonate (U50,488H; Upjohn Co., Kalamazoo, MI), and MK-801 (Merck, Sharp & Dohme, Italy) were freshly dissolved in distilled water to a final volume of 1 mg/kg. HAL was administered as injectable Serenase (Lusofarmaco, Italy).

RESULTS

Control values obtained across the three sets of experiments were consistent for all the parameters studied, except

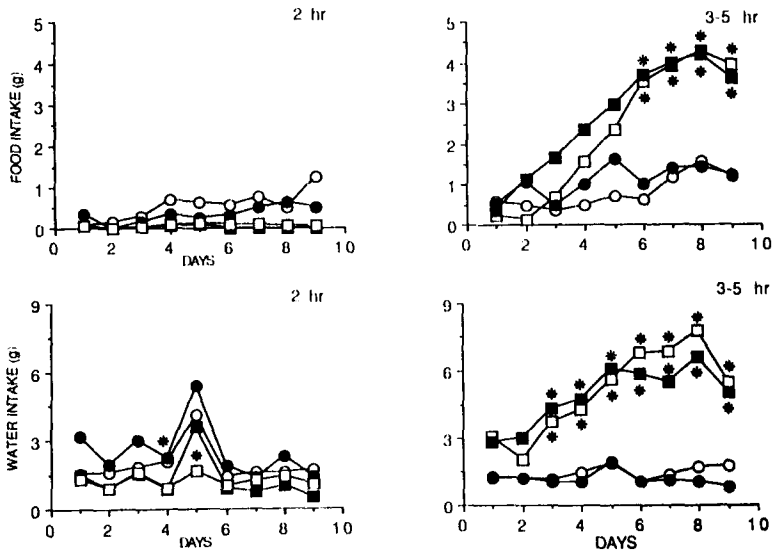

FIG. 3. Mean food and water intake at 2 and 5 h in groups treated with amphetamine (AMPH) alone (3 mg/kg IP, □) or in combination with MK-801 (0.2 mg/kg IP, ■). Groups treated with the solvent or with MK-801 alone are represented by ○ and by ●, respectively. *$p < 0.05$ vs. solvent group, Tukey's test.

2-h food intake. In this case, ANOVA for the three groups of controls was $F(2, 15) = 3.99$, $p = 0.041$. Post hoc Tukey's test attributed this difference to lower levels of food intake during the first three days in the MK-801 experiment and on the first day in the U50 experiment. We cannot explain such low levels restricted to the first 2 h of observations, but presumably they had little influence on pharmacological responses, since the inhibition of food intake produced by 3 mg/kg of AMPH during the first 2 h remained constant across the three sets of experiments and changed minimally throughout the nine days of drug administration (Figs. 1-3). During the second interval of observation (2-5 h) food intake was not only reinstated in the AMPH-treated animals, but it progressively increased throughout the nine days of treatment. As a result, ANOVA revealed an overall AMPH effect, U50 experiment $F(1, 20) = 15.68$, $p = 0.001$; HAL experiment $F(1, 20) = 12.15$, $p = 0.002$; MK-801 experiment $F(1, 20) = 13.89$, $p = 0.001$, and an interaction AMPH × Days effect, U50 experiment $F(8, 160) = 9.70$, $p < 0.001$; HAL experiment $F(8, 160) = 2.75$, $p = 0.002$; MK-801 experiment $F(8, 160) = 11.68$, $p < 0.001$. The total amount of food eaten by AMPH-treated rats during 5 h of observation only occasionally differed from the food intake of water-treated controls (data not shown).

An increase in water intake during the last 3 h of observation was also observed in the group treated with AMPH, and ANOVA showed a significant effect of AMPH, U50 experiment $F(1, 20) = 42.64$, $p < 0.001$; HAL experiment $F(1, 20) = 32.52$, $p < 0.001$; MK-801 experiment $F(1, 20) = 50.27$, $p < 0.001$. However, the animals did not simply compensate for the initial adipsia, and the cumulative 5-h water intake significantly exceeded that of controls, AMPH factor: U50 experiment $F(1, 20) = 15.507$, $p < 0.001$; HAL experiment $F(1, 20) = 8.835$, $p = 0.008$ (data not shown).

Effects of U50

Figure 1 shows the effects of U50 given alone or in combination with AMPH on food and water intake at 2 and 3-5 h. As expected, during the first 2 h of observation U50 increased food intake. AMPH completely suppressed this U50-induced feeding, U50 × AMPH $F(1, 20) = 17.419$, $p < 0.001$. During the following 3 h the roles reversed and it was U50 that prevented AMPH-induced feeding, U50 factor $F(1, 20) = 19.239$, $p < 0.001$. The cumulative 5-h food intake was thus remarkably reduced by the combined administration of U50 and AMPH, AMPH × U50 $F(1, 20) = 6.726$, $p < 0.017$. Post hoc comparison between groups shows that from day 2 to day 8 the group treated with AMPH and U50 had a significantly lower food intake during the 3-5 h interval than the group treated with AMPH alone. Occasionally (on days 2 and 8), the U50 group also ate a significantly smaller amount of food than controls. The sudden disappearance of the inhibitory interaction between U50 and AMPH on day 6 probably resulted from the inadvertent administration of solvent instead of U50, since in the same day urine output also dropped abruptly (Fig. 4). Since we had no conclusive evidence of the mistake, the results of day 6 were included in the ANOVA.

U50 enhancement of the inhibitory effects of AMPH did not involve drinking. U50 affected neither the 2-h inhibition, $F(1, 20) = 50.788$, $p < 0.001$, nor the 3-5-h increase, $F(1, 20) = 42.64$, $p < 0.001$, of water intake produced by AMPH. The only exception was day 1, when the group treated with U50 and AMPH significantly increased their water intake. U50 given alone had little effect on drinking, as confirmed by post hoc comparison between groups: 3-5-h water intake in the U50 group increased on days 1 and 4 only.

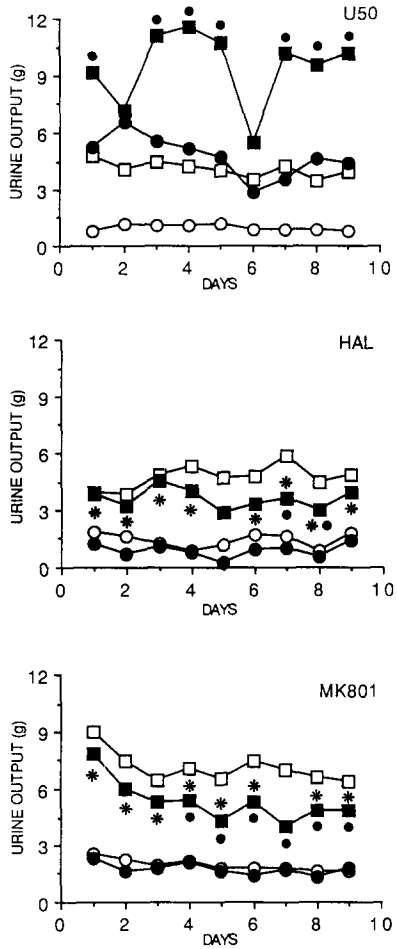

FIG. 4. Mean 2-h cumulative urine output in the U50, HAL, and MK-801 experiments (see Figs. 1-3). *$p < 0.05$ vs. solvent group, Tukey's test. •$p < 0.05$ vs. AMPH group, Tukey's test.

As expected, both U50, $F(1, 20) = 136.647$, $p < 0.001$, and AMPH, $F(1, 20) = 100.616$, $p < 0.001$, increased urine output (Fig. 4). This effect reached the nadir at 2 h. When the two drugs were given in combination, their diuretic effects appeared to be roughly additive, as shown by ANOVA, U50 × AMPH $F(1, 20) = 4.152$, $p = 0.055$.

Because of their additivity in suppressing feeding and in stimulating diuresis, U50 and AMPH should also have had additive effects in slowing body weight growth. But ANOVA comparing the body weight on the first and last days of treatment showed a significant effect for AMPH treatment alone, $F(1, 20) = 5.535$, $p < 0.029$. This suggests that during the rest of the day the animals were able to compensate for the negative water balance and for the suppression of feeding produced by the drug combination.

Effects of HAL

The effects of HAL on feeding differed sharply from those of U50 (Fig. 2). In general, HAL reduced food intake when it was given alone, and increased food intake over AMPH levels when it was given in combination with AMPH. In particular,

ANOVA showed a significant interaction between HAL and AMPH on the feeding response at 2 h, HAL × AMPH $F(1, 20) = 6.327$, $p = 0.021$. In addition, from day 6 onward HAL progressively enhanced the late feeding response to AMPH (3–5 h).

HAL also interfered with the suppressant effect of AMPH on the 2-h water intake, as shown by a significant interaction between AMPH and HAL, $F(1, 20) = 8.795$, $p = 0.008$. According to ANOVA, HAL did not influence the late hyperdipsic response to AMPH. However, HAL must have slowed the development of hyperdipsia, since water intake in the HAL–AMPH group exceeded control values only from day 6 onward. HAL antagonized the body weight reduction produced by AMPH, and ANOVA revealed a significant interaction between HAL and AMPH, $F(1, 20) = 6.259$, $p = 0.021$.

Values of urine output across the experiment were lower in the group receiving AMPH and HAL than they were in the group treated with AMPH alone (Fig. 4). Post hoc Tukey's test showed significant differences between the two groups on days 7 and 8.

MK-801

The compound MK-801 had no effect on feeding or drinking, either in basal conditions or in the presence of AMPH (Fig. 3). In contrast, ANOVA showed a significant interaction between AMPH and MK-801 on urine output at 2 h, $F(1, 20) = 10.771$, $p = 0.004$, consisting of MK-801 inhibition of the AMPH-mediated diuresis. This inhibitory effect became statistically significant from day 4 onwards (Fig. 4).

DISCUSSION

Our study shows that U50 and AMPH interact in suppressing food intake. Apparently, AMPH suppressed the initial stimulation of appetite produced by U50, whereas U50 prevented the compensatory increase in food intake that AMPH-treated animals exhibited after the initial suppression of feeding. At the same time, water intake was not inhibited: On the first day of treatment U50 brought the 5-h drinking in the AMPH group to a significant increase over control levels. Thus, it is unlikely that the suppression of feeding resulted from a generalized behavioral impairment produced by the interaction between AMPH and U50. That antagonism was not the only kind of interaction between U50 and AMPH was further shown by the U50-induced enhancement of AMPH-mediated diuresis, probably caused by the additivity of the independent diuretic effects of the two drugs.

Thus, U50 and AMPH, given chronically in combination, produced a reciprocal enhancement of their diuretic actions, an almost null effect on drinking, and a reciprocal antagonism of their prophagic actions. Feeding belongs then to the behaviors on which the effects exerted by U50 and AMPH are reciprocally antagonists. Considering that U50 is a prophagic drug and AMPH is an anorexant, this would seem obvious. The salient point is that each drug antagonized the feeding activation elicited by the other. For this reason, the apparent overall result was an enhancement of the anorectic effect of AMPH.

U50 has been found to antagonize some central effects of psychomotor stimulants. It inhibits the ipsilateral circling behavior elicited by methamphetamine in rats with unilateral nigral lesions (19), and more recent evidence has shown that U50 also attenuates the discriminative stimulus and rate-altering effects of cocaine in monkeys (21). These effects have been attributed to the antidopaminergic action of U50, since κ-opioids suppress firing of dopaminergic neurons in the substantia nigra (22,26) and inhibit dopamine release in the striatum, accumbens, and cortex (3,4,14,28).

The fact that U50 inhibits dopamine release in the accumbens may be relevant to its inhibition of the late prophagic effect of AMPH, since the administration of AMPH into this area both releases dopamine and activates feeding (3,6,29). On the other hand, a direct involvement of dopamine in the suppression of AMPH hyperphagia produced by U50 is not supported by the comparison between the effects of U50 and those of HAL. In our experimental conditions HAL speeded up the process of augmentation of the late hyperphagia induced by AMPH, but slowed the development of its hyperdipsic response and slightly antagonized its diuretic effect. U50 and HAL therefore seemed to exert roughly opposite influences on feeding, drinking, and diuretic responses to chronic AMPH.

The results obtained with MK-801 also converge in excluding a role of dopamine in the interaction between U50 and AMPH. This noncompetitive antagonist of the NMDA receptors for glutamate has been found to inhibit dopamine release elicited by psychomotor stimulants (2,27). Yet, in our study MK-801 affected neither the feeding nor drinking response to AMPH. The only effect of MK-801 that we observed was a partial inhibition of the AMPH-mediated urine output, in accordance with its known ability to suppress micturition reflex in rats (13). The lack of activity of MK-801 on the increased water intake produced by AMPH is particularly interesting, since this increase is considered the expression of AMPH sensitization (20) and early studies have proposed that MK-801 prevents the augmentation of locomotor and stereotyped responses to amphetamines (9). This suggestion has been contradicted by a recent study showing that MK-801 attenuates the expression of methamphetamine-induced sensitization but does not prevent the induction of sensitization (23). Inasmuch as hyperdipsia is due to sensitization to AMPH, our data confirm that this sensitization is resistant to the noncompetitive block of NMDA receptors for glutamate.

In conclusion, we have provided further evidence that κ-opiate receptors play a role in the effects of AMPH on feeding behavior. Chronic intermittent administration of AMPH-like drugs augments the prophagic response to U50 (15,16), whereas U50 inhibits the late prophagic response to AMPH. The mechanisms involved in this interaction remain elusive, and this is not surprising, considering that the site and the mechanism of the effects of κ-opioids on ingestive behavior are still unknown.

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