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Effects of Ephedrine Enantiomers on Conditioned Taste Aversion and Kaolin Intake in Rats

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MCMAHON, L. R., S. L. JONES, T. R. GILLILAND, W. D. HALL AND P. J. WELLMAN. *Effects of ephedrine enantiomers on conditioned taste aversion and kaolin intake in rats.* PHARMACOL BIOCHEM BEHAV **63**(1) 119–124, 1999.—The ephedrine (EPH) enantiomers, (−)-EPH and (+)-EPH, have different biological activity in the rat, with the (−)-EPH enantiomer exerting a greater impact on suppression of feeding, induction of locomotion, and activation of brown adipose tissue thermogenesis. Recent studies document that (−)-EPH treatment produces an alteration of extracellular dopamine in the brain, an effect that is consistent with the locomotor-stimulating and reinforcing effects of this drug. Whether the EPH enantiomers exert aversive actions in the rat is unknown. Experiment 1 examined the impact of systemically administered (+)-EPH (0, 5, 10, or 20 mg/kg) or (−)-EPH (0, 5, 10, or 20 mg/kg) on conditioned taste aversion (CTA) in adult male rats relative to the effect of 32 mg/kg lithium chloride (LiCl). No dose of either enantiomer produced CTA, whereas strong CTA was evident for LiCl. In Experiment 2, consumption of kaolin (a nonnutritive clay) over a 24-h period was used to assess drug toxicity. Rats treated with either 0, 5, 10, 20, or 40 mg/kg (+)-EPH or 0, 5, 10, 20, or 40 mg/kg (−)-EPH did not exhibit alteration of kaolin intake. In contrast, systematic increases in kaolin intake were observed in rats after systemic administration of LiCl (0, 16, 32, 64, and 96 mg/kg). These findings suggest that the enantiomers of EPH do not exert aversive effects at behaviorally relevant doses. © 1999 Elsevier Science Inc.

Malaise Anorexia Saccharin

THE sympathomimetic agent ephedrine (EPH) is a racemic mixture of (+)-EPH and (−)-EPH enantiomers. These enantiomers are known to have differing biological activity with the (−)-EPH enantiomer exerting greater activity with regard to the suppression of feeding (3,16), induction of locomotion (13), activation of brown adipose tissue thermogenesis (15), and reduction of body fat content (3).

EPH readily crosses the blood–brain barrier. The (−)-EPH enantiomer produces a greater increase of the extracellular levels of dopamine within rat nucleus accumbens (nAC) relative to the impact of the (+)-EPH enantiomer (16). The impact of the EPH enantiomers on dopamine processes within the rat brain is consistent with the known stimulant properties of EPH (9,13). EPH induces reinforcement as measured via drug self-administration (12). EPH, however, is also known to produce toxicity at doses that appear to be behaviorally relevant (2,4,5,7,11,17). Whether EPH induces an aversive motivational state at doses near or in excess of those that alter locomotion and reinforcement is unknown. The intent of the present experiments was to evaluate the aversive actions of the EPH enantiomers (0, 5, 10, 20, or 40 mg/kg) using a conditioned taste aversion paradigm (Experiment 1) or a pica paradigm (Experiment 2). In the former, drug administration is paired with a novel saccharin flavor, and an aversive drug action is indexed by reductions in subsequent consumption of the drug-paired flavor. In the pica paradigm, rats consume a nonnutritive substance such as kaolin following the administration of aversive agents such as lithium chloride (LiCl).

EXPERIMENT 1

Method

Animals. The animals were 63 male Sprague–Dawley albino rats (Harlan Industries, Houston, TX) weighing between

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200–224 g at the beginning of the study. The rats were housed individually in standard plastic rodent cages and were allowed a 1-week adaptation period prior to onset of behavioral testing to acclimate them to daily handling and maintenance. The rats received continuous access to rodent pellets (Teklad) throughout the experiment, except during the testing periods described in the experimental protocol below. The animal holding room was maintained at 23 ± 1.0°C, with a 12 h/12 h light/dark schedule (lights on at 0600 h).

Drugs. A vehicle solution was prepared using 0.9 % (w/v) sodium chloride dissolved into sterile distilled water. Ephedrine solutions (2.5, 5, and 10 mg/ml) were prepared by dissolving either (+)-ephedrine hydrochloride or (−)-ephedrine hydrochloride (Sigma Chemical Company, St. Louis, MO) into the vehicle solution. A solution of lithium chloride (32 mg/ml; Fisher Scientific) was similarly prepared. The drug solutions were calculated as the weight of chemical (base and salt) per volume and were prepared immediately prior to injection.

Procedures. The rats were trained to consume tap water from metal sipper tubes attached to Wahmann 100-ml graduated drinking bottles during a 30-min drinking session on 6 consecutive baseline days (days 1–6). The rats were water deprived for 23 h prior to the drinking sessions, and food was available at all times except during the drinking sessions. The rats were weighed prior to each drinking session. The sipper tubes were inserted through holes in the wire mesh above each cage. Fluid intakes were recorded to the nearest 1.0 ml for each rat. All drinking sessions were conducted in the home cages between 1530 and 1730 h.

Following the baseline period, the rats were randomly assigned to one of nine groups: 0 mg/kg (+)-EPH ($n = 7$), 2.5 mg/kg (+)-EPH ($n = 7$), 5 mg/kg (+)-EPH ($n = 7$), 10 mg/kg (+)-EPH ($n = 7$), 0 mg/kg (−)-EPH ($n = 8$), 2.5 mg/kg (−)-EPH ($n = 7$), 5 mg/kg (−)-EPH ($n = 7$), 10 mg/kg (−)-EPH ($n = 7$), or 32 mg/kg LiCl ($n = 6$).

On day 7, the training day, all rats were presented with a 0.1% saccharin solution (Sigma Chemical) instead of tap water during the 30-min drinking test. Immediately following the 30-min access to saccharin, the bottles were removed and each rat was injected (IP) with either VEH, one of the EPH enantiomer doses, or LiCl. Days 8–11 constituted the extinction phase of the experiment. During each 30-min session, a two-bottle preference procedure was used in which the rats were presented with two Wahmann drinking bottles containing either tap water or the 0.1% saccharin solution (7). Bottle position was alternated daily according to a left or right position above the cage to control for position preference. Both bottles were removed from each cage immediately following the 30-min test, and the rats were water deprived until the beginning of the drinking test on the following day.

Data analyses. Separate two-way analyses of variance (ANOVAs), using the between-group factors of EPH enantiomer [(+)- or (−)-EPH] and EPH dose (0, 2.5, 5, or 10 mg/kg), were computed (SigmaStat) to compare baseline water intakes (averaged across days 5 and 6) and to compare saccharin intakes on the training day. The saccharin and water intakes collected during the extinction phase of the experiment were converted into standard suppression ratios [saccharin intake/(saccharin intake + water intake)] for each rat. A three-way ANOVA (SigmaStat), using the between group factors of EPH enantiomer [(+)- or (−)-EPH) and EPH Dose (0, 2.5, 5, or 10 mg/kg), and the within-group factor of extinction day (1–4), was used to compare saccharin suppression ratios recorded during the extinction.

The positive control condition of 32 mg/kg LiCl was compared to the vehicle treatment group for each of the EPH conditions, that is 0 mg/kg (+)-EPH and 0 mg/kg (−)-EPH. For the LiCl and EPH vehicle treatments, a one-way ANOVA was used to compare baseline water intakes and saccharin intake on the training day. In addition, a two-way ANOVA (SigmaStat), using the between group factor of LiCl positive control [0 mg/kg (+)-EPH, 0 mg/kg (−)-EPH, or 32 mg/kg LiCl] and the within-group factor of extinction day [1–4], was used to compare saccharin suppression ratios recorded during the extinction phase (days 8–11). Differences are noted as statistically significant for probability values less than 0.05 for all analyses.

Results

The average baseline water intakes [ml; mean (± SEM)] for the (+)-EPH group (collapsed across dose) and the (−)-EPH group (collapsed across dose) were 13.0 (± 0.25) and 13.3 (± 0.25), respectively. For baseline water intakes, a two-way ANOVA revealed no significant effect of EPH enantiomer, $F(1, 43) = 0.67$, $p = 0.42$, and no significant effect of EPH dose, $F(3, 43) = 0.62$, $p = 0.61$. There was no significant EPH enantiomer × EPH dose interaction, $F(3, 43) = 0.21$, $p = 0.89$. The average baseline water intakes (ml; mean (± SEM)) for the 0 mg/kg (+)-EPH, 0 mg/kg (−)-EPH, and the 32 mg/kg LiCl groups were 13.3 (± 0.54), 13.3 (± 0.46), and 12.2 (± 0.64), respectively. For baseline water intakes, a one-way ANOVA revealed no significant effect of LiCl positive control, $F(2, 18) = 1.37$, $p = 0.28$.

On the saccharin training day, the average saccharin intakes [ml; mean (± SEM)] for the (+)-EPH group (collapsed across dose) and (−)-EPH group (collapsed across dose) were 12.2 (± 0.35) and 11.6 (± 0.33), respectively. For saccharin intakes on the training day, a two-way ANOVA revealed no significant effect of EPH enantiomer, $F(1, 43) = 1.60$, $p = 0.21$, and no significant effect of EPH dose, $F(3, 43) = 1.70$, $p = 0.18$. There was no significant EPH enantiomer × EPH dose interaction, $F(3, 43) = 0.83$, $p = 0.49$. The average saccharin intakes [ml; mean (± SEM)] for the 0 mg/kg (+)-EPH, 0 mg/kg (−)-EPH, and 32 mg/kg LiCl groups were 12.7 (± 0.41), 12.0 (± 0.83), and 12.6 (± 0.63), respectively. For saccharin intakes on the training day, a one-way ANOVA revealed no significant effect of LiCl positive control, $F(2, 18) = 0.30$, $p = 0.74$.

Figure 1 depicts mean group percent saccharin suppression ratios during extinction days 1–4 for the EPH and LiCl treatments. Rats receiving systemic administration of 0 mg/kg of either (+)- or (−)-EPH exhibited a mean saccharin suppression ratio of approximately 60–80% across the 4 extinction days. Rats receiving the various doses of the EPH enantiomers exhibited saccharin suppression ratios comparable to those of the vehicle treatment groups. For saccharin suppression ratios, a three-way ANOVA revealed no significant effect of EPH enantiomer, $F(1, 49) = 1.05$, $p = 0.31$, and no significant effect of EPH dose, $F(3, 49) = 2.64$, $p = 0.06$. There was a significant effect of extinction day, $F(3, 147) = 7.46$, $p < 0.001$. There were no significant interactions between any of the factors: EPH enantiomer × EPH dose, $F(3, 49) = 0.68$, $p = 0.57$, EPH enantiomer × extinction day, $F(3, 147) = 1.29$, $p = 0.28$, EPH dose × extinction day, $F(9, 147) = 1.16$, $p = 0.32$, EPH enantiomer × EPH dose × extinction day, $F(9, 147) = 1.03$, $p = 0.42$.

In contrast to the lack of effect of either EPH enantiomer for the induction of CTA, the LiCl positive control condition induced significantly smaller suppression ratios during extinc-

tion days 1–4 (Fig. 1, lower panel). For saccharin suppression ratios, a two-way ANOVA revealed a significant effect of positive control, $F(2, 18) = 25.91$, $p < 0.001$, and a significant effect of extinction day, $F(3, 54) = 6.66$, $p < 0.001$. There was a significant control × extinction day interaction, $F(6, 54) = 3.86$, $p < 0.01$. The latter interaction reflects a marked suppression of saccharin consumption in LiCl-treated rats on day 1 that waned over days, in contrast to the stable consumption of saccharin by vehicle-treated rats.

The results of Experiment 1 document that administration of 32 mg/kg LiCl induces significant CTA, whereas the enantiomers of EPH did not. These results tentatively suggest that the enantiomers of EPH do not induce an aversive state as indexed by the conditioned taste aversion procedure. Yet, it is possible that the CTA procedure, as used in this study, may not fully capture aversive motivational properties. Other paradigms have been used to assess aversive motivational states. Pica, for example, refers to the consumption of nonnutritive substances, such as clay, following ingestion of toxins that induce emesis. Mitchell et al. (10) as well as McCutcheon et al (8) suggest that pica can be indexed by the 24-h consumption of kaolin, a nonnutritive clay. In support of this, these studies note that LiCl and other toxins induce the consumption of kaolin in rats. To further examine the aversive properties of EPH, Experiment 2 examined the impact of administration of either (+)-EPH or (−)-EPH (0, 5, 10, 20, or 40 mg/kg) on kaolin consumption in rats. To provide a comparison, the effects of an extended range of lithium chloride doses (0, 16, 32, 64, 96 mg/kg) on kaolin consumption were also assessed in Experiment 2.

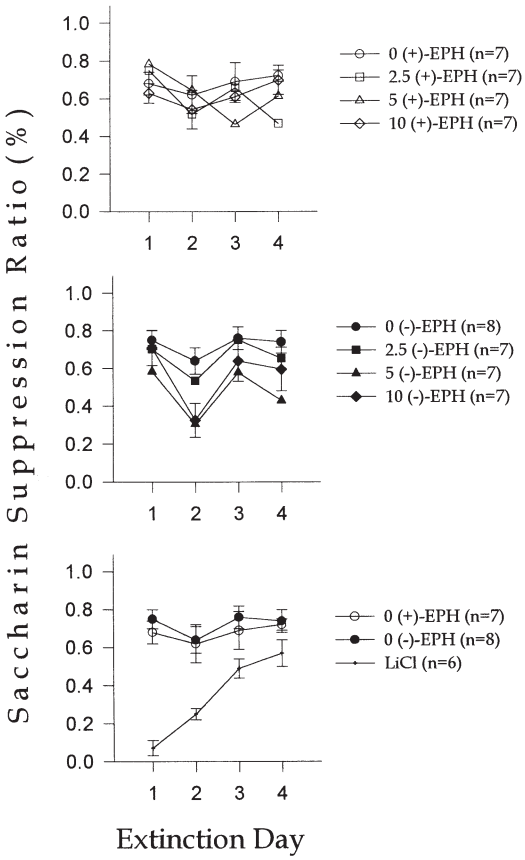

FIG. 1. Mean group saccharin suppression ratios (%) for the systemic doses (0, 2.5, 5, or 10 mg/kg) of the (+)-EPH group (top panel) and the (−)-EPH group (middle panel), and for the VEH and LiCl (32 mg/kg) groups (bottom panel) on extinction days 1–4. The vertical lines extending above and below each symbol represent the standard error of the mean.

EXPERIMENT 2

Method

Animals. The animals were 24 male Sprague–Dawley albino rats (Harlan Industries; Houston, TX) weighing approximately 185–215 g at the beginning of the study. The rats were housed individually in standard hanging metal rodent cages in a colony room maintained at 23 ± 1.0°C under a 12 h/12 h illumination schedule (lights on at 0600 h). The rats were provided continuous access throughout the study to tap water and to rodent pellets (Teklad) in the home cage.

Kaolin. Kaolin (Hydrated aluminum silicate, Sigma Chemical; St. Louis, MO) was compressed into 20-ml Pyrex beakers. Each beaker was attached to the inside front of each wire cage using loops of copper wire.

Drugs. A vehicle solution was prepared using 0.9% (w/v) sodium chloride dissolved in sterile distilled water. Both (+)-ephedrine and (−)-ephedrine solutions (5, 10, 20, 40 mg/kg) were prepared using (+)-ephedrine HCl and (−)-ephedrine HCl (Sigma Chemical) dissolved into the saline vehicle. The LiCl solutions (16, 32, 64, 96 mg/kg) were prepared using LiCl (Sigma Chemical) dissolved in the vehicle. Drug solutions were calculated as the salt and were administered in a volume of 1.0 ml/kg (IP).

Procedures. The rats were maintained in the colony room for 1 week prior to the start of the experiment to acclimate them to daily handling and routine colony procedures. On Baseline days 1–6, a kaolin container was placed in each cage to adapt the rats to the presence of kaolin. At 0900 h each day the pellet feeders and water bottles were weighed to the nearest 0.1 g, refilled with pellets and water, then weighed, and returned to the home cage. Kaolin beakers were also weighed, refilled, weighed, and returned to the home cage. Cardboard pads placed beneath each cage were used to collect food and kaolin spillage. These pads were removed daily and dried overnight to determine food and kaolin spillage. Food and kaolin intakes were recorded to the nearest 0.1 g after correction for spillage. Water intakes were recorded to the nearest 0.1 g, but were not corrected for spillage.

On baseline days 5 and 6, the rats were injected IP with 1.0 mg/kg vehicle at 1000 h to adapt them to the injection procedures. The food intake values and the kaolin intake values averaged across baseline days 4–6 were used to form three groups of rats of comparable food and kaolin intake. These groups were, in turn, randomly assigned to one of three treatment conditions: (+)-ephedrine, (−)-ephedrine, and LiCl.

On treatment days 7, 10, 13, 16, and 19, the rats received one of the doses of their respective treatment condition. Each rat received all drug doses. The doses were 0, 5, 10, 20, 40 mg/kg of (+) EPH or (−) EPH, or 16, 32, 64, 96 mg/kg of LiCl. On the days between successive drug tests (days 8 and 9, 11 and 12, 14 and 15, and 17 and 18), the rats received no drug injections.

Data analyses. The design of the experiment was a split-plot factorial with drug as the between-subjects variable and drug dose as a within-subjects variable. Separate mixed two-way analyses of variance (ANOVA) on drug group (LiCl,

(+)-EPH, and (−)-EPH) and drug dose (0, 5, 10, 20, 40 mg/kg for (+)- and (−)-EPH and 0, 16, 32, 64, 96 mg/kg for LiCl) were computed using SigmaStat for the dependent measures of kaolin intake, food intake, water intake, and body weight (6). Subsequent contrasts between groups were computed used Dunnett's test. Differences are noted as statistically significant for probability values less than 0.05.

Results

Baseline analyses averaged across days 4–6, revealed no significant differences between the groups with regard to either body weight, kaolin intake, food intake or water intake ($ps > 0.05$).

Kaolin intake. The rats exhibited comparable intakes of the kaolin diet after injection of vehicle (see Fig. 2). The average kaolin intakes [g; mean (+ SEM)] for the 0 mg/kg (+)-EPH, 0 mg/kg (−)-EPH, and 0 mg/kg LiCl conditions were 0.06 (± 0.05), 0.05 (± 0.05), and 0.05 (± 0.05), respectively. A two-way ANOVA using the between-group factor of eph enantiomer [(+) vs. (−)] and the within-group factor of drug dose (0, 5, 10, 20, and 40 mg/kg) revealed no significant effect of the factors of EPH enantiomer, dose, or the interaction between the factors of EPH enantiomer and dose ($ps > 0.529$). The impact of lithium chloride on kaolin intake was examined using a one-way ANOVA with drug dose as the within-group factor. This analysis revealed a significant effect of dose, $F(4, 28) = 2.857$, $p < 0.042$, indicating that treatment with LiCl significantly increased 24-h intake of the kaolin diet. Subsequent Dunnett contrasts of 24-h kaolin intakes revealed that the 96-mg/kg LiCl dose produced a significant increase in 24 h kaolin intake compared to intake after injection of vehicle.

Food and water intake. After treatment with vehicle, the rats in each group consumed an average of 25 g of food per 24-h interval (see Fig. 3). A two-way ANOVA using the between-group factor of EPH enantiomer [(+) vs. (−)] and the within-group factor of drug dose (0, 5, 10, 20, and 40 mg/kg) revealed a significant effect of EPH dose, $F(4, 56) = 4.775$, $p < 0.002$), but no significant effect of EPH group or of the interaction between these factors ($ps > 0.169$). Subsequent Tukey contrasts of 24-h food intakes, collapsed across enantiomer group, revealed that the 40 mg/kg EPH doses produced a significant reduction in 24-h food intake compared to the intakes after injection of either vehicle or 5 mg/kg or 10 mg/kg EPH. In contrast, no dose of LiCl produced a significant change in 24-h food intake ($p > 0.490$).

After injection of vehicle, the rats ingested an average of 40 ml of water over a 24-h interval (see Fig. 4). Separate ANOVAS computed for the impact of the EPH enantiomers and of LiCl on water intake revealed no significant effects ($ps > 0.179$).

GENERAL DISCUSSION

The intent of the present experiments was to assess the aversive properties of the enantiomers of the sympathomimetic agent EPH. In Experiment 1, systemic administration of either (+)-EPH or (−)-EPH did not induce a significant conditioned taste aversion to saccharin at doses ranging from 2.5 to 10 mg/kg. At these doses, the enantiomers of EPH are known to exert significant behavioral and metabolic effects, including activation of locomotion (13), suppression of food intake (1,16), and induction of brown adipose tissue thermogenesis (15). Although CTA was not observed in Experiment 1 to the EPH enantiomers, rats treated with 32 mg/kg LiCl exhibited significant CTA.

In Experiment 2, the impact of the EPH enantiomers on kaolin consumption was compared with that of lithium chloride. To exclude the possibility that aversive effects of EPH might be evident at higher doses than those that exert behavioral actions, this experiment examined an extended dose range for each of the EPH enantiomers. As has been observed by others, systemic administration of lithium chloride induced significant increases in kaolin consumption (8). No such increases in kaolin intake were evident for any dose of either (+)-EPH or (−)-EPH. It should be noted that these doses of EPH were up to 40 mg/kg or four fold higher than those used in Experiment 1.

Taken together, these two studies suggest that neither enantiomer of EPH is associated with aversive motivational proper-

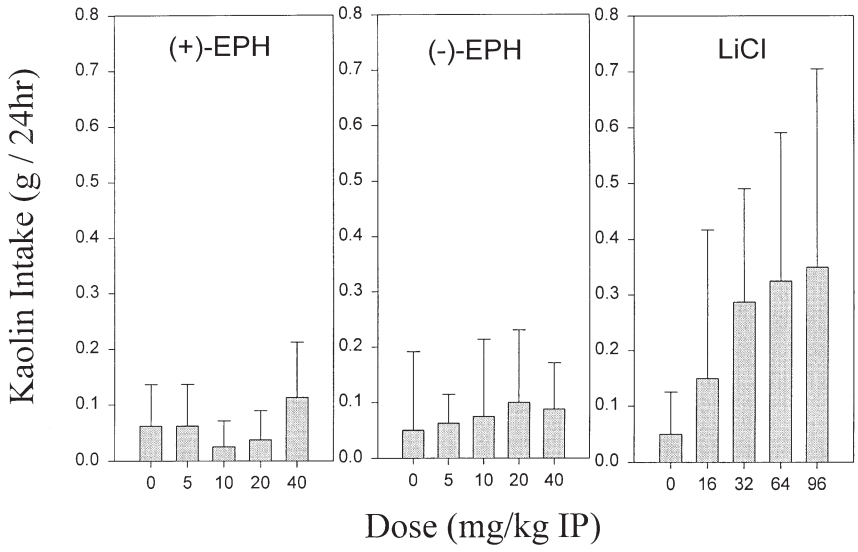

FIG. 2. Mean group kaolin intake (g/24 h) for rats treated with various doses of either (+)-EPH (left panel), (−)-EPH (middle panel), or LiCl (right panel). The lines above each bar represent the standard error of the mean.

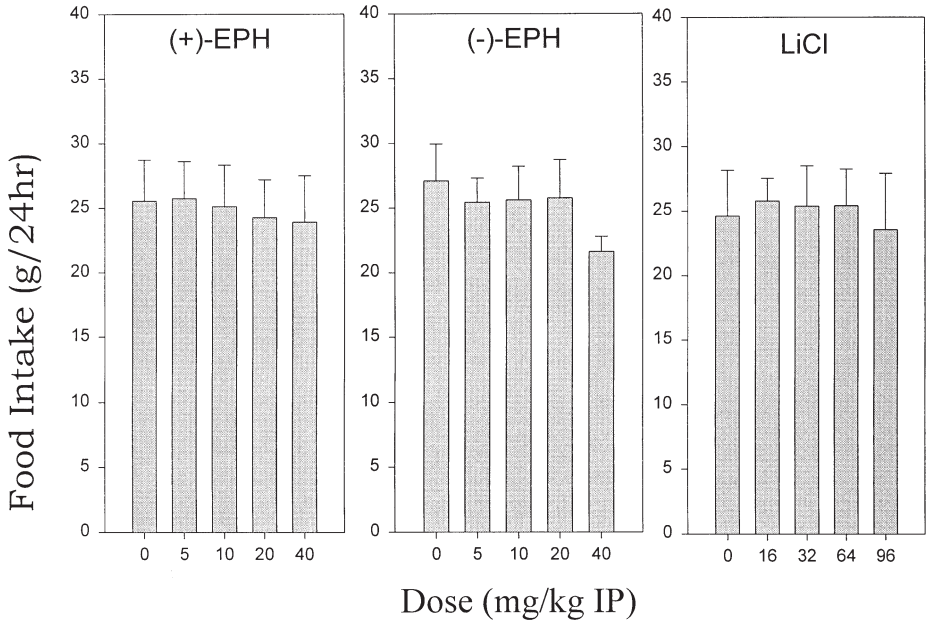

FIG. 3. Mean group food intake (g/24 h) for rats treated with various doses of either (+)-EPH (left panel), (−)-EPH (middle panel), or LiCl (right panel). The lines above each bar represent the standard error of the mean.

ties at even relatively high doses. Although the EPH enantiomers do not exhibit aversive motivational properties, the neurochemical actions of these enantiomers may be associated with reinforcing properties. EPH is known to enhance extracellular levels of brain dopamine (16), a finding that may explain the impact of these enantiomers on locomotion and the likelihood that EPH possesses positively reinforcing effects (12). Whether the anorectic action of EPH reflects the these changes in dopamine or action at adrenergic receptors (14) is presently unknown.

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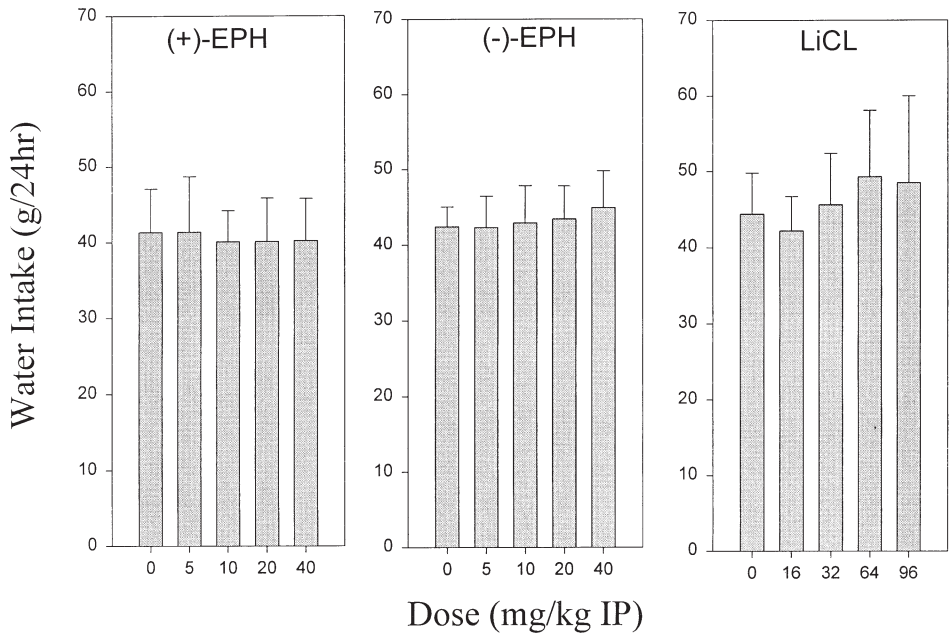

FIG. 4. Mean group water intake (g/24 h) for rats treated with various doses of either (+)-EPH (left panel), (−)-EPH (middle panel), or LiCl (right panel). The lines above each bar represent the standard error of the mean.

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