Pharmacology Biochemistry and Behavior, Vol. 47, pp. 215–218, 1994
Printed in the U.S.A.

0091-3057/94 $6.00 + .00

Systemic Clonidine Increases Feeding and Wheel Running but Does Not Affect Rate of Weight Loss in Rats Subjected to Activity-Based Anorexia

THOMAS S. RIEG[1] AND PAUL F. ARAVICH

Department of Anatomy & Neurobiology, Eastern Virginia Medical School, Norfolk, VA 23501 and Medical Research Service, VA Medical Center, Hampton, VA 23667

Received 26 October 1992

RIEG, T. S. AND P. F. ARAVICH. *Systemic clonidine increases feeding and wheel running but does not affect rate of weight loss in rats subjected to activity-based anorexia.* PHARMACOL BIOCHEM BEHAV 47(2) 215–218, 1994.– Activity-based anorexia (ABA) is an animal model of anorexia nervosa with two characteristics of the disorder, decreased food intake and increased activity. We have shown that chronic noradrenergic stimulation of the paraventricular hypothalamus exacerbates ABA rather than ameliorates it. This study determined if peripheral chronic administration of clonidine affects ABA. Rats were implanted SC with osmotic minipumps infusing 0, 30, or 300 μg/kg/day of clonidine and exposed to ABA (1.5 h/day ad lib food, 22.5 h/day ad lib wheel access). Results showed that clonidine did not affect the rate of weight loss during ABA, but increased food intake at the lower dose and wheel activity at the higher dose. It is proposed that increased energy expenditure due to wheel running is counteracted by an inhibition of sympathetically mediated diet-induced thermogenesis, and that the elevation in running by the higher dose potentially increases the risk of developing ABA.

Anorexia nervosa Exercise Feeding Clonidine Energy expenditure Starvation

ANOREXIA nervosa is associated with excessive exercise (5,16,28). In fact, hyperactivity is one of the first symptoms to appear and may be a primary feature of the disorder (16). Subpopulations where weight loss and exercise are encouraged are at increased risk for developing anorexia (26). Such populations include long distance runners (14) and ballet dancers (28). Finally, the reinforcing effect of exercise is so powerful that it can be used as a reinforcer to promote weight gain in underweight anorexics (3). Further research is clearly needed to determine the relationship between exercise and anorexia nervosa.

Anorexia nervosa is also associated with noradrenergic abnormalities. For instance, a urinary marker for central noradrenergic activity, the metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), is reduced in acutely ill anorexics and recovers with weight gain (11,12). Central (15) and peripheral (11) noradrenergic abnormalities also occur. These data raise the possibility of central noradrenergic dysfunction in anorexia nervosa.

It is well established that noradrenergic stimulation of the paraventricular hypothalamus (PVN) increases food intake in experimental animals (10,19). An elegant series of studies has demonstrated that this effect is mediated by α_2 adrenergic receptors. Numerous investigators have shown that α_2 adrenergic agonists such as clonidine increase food intake when administered directly into the paraventricular hypothalamic nucleus (19) or when administered systemically (18,25). If anorexia nervosa is related to a decrease in the activity of the paraventricular hypothalamic noradrenergic-feeding system, clonidine should be useful in promoting weight gain.

This possibility has been tested in acutely ill anorexics (4). Unfortunately, no beneficial effect of systemically administered clonidine was observed. The null effect was attributed to the possibility that an insufficient dose was administered; larger doses were not tested because of the possibility of deleterious side effects such as bradycardia, hypotension, and excessive sedation. It was proposed, however, that the sedative effects of the drug might be useful in treating anorexic patients with hyperactivity. An appropriate animal model is needed to test this possibility.

One such animal model is the weight-loss syndrome produced by voluntary exercise in food-restricted rats (27). It has

[1] Requests for reprints should be addressed to Thomas S. Rieg, Department of Anatomy & Neurobiology, Eastern Virginia Medical School and Medical Research Service (151), VA Medical Center, Hampton, VA 23667.

been called self-starvation (24) or activity-based anorexia (ABA) (9). When rats are given free access to a running wheel and fed 90 min per day they progressively lose body weight, self-starve, and die without experimenter intervention (24,27). Control animals on the same restricted feeding schedule without wheel access have increased food intake and stabilized body weight. This is a potential model of anorexia nervosa because it embodies two characteristics of the disorder, dieting and exercise. For these reasons, several authors have stressed its merits (1,2,6,8,9,22,23).

Using this animal model, we have found that clonidine chronically infused into the paraventricular hypothalamus increases rather than decreases susceptibility to the syndrome (23). This was attributed to a downregulation of α_2 adrenergic receptors by chronic stimulation, which decreased food intake. The purpose of the current investigation was to determine if chronic clonidine treatment has a beneficial effect on the syndrome when administered systemically. Because of its centrally active feeding effects (10,19) and its sedentary actions (7) it was predicted that clonidine would increase the number of days necessary to lose 25% of original body weight, increase food intake, and reduce running. In addition to these measures, three other correlates of the weight-loss phenomenon were evaluated: activity-stress ulcers, which are produced by the syndrome (6), and relative adrenal and thymus weights, which are increased and deceased, respectively, by the syndrome (1,13,22).

METHODS

Subjects and Apparatus

The subjects were 30 experimentally naive male Sprague–Dawley rats (Harlan Sprague–Dawley, Madsion, WI). Prior to the experiment all animals were maintained on ad lib food (Purina rodent lab chow #5001) and water in a 22 ± 2°C (12-h light/dark) vivarium. Animals were habituated to standard Wahmann running wheels with the door between wheel and outside compartment closed prior to ABA onset.

Procedure

Following one week of habituation to the animal colony, the rats were anesthetized and implanted with osmotic minipumps (Alzet, Palo Alto, CA, model 2002). The minipumps had a saline-filled catheter attached to delay drug infusion for one day. Pumps were filled to infuse one of three clonidine doses: 0, 30, and 300 μg/kg/day. The vehicle was 0.2% ascorbic acid in 0.09% saline. Following one day of postsurgical recovery all animals were exposed to activity-based anorexia. Rats were fed once per day for 90 min and had free wheel access during the remaining 22.5 h. Body weight, food intake, and wheel revolutions were recorded daily. When an animal met a 25% body weight loss criterion for ABA it was removed from the apparatus and sacrificed. The stomach was removed and evaluated for lesions according to Doerries et al. (6). The thymus and left adrenal were dissected. Organ weights were expressed relative to total body weight. All parametric data were analyzed using an analysis of variance followed by Tukey protected t tests. Significance was achieved at the $p < .05$ level.

RESULTS

All animals began the experiment at equivalent body weights (respective mean ± SE: 0 μg/kg = 252 ± 3.16 g; 30 μg/kg = 255 ± 3.50 g; 300 μg/kg = 255 ± 3.13 g), $F(2, 24) = 0.213$, $p = .812$, and were sacrificed at approximately 75% of their free feeding body weight. Figure 1 shows the number of days for the animals to reach the weight loss criterion for ABA and food intake during the last three days of the experiment. There were no differences in the number of days to reach the weight-loss criterion as a function of drug dose, $F(2, 24) = 1.27$, $p = .30$. Despite this, the 30-μg group ate more than the saline and 300-μg groups during the last three days prior to sacrifice, $F(2, 24) = 2.42$, $p > .05$ (Fig. 1). In particular, Tukey protected t tests between the 0 μg and 30 μg injected animals were found to be significant on the day prior to sacrifice, two days prior to sacrifice, and three days prior to sacrifice, $t = -2.32$, $p < .05$; $t = -2.53$, $p < .05$; $t = -3.561$, $p < .05$, respectively. Similar differences were found when comparing the 30-μg and 300-μg groups the day prior to sacrifice, two days prior to sacrifice, and three days prior to sacrifice, $t = 2.12$, $p < .05$; $t = 2.19$, $p < .05$; $t = 2.81$, $p < .05$, respectively.

Figure 2 shows the effects of clonidine on wheel running.

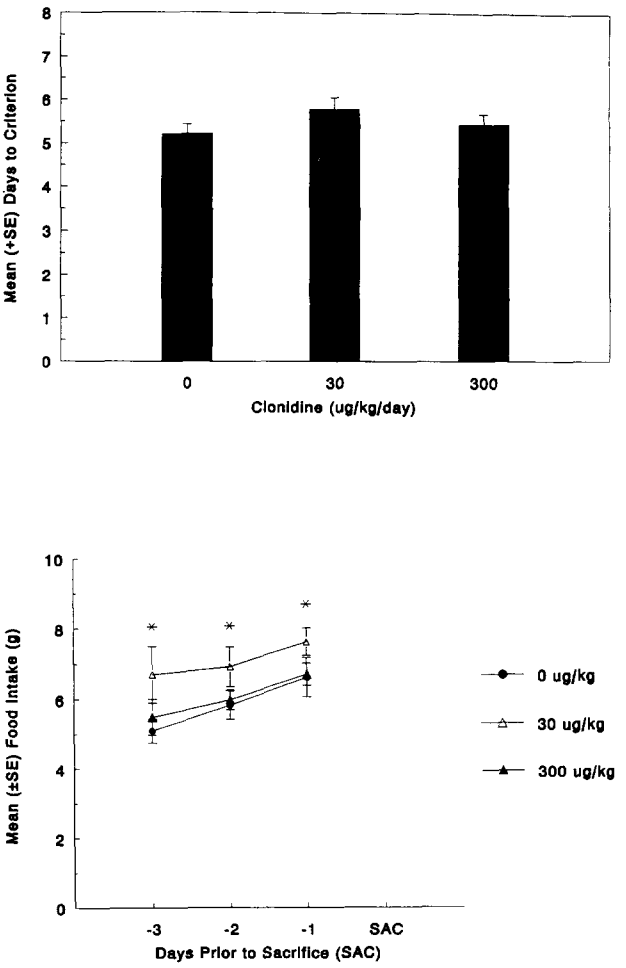

FIG. 1. Top panel shows susceptibility to activity-based anorexia as measured by the mean (± SE) number of days to reach the 25% body weight loss criterion for the three drug doses. Bottom panel depicts the mean (± SE) food intake during the last three days prior to sacrifice for the three doses of clonidine (0, 30, and 300 μg/kg/day, SC). *30 μg/kg/day > 0 and 300 μg/kg/day.

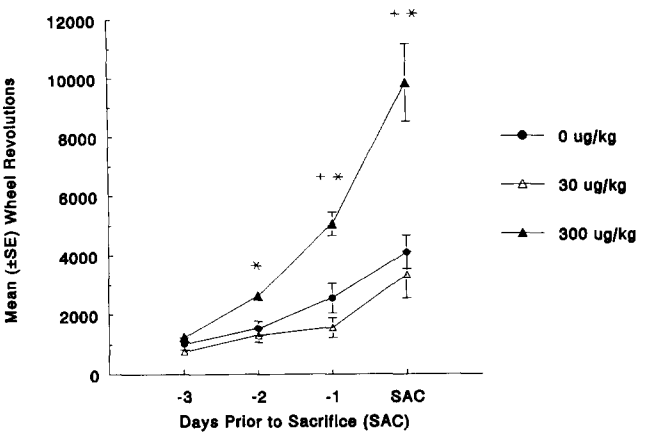

FIG. 2. Mean (± SE) running wheel revolutions for the three drug doses (0, 30, and 300 μg/kg/day, SC) during the last four days of the experiment. *300 μg/kg/day > 30 μg/kg/day; +300 μg/kg/day > 0 μg/kg/day.

Both the drug main effect, $F(2, 81) = 15.64$, $p < .001$, and the days main effect, $F(3, 72) = 12.56$, $p < .001$, were significant. Tukey protected t-tests revealed that the 300-μg group ran more than the 30-μg group during the last three days of the experiment, $t = -10.92$, $p < .01$; $t = -5.90$, $p < .01$; and $t = -2.22$, $p < .05$, respectively, and more than the saline group during the last two days of the experiment, $t = 9.68$, $p < .01$; $t = -4.23$, $p < .01$, respectively.

Percent body weight loss for the three treatment conditions are pictured in Fig. 3. These data show that over the course of the experiment all three groups lost weight at equivalent rates.

As with the rate of body weight loss, there was no effect of clonidine on the incidence of gastric lesions, $\chi^2(16, N = 27) = 2.85$, $p = .99$; relative adrenal weights, $F(2, 24) = .5616$, $p = .58$; and relative thymus weights, $F(2, 24) = 1.77$, $p = .19$ (Table 1).

DISCUSSION

This investigation demonstrates that systemic clonidine elevated food intake at the low dose, and at the higher dose markedly elevated wheel running in animals subjected to activity-based anorexia. Despite these changes, it had no effect on the number of days to lose 25% of original body weight and no effect on percent of body weight loss across days. The experiment therefore supports the prediction that systemic clonidine would increase food intake in ABA, but failed to support the prediction that it would slow the rate of weight loss. It also did not slow wheel running as predicted. In fact, the high dose group increased wheel running to levels more than double those of the other two groups.

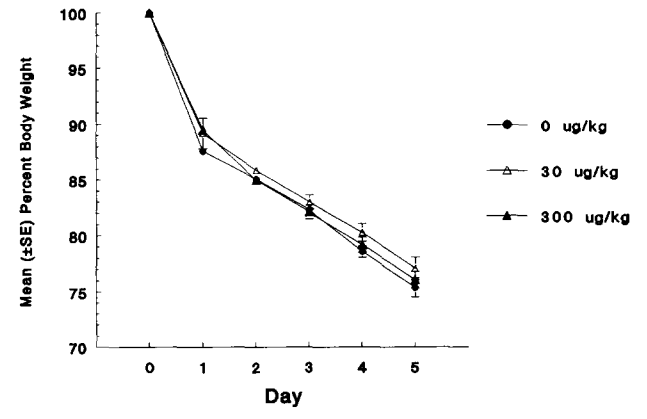

FIG. 3. Mean (± SE) percent body weight for the three drug doses (0, 30, and 300 μg/kg/day, SC) during the five days of wheel exposure.

TABLE 1

LESION INCIDENCE AND MEAN (±SE) BODY WEIGHT RELATIVE ADRENAL AND THYMUS WEIGHTS FOR THE THREE DRUG DOSES

	Lesion Incidence	Adrenal Weight (g/kg)	Thymus Weight (g/kg)
0 mg/kg/day	3/9	0.131 ± 0.005	1.407 ± 0.075
30 mg/kg/day	2/9	0.130 ± 0.004	1.631 ± 0.146
300 mg/kg/day	2/9	0.123 ± 0.007	1.373 ± 0.079

The increased feeding of the 30-μg/kg/day group but not of the 300 μg/kg/day group is not surprising. McCabe et al. (21) have presented a dose-response curve with maximal food intake following clonidine at doses of 12.5 to 50 μg/kg with a return to baseline levels at 100 μg/kg. Our data replicate these findings under chronic conditions and extend the dose-response curve to three times their highest dose. While the increases for the 30 μg were statistically significant, it is argued that this effect was small and not sufficient to attenuate the rate of weight loss.

This investigation also indicates that clonidine under conditions of food deprivation and exercise does not have a sedative effect. Because the high dose dramatically increased wheel running it is tempting to argue that this dose of clonidine actually increases the risk of developing ABA. Regardless, while the 300-μg/kg animals ran almost three times as much as the other animals, they did not become anorexic any quicker. Thus, they were able to compensate for this increased energy expenditure. The mechanism for the increased running remains to be determined. It is not due to hypothermia, since chronic clonidine actually increases body temperature (20). It is also not due to a reduction in food intake, since the high dose animals did not differ from the vehicle controls. Finally, it is not related to differential effects on relative adrenal and thymus weights, which are affected by glucocorticoid secretion (13).

The results of this investigation as well as other data indicate that clonidine has various ingestive and metabolic effects depending on the method and site of administration. Its central effects, especially within the PVN, produce increased feeding when given intermittently (10,19) and decreased feeding when given chronically with osmotic minipumps (23). In the periphery, on the other hand, α_2 adrenergic antagonists increase sympathetically mediated diet-induced thermogenesis and lipid mobilization (17). Since clonidine is an α_2 adrenergic agonist, it should have the opposite effect and decrease sympathetically mediated diet-induced thermogenesis and lipolysis. It is this reduction in sympathetic nervous system activity that may protect the highly active animals that received the high dose from becoming anorexic sooner. The same mechanism may also have protected against a greater incidence of

gastric stress ulcers. The low dose, on the other hand, may not have inhibited the sympathetic system sufficiently to slow the rate of weight loss.

The clonidine effect reported here contrasts with that of Casper et al. (4). They report that at low doses clonidine produces sedation and a tendency to nap, which suggests its potential use in the treatment of hyperactive anorexic patients. Our data argue just the opposite, since clonidine actually increased activity.

In conclusion, clonidine does not affect the rate of weight loss in ABA when given systemically, but potentially increases the risk of developing ABA by drastically increasing activity levels at high doses, while only marginally increasing food intake at low doses only. The inhibitory effects of clonidine on sympathetic nervous system activity may counteract the increase in energy expenditure produced by hyperactivity in the high dose group. Further research is needed to test this possibility. Finally, this investigation fails to support the hypothesis that clonidine should be used to treat anorexics that present with hyperactivity.

ACKNOWLEDGEMENTS

This research was supported by an NIMH grant (F32MH09805) to T.S.R. and a Department of Veteran Affairs Merit award to P.F.A. These data were presented at the 22nd annual meeting of the Society for Neuroscience, Anaheim, CA, October 25-30, 1992. We wish to thank John J. Choi for help in collecting the data.

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