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Sertraline Attenuates Hyperphagia in Rats Following Nicotine Withdrawal

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LEVIN, E. D., S. J. BRIGGS, N. C. CHRISTOPHER AND J. E. ROSE. *Sertraline attenuates hyperphagia in rats following nicotine withdrawal.* PHARMACOL BIOCHEM BEHAV 44(1) 51–61, 1993.—Chronic nicotine administration can decrease food consumption and body weight. Abrupt withdrawal from nicotine can cause the reverse effect, hyperphagia and rapid weight gain. In the current study, the efficacy of sertraline, a serotonin reuptake inhibitor, on nicotine withdrawal-induced hyperphagia and rapid weight gain was assessed in rats. Sertraline was found to be effective in reversing the increase in feeding that occurred after withdrawal from chronic nicotine administration. Sertraline caused a dose-related decrease in food consumption in control rats not given nicotine. Doses of 5 and 10 mg/kg/day caused significant decreases while 2.5 mg/kg/day caused a slight though nonsignificant decrease in food consumption. Rats in which nicotine was abruptly withdrawn after 3 weeks of administration showed a significant increase in food consumption relative to controls. This increase was eliminated by the high dose of sertraline (10 mg/kg/day), but not by the lower two doses (2.5 and 5 mg/kg/day). Water consumption was affected in a similar fashion. Body weight gain was also affected by sertraline. During the first week after nicotine withdrawal, rats rapidly gained weight, but sertraline attenuated this. The 10-mg/kg dose of sertraline significantly attenuated the nicotine withdrawal-induced weight gain. These results suggest that sertaline can counteract the hyperphagia and rapid weight gain associated with nicotine withdrawal, and might therefore be a useful adjunct to smoking cessation.

Sertraline Nicotine Chronic Weight Feeding Serotonin Nicotine withdrawal Smoking

THE adverse effects of nicotine withdrawal contribute to the relapse of many people who have stopped using tobacco. One of the most common withdrawal effects is increased appetite and weight gain [for reviews, see (4,14)]. This may contribute significantly to smoking relapse. This effect can also be seen in experimental animal models. Experiments in our laboratory and others have demonstrated that chronic nicotine administration in rats decreases food consumption and body weight and subsequent withdrawal increases feeding behavior and weight (3,5,6,8) [for review, see (15)]. The rat model can be used to assess the efficacy of drug treatments for alleviating nicotine withdrawal-induced hyperphagia and weight gain.

Serotonergic activity has been found to inhibit feeding behavior. A variety of drugs that increase serotonergic stimulation have been found to cause anorexia in humans and laboratory animals (10). Sertraline, a specific serotonergic reuptake inhibitor, decreases food intake in rats (7,11–13). The objective of the present study was to examine the effect of sertraline on hyperphagia and weight gain following nicotine withdrawal. A dose–effect function of sertraline was obtained in control and nicotine-treated rats to gain information concerning the relative potency of sertraline effects on nicotine withdrawal-induced hyperphagia vs. normal feeding. Some nicotine effects in the CNS may be mediated via actions on serotonergic systems (1). A finding that sertraline is more potent in counteracting nicotine withdrawal-induced hyperphagia than producing hypophagia in control animals would support the idea that sertraline is specifically addressing mechanisms underlying the hyperphagia. Whatever the mechanism, a finding that sertraline attenuates hyperphagia and weight gain after nicotine withdrawal would point to its potential utility in helping attenuate these effects in smokers who quit.

METHOD

Subjects

Adult, female Sprague-Dawley rats (Zivic-Miller, Allison Park, PA) were housed singly in a vivarium room on a 12 L : 12 D cycle (lights came on at 6:00 a.m.). They were given ad lib access to water throughout the day and ad lib access to powdered Purina rat chow for 16 h/day (approx. 5:00 p.m.–9:00 a.m.). The food and water consumption and the body weight of rats were measured every day at approximately 9:00 a.m.

Drug Treatments

After an initial period of 2 weeks of baseline measurement, Alzet osmotic minipumps were implanted subcutaneously between the scapulae while rats were anesthetized with 40 mg/

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TABLE 1

TIMETABLE FOR NICOTINE AND SERTRALINE ADMINISTRATION

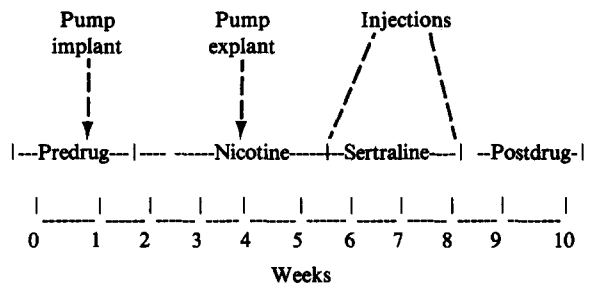

TABLE 2

GROUP SIZES FOR NICOTINE AND SERTRALINE ADMINISTRATION

Sertraline (mg/kg/day)	Placebo	Nicotine
0	13	14
2.5	9	10
5	10	9
10	11	11

kg pentobarbital (Nembutal). Rats were assigned to control and nicotine treatment groups balanced for baseline body weight and feeding for the previous 2 weeks. Nicotine ditartrate was administered via minipumps in a dose of approximately 12 mg/kg/day (expressed as free base). This is the dose we previously found to cause hypophagia and a moderate degree of weight loss in rats (5,6). Controls were implanted with identical pumps containing saline. The flow rate for these Alzet osmotic minipumps (Model 2ml4) was 2.52 μl/h (information supplied by the manufacturer). The nicotine pumps were removed after 3 weeks of administration. We previously found this withdrawal to cause a significant degree of hyperphagia, hyperdipsia, and rapid weight gain (5). One cohort of rats received 4 additional days of nicotine or saline administration. These additional days of treatment were not found to affect significantly the subsequent withdrawal effects and so data obtained from these animals were pooled for the purpose of analysis. The study design is given in Table 1.

Sertraline was administered IP in doses of 0, 2.5, 5, or 10 mg/kg/day for 3 weeks after the end of nicotine administration. The number of animals per group is listed in Table 2. The volume of injection was 2.5 ml/kg. Saline was used for the control group. Injections were given just prior to the onset of the dark phase, when food was reintroduced to rats.

Data Analysis

Food and water consumption and body weight data were analyzed separately by mixed-design analyses of variance (ANOVAs) for two between-groups factors (nicotine and sertraline treatment) and repeated measures (days). Subsequent comparisons of control and the sertraline drug treatments were made using Dunnett's test for multiple comparisons. Significant interactions were followed up by tests of the simple main effects.

RESULTS

Nicotine Effects

The 3-week chronic nicotine infusion caused dramatic effects on food and water intake and body weight gain. As shown in Fig. 1, food consumption was substantially reduced by nicotine treatment. The main effect of nicotine was highly significant, $F(1, 85) = 129.39$, $p < 0.0001$. The nicotine × days interaction was also significant, $F(20, 1{,}700) = 18.92$, $p < 0.0001$. Analyses of the simple main effects of nicotine at each day detected significant nicotine-induced hypophagia from the day after implantation of the nicotine pellet until day 16 ($p < 0.05$). In addition, significant nicotine-induced hypophagia was seen on days 18 and 21 ($p < 0.05$). The effect of nicotine was greatest during the first few days of administration. There was approximately a 60–70% decrease in food consumption during the first 4 days after the start of nicotine infusion. A 35–50% decrease was seen from the 5th through

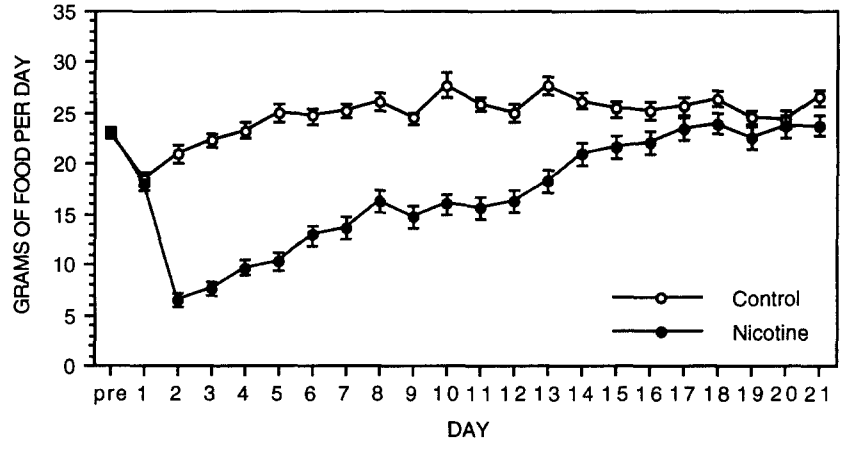

FIG. 1. Chronic nicotine effects on food consumption (mean ± SEM).

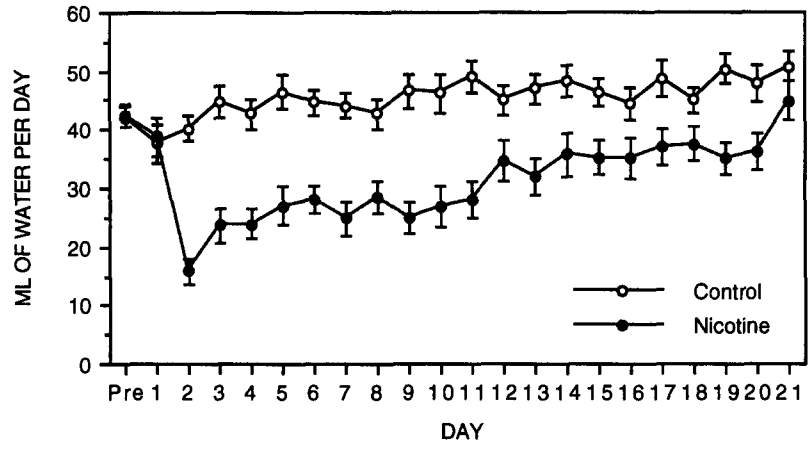

FIG. 2. Chronic nicotine effects on water consumption (mean ± SEM).

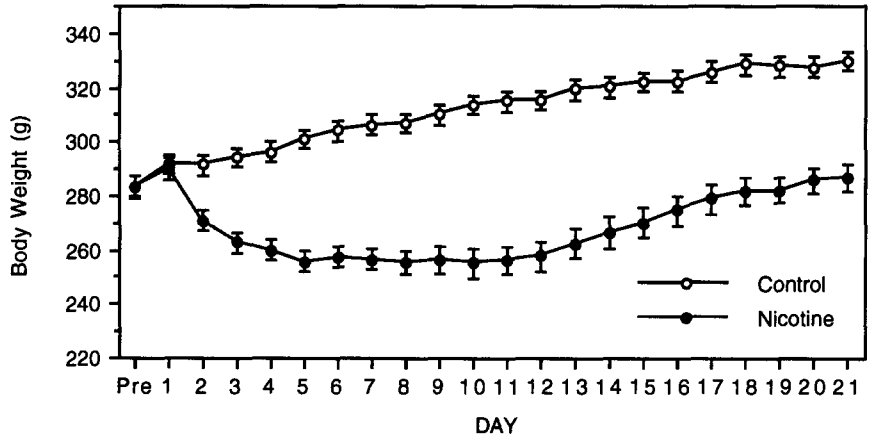

FIG. 3. Chronic nicotine effects on body weight (mean ± SEM).

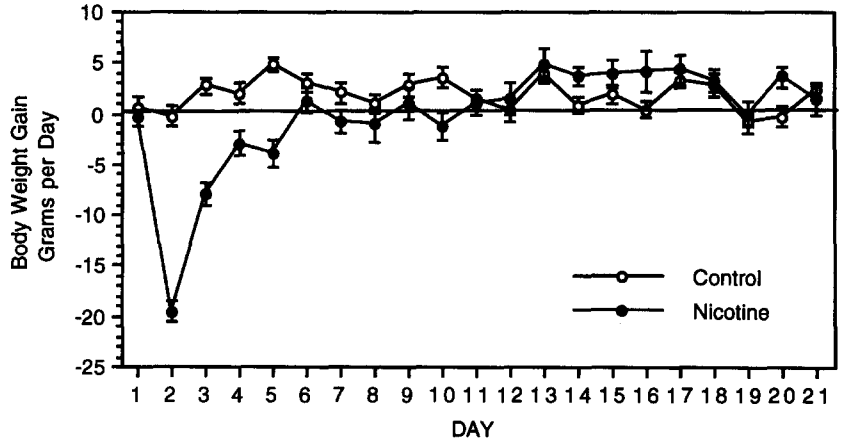

FIG. 4. Chronic nicotine effects on daily weight gain (mean ± SEM).

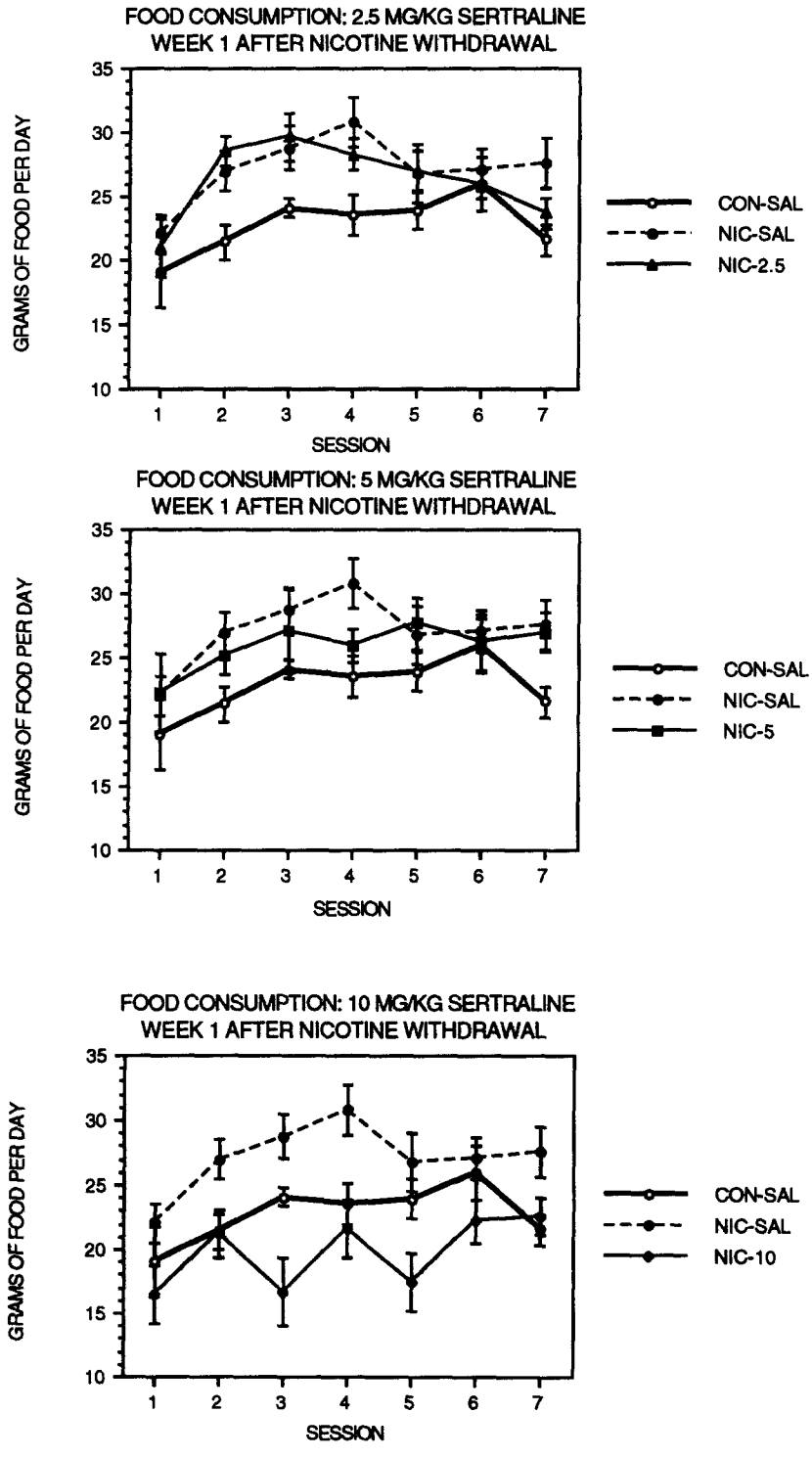

FIG. 5. Daily means for nicotine (NIC) and sertraline (SAL) effects on food consumption during the first week after nicotine withdrawal (mean ± SEM). CON, control.

12th days. The effect became attenuated so that there was only a 10% decrease in food consumption during the 3rd week of nicotine administration.

Similar effects were seen in water consumption (Fig. 2). The main effect of nicotine was highly significant $F(1, 85) = 28.67$, $p < 0.0001$, as was the nicotine × days interaction, $F(20, 1{,}700) = 4.03$, $p < 0.0001$. Significant nicotine-induced hypodipsia was seen during the entire period from the day after implant of the nicotine pump until the day before it was removed ($p < 0.05$). The day after the start of nicotine administration, water consumption was reduced by about 60%. There was a continuing 35–50% decrease from baseline water consumption for the next 9 days. During the third week of nicotine administration, there was an average 22% deficit in water consumption.

As shown in Fig. 3, nicotine significantly decreased body weight relative to controls, $F(1, 85) = 66.68$, $p < 0.0001$. The interaction of nicotine × days was significant as well, $F(20, 1{,}700) = 28.37$. Analyses of the simple main effects of nicotine showed that starting the day after the start of nicotine administration there was a highly significant nicotine-induced weight decrease relative to controls every day during nicotine administration ($p < 0.0001$). Nicotine-treated rats quickly lost about 10% of their body weight during the first few days of nicotine administration and then more gradually lost about another 9% of body weight relative to controls to a nadir of 81% of control weight by 10 days after the start of nicotine administration. Then, they gradually increased in weight to reach 87% of control weight by the end of the period of nicotine administration.

Nicotine effects on daily weight gain were also assessed (Fig. 4). There was a significant main effect of nicotine, $F(1, 85) = 73.56$, $p < 0.0001$, as well as a significant nicotine × days interaction, $F(20, 1{,}700) = 10.84$, $p < 0.0001$. Analyses of simple main effects detected significant nicotine-related weight gain deficits on the first through fourth days after the start of nicotine administration ($p < 0.005$). A significant nicotine-induced deficit was also seen on day 10 ($p < 0.005$). Nicotine-treated rats lost an average of 4.9 ± 0.4 g/day during the first week while controls gained an average of 2.2 ± 0.3 g/day. There was no significant difference during the second week of nicotine administration. During the later portion of nicotine administration, there was evidence for increased weight gain in nicotine-treated rats compared to controls as they gradually regained weight. Significant weight gain was seen in nicotine rats relative to controls on days 14 and 20 ($p < 0.025$). During the third week, nicotine-treated rats showed significantly greater ($p < 0.01$) weight gain compared to controls as they started to recoup the weight they had lost previously. During this period, nicotine-treated rats gained an average of 2.9 ± 0.5 g/day while controls gained an average of 1.4 ± 0.2 g/day.

Nicotine Withdrawal and Sertraline Effects

During the first week after withdrawal, nicotine-treated rats showed a significant increase in food consumption relative to controls ($p < 0.001$). Figures 5A–C display the effects of sertraline during the first 7 days after nicotine withdrawal. The nicotine withdrawal-induced hyperphagia can clearly be seen by comparing the control and nicotine groups not given sertraline. The 2.5- and 5-mg/kg doses of sertraline showed little if any signs of attenuating this increase in food consumption. In contrast, the 10-mg/kg dose of sertraline completely abolishes the nicotine withdrawal-induced hyperphagia. There were significant sertraline-related effects during the first ($p < 0.001$) and second ($p < 0.05$) weeks of sertraline administration. The sertraline effect was only marginally significant during the third week of sertraline administration ($p < 0.08$). The overall effects of previous nicotine treatment and the dose–effect of sertraline during the first week after nicotine withdrawal is shown in Fig. 6. Week-by-week effects of nicotine and sertraline on food consumption are shown in Figs. 7A–D.

Similar effects were seen with water consumption (Figs. 8A–D). During the first week after nicotine withdrawal, there was a significant hyperdipsia in the nicotine-treated group relative to controls ($p < 0.005$). During each of the 3 weeks of sertraline administration, there were significant sertraline effects ($p < 0.01$) characterized by decreased water consumption in sertraline-treated rats.

There were significant nicotine-induced deficits ($p < 0.05$) in weight during all weeks of sertraline administration (Figs. 9A–D). There were no significant sertraline effects on body weight; however, there were effects on weight gain measurements (Figs. 10A–D). There was a significant nicotine-related

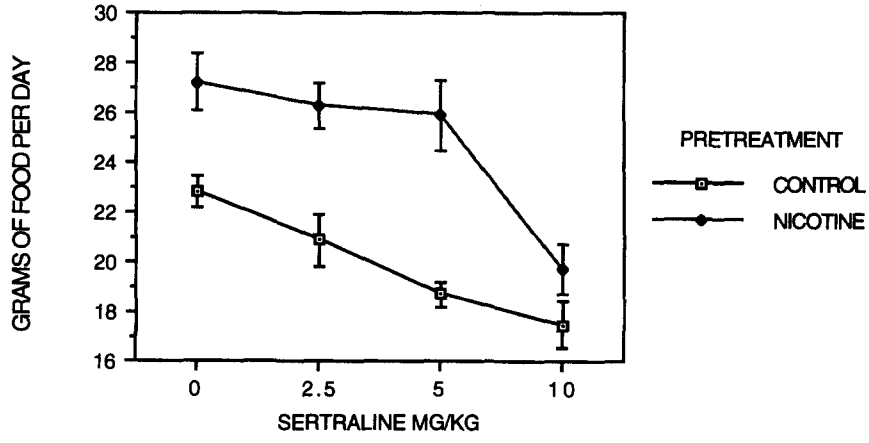

FIG. 6. Dose–response effect of sertraline on food consumption during the first week after nicotine withdrawal (mean ± SEM).

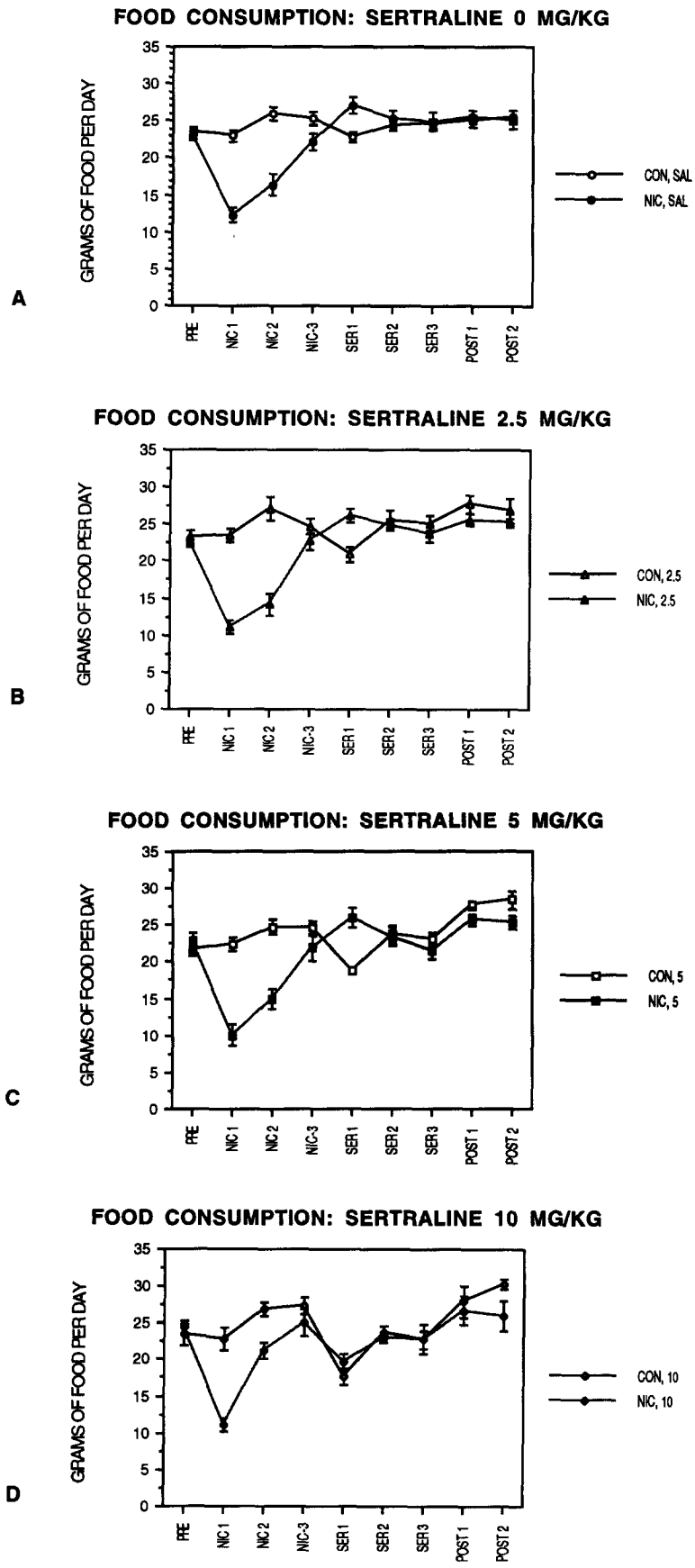

FIG. 7. Weekly means for nicotine (NIC) and sertraline (SAL) effects on food consumption (mean ± SEM). CON, control.

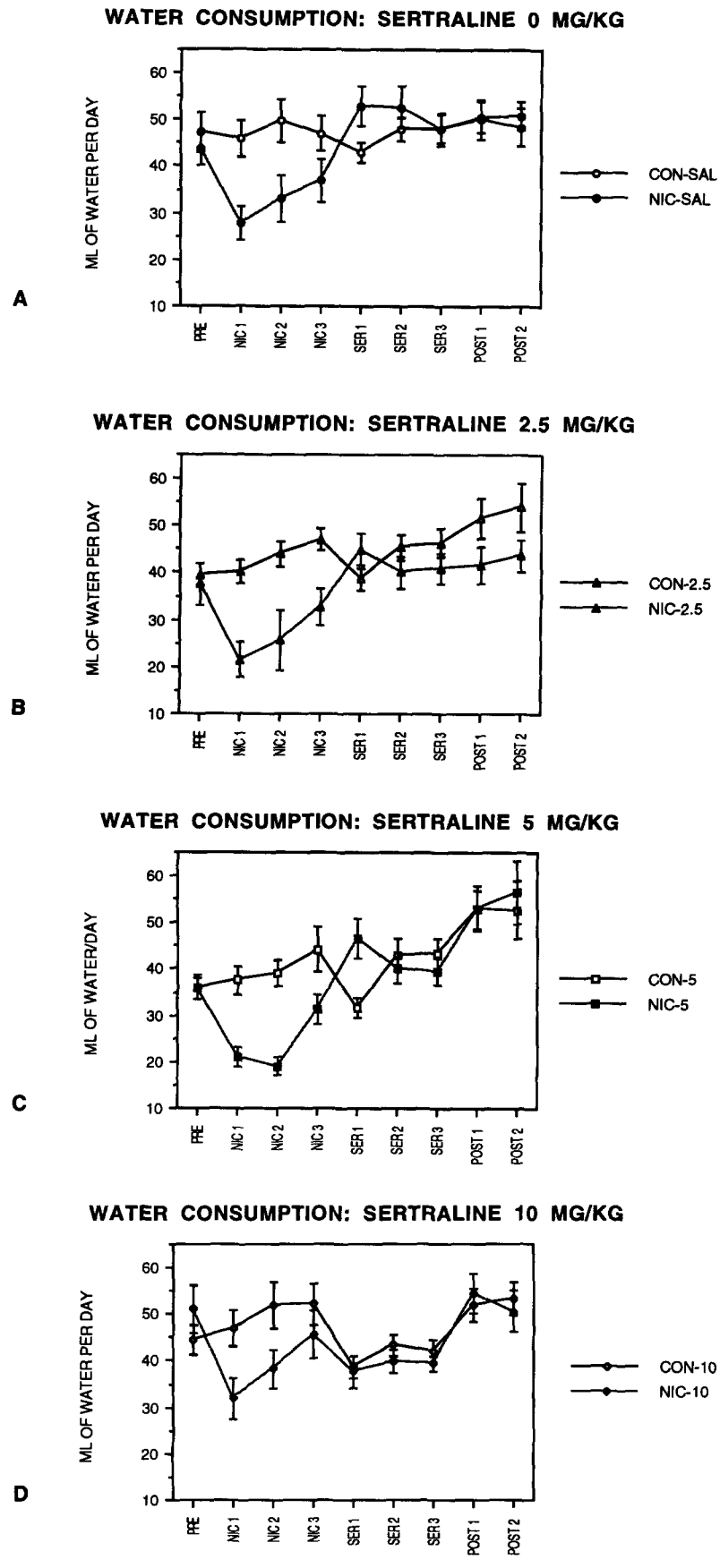

FIG. 8. Weekly means for nicotine (NIC) and sertraline (SAL) effects on water consumption (mean ± SEM). CON, control.

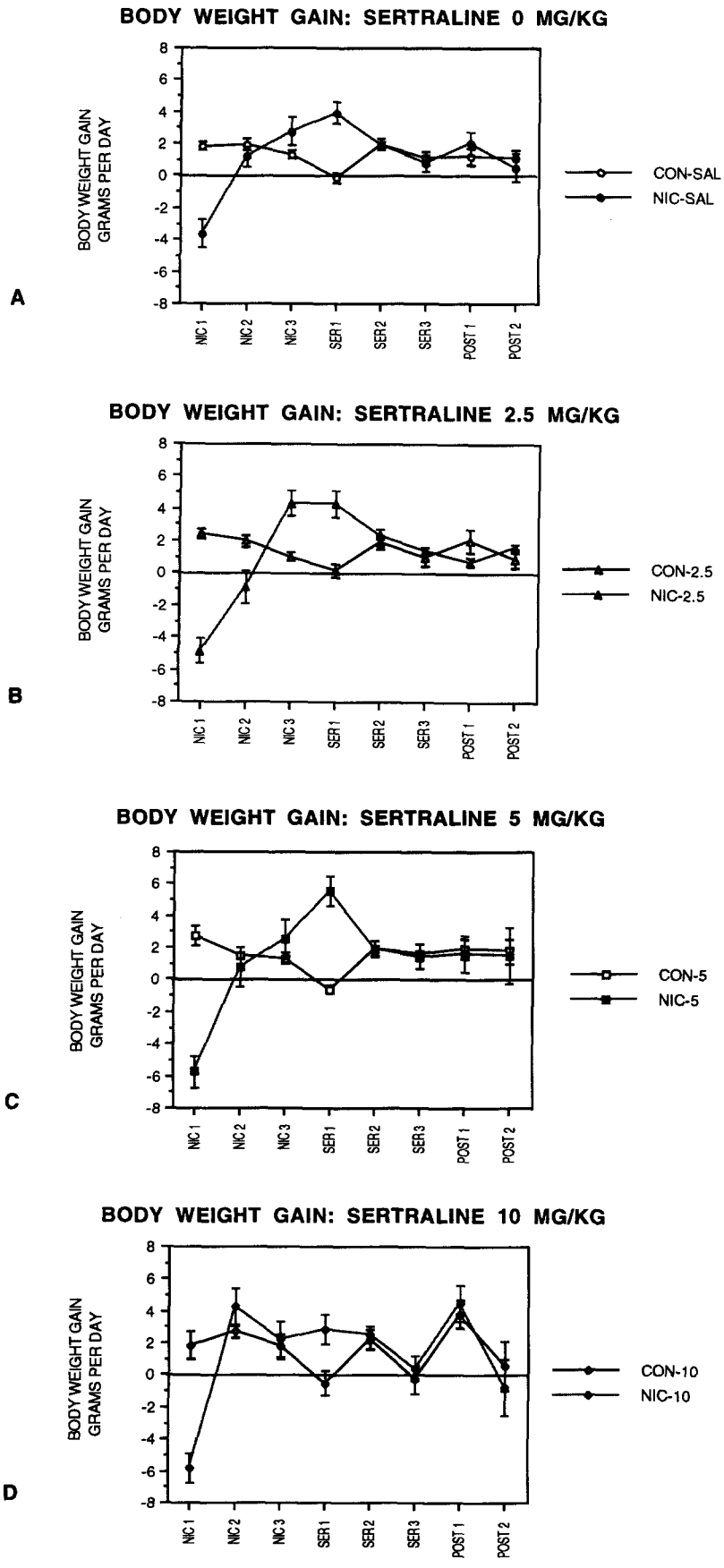

FIG. 10. Weekly means for nicotine (NIC) and sertraline (SAL) effects on daily weight gain (mean ± SEM). CON, control.

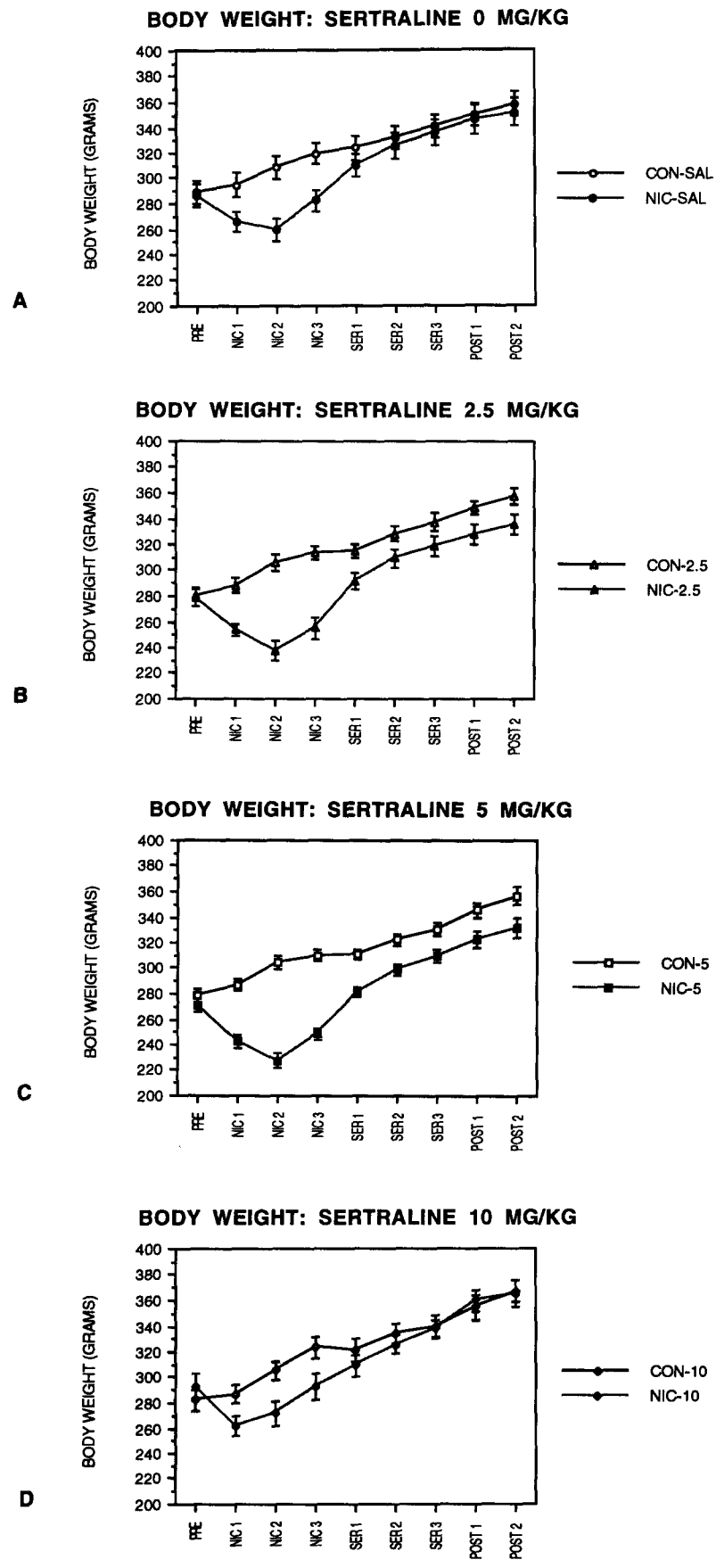

FIG. 9. Weekly means for nicotine (NIC) and sertraline (SAL) effects on body weight (mean ± SEM). CON, control.

increase in weight gain during the first week ($p < 0.001$). During this first week, there was also a significant effect of sertraline reducing weight gain ($p < 0.001$). Posthoc Dunnett's tests showed that both the 5- and 10-mg/kg groups had a significantly lower weight gain compared to saline-treated rats ($p < 0.05$). After withdrawal from nicotine, there was a significantly greater rate of weight gain. This effect was reversed by administration of 10 mg/kg/day sertraline. The lower doses were not effective. During the second week of sertraline administration, there was not a significant nicotine effect but there was a significant sertraline effect ($p < 0.05$). The 5- and 10-mg/kg groups had lower mean weight gains during this period compared to saline-treated rats but these differences were not significant by Dunnett's test. There were no significant nicotine or sertraline effects during the third week of sertraline administration.

Sertraline Withdrawal

There were no significant effects of nicotine or sertraline during the 2 weeks after sertraline withdrawal in terms of water consumption or body weight. With food consumption and weight gain, there were significant effects. There was a significant nicotine effect ($p < 0.05$) on food consumption following sertraline withdrawal. Interestingly, nicotine-treated rats had lower food consumption (25.6 ± 0.4 g/day) for the 2 weeks after sertraline withdrawal than control rats (27.3 ± 0.4 g/day). With weight gain, there was a significant sertraline × week interaction ($p < 0.025$). Analyses of the simple main effects at each week showed that there was a significant ($p < 0.001$) sertraline effect during week 1 after sertraline withdrawal. There was no significant effect during week 2. Posthoc Dunnett's tests for week 1 showed that the 10-mg/kg sertraline group (4.2 ± 0.7) had significantly greater ($p < 0.01$) daily weight gain than controls (1.6 ± 0.4).

DISCUSSION

As has been previously reported (6), nicotine proved to be a powerful anorectic agent that became gradually less effective over a period of 3 weeks of continuous administration. It caused a dramatic loss in weight during the first several days. During the later part of the 3-week nicotine exposure, rats gained weight at faster than control levels but the overall deficit in body weight persisted throughout the period of nicotine exposure. As previously seen, nicotine withdrawal was characterized by hyperphagia, hyperdipsia, and rapid weight gain (6).

Sertraline was effective in blocking the hyperphagia, hyperdipsia, and rapid weight gain seen after withdrawal from chronic nicotine administration. The high dose of 10 mg/kg/day was necessary to see this effect. The dose of 5 mg/kg/day was not found to reduce the hyperphagia despite the fact that it caused a significant reduction in food consumption in rats not given nicotine. This suggests that the effectiveness of sertraline in counteracting the nicotine withdrawal-induced hyperphagia may be due to its general anorectic effects and not to a specific action on mechanisms underlying nicotine withdrawal-induced hyperphagia.

Withdrawal from 10 mg/kg sertraline caused a transient increase in weight gain during the first week. No significant sertraline withdrawal effects were seen in feeding, drinking, or body weight. In terms of the potential clinical use of sertraline as an aid to smoking cessation, these data suggest that sertraline may be useful in counteracting hyperphagia and weight gain after smoking cessation if a sufficient dose is administered.

Fluoxetine, another serotonin reuptake inhibitor, has also been found to reduce nicotine withdrawal-induced weight gain. Pomerleau et al. (9) measured the weight and food consumption of smokers before and after they reduced or stopped smoking cigarettes. Subjects given placebo treatment gained significantly more weight over a period of 10 weeks (+3.3 ± 0.7 kg, mean ± SEM) than subjects given 60 mg/day PO fluoxetine (−0.6 ± 1.2 kg).

Sertraline is an interesting candidate for treating nicotine withdrawal-induced weight gain not only because it is effective in reducing the weight gain but also because it has shown promise in treating obsessive-compulsive behavior (2). Sertraline may be effective in reducing both weight gain and the obsessive desire for smoking cigarettes.

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