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RAPID COMMUNICATION

Chronic Treatment with Valproate Decreases the Hypothermic Response to Clonidine

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DILSAVER, S. C., D. MINKUS AND A. C. SWANN. *Chronic treatment with valproate decreases the hypothermic response to clonidine.* PHARMACOL BIOCHEM BEHAV 45(1) 247-249, 1993.—Treatment with lithium (the prototype of an antimanic agent) attenuates responsiveness to the α_2-agonist clonidine in animal models. Valproate is now used to treat mania. The effect of treatment with this drug on responses mediated by an α_2-agonist have yet to be reported. The authors assessed the effect of a 14-day course of orally administered valproate on the rat's hypothermic response to clonidine. Treatment with valproate decreased this response.

Affective disorders α_2-Receptors Anticonvulsants Bipolar disorder Clonidine Mania Noradrenergic Thermoregulation Valproate Valproic acid

THE presynaptic α_2-adrenoceptor regulates the release of norepinephrine (14,24). Dysfunction of this receptor may be involved in the pathogenesis of affective illness. There may be a link between treatment-induced changes in the function this autoreceptor and the efficacy of treatments (9-12).

Clonidine is an α_2-agonist. Change in responsiveness to clonidine is used to assess the effect of treatments on the functional status of the α_2-autoreceptor. The reports published to date indicate that treatments for mania and depression attenuate responsiveness to clonidine (4,5,9-12,18,19,21-23). Valproate is now used to treat mania (1,8, 15-17,20). The effect of treatment with this drug on an organism's responsiveness to an α_2-agonist is not known. Clonidine reliably produces hypothermia (3,13) in both the rat and man. This study was conducted to determine if treatment with valproate alters this response to clonidine.

METHOD

Animals

Adult, male Sprague-Dawley rats were purchased from Harlan Laboratories (Indianapolis, IN). Animals were housed in a vivarium with a 12 L : 12 D cycle at The Ohio State University. Rat chow (Ralston Purina, St. Louis, MO) and water were available ad lib.

Pharmaceutical Agents

Clonidine HCl and valproate were purchased from Sigma Chemical Co. (St. Louis, MO). The dose of clonidine refers to the salt.

Measurement of Temperature

Rectal temperature was measured by the insertion of a thermistor probe about 6 cm into the rectum. Output was displayed on a digital Telethermometer (YSI Model 43TF, Yellow Springs Instruments, Yellow Springs, OH).

Valproate Assay

Serum levels of valproate were measured by The Ohio State University Reference Laboratory using the Tdx System developed by Abbott Laboratories (Abbott Park, IL). This method involves the use of fluorescence polarization immunoassay (FPIA) technology and a competitive protein binding immunoassay. A formal description of this assay can be obtained from Abbott Laboratories.

Experimental Design

Experiment 1. Twelve rats were fed chow reduced to a semipowdered state with a coffee grinder. The quantity of val-

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proate added to chow was based upon the expectation that the average rat would consume 50 g chow/kg body weight daily (13). The chow was devoid of valproate between days −14 to 0. It contained 2.44 and 4.44 g valproate/kg chow between days 1–7 and 8–22, respectively. This provides daily doses of 200 and 350 mg valproate/kg, respectively. Steady-state levels should be reached within 2–3 days of a change in daily dose. Animals were sacrificed on the morning of the 22nd day of treatment. The concentration of valproate was measured in serum obtained from trunk blood.

Descriptive statistics are used to present the results.

Experiment 2. The hypothermic response of 11 rats to 0.1 mg/kg IP-injected clonidine was measured prior to and after 7 and 14 days of treatment with valproate. Three injections of clonidine at 7-day intervals does not alter the rat's hypothermic response to clonidine (6). The projected doses of valproate during days 1–7 and 8–14 of were 200 and 350 mg/kg, respectively.

Hypothermic response was calculated as follows:

1. The baseline temperature of each subject was measured ($t = 0$).
2. The temperature of each rat was remeasured 60 ($t = 60$) and 120 ($t = 120$) min after injection of clonidine. Hypothermic response is the difference between a subject's temperature at $t = 0$ and $t = 60$ or 120 min.
3. The hypothermic response of the sample is the mean of the responses of subjects.

Change in hypothermic response in the course of treatment was assessed for significance using an analysis of covariance (ANCOVA). Hypothermic response at $t = 0$, $t = 60$, and $t = 120$ simultaneously entered into the ANCOVA. Baseline temperature was the covariate. The difference in hypothermic response at $t = 60$ and 120 relative to $t = 0$ before and after 7 and 14 days of treatment was assessed for significance using the Bonferroni multiple comparison posttest. The critical value of t was 3.05.

Significance was set for $p < 0.05$. Measures of variation refer to the SEM.

RESULTS

Experiment 1

The 12 rats remained healthy throughout the 35 days of this experiment. Their mean mass prior to and after receiving ground chow devoid of valproate for 14 days was 300.8 ± 2.9 and 324 ± 4.4 g, respectively. Mean mass after 7, 14, and 21 days of treatment with valproate was 344.5 ± 6.1, 364 ± 6.3, and 372.6 ± 6.0 g, respectively. The mean doses of valproate during days 1–7, 7–14, and 14–21 of treatment were 206.3 ± 10.1, 347.1 ± 16.2, and 356.1 ± 12.4 g, respectively. The mean serum concentration of valproate after 21 days of treatment was 93.9 ± 7.5 mcg/ml (range 57–128 mg/ml).

Experiment 2

The mean mass of subjects was 561.4 ± 11.9 g. Mean baseline temperature prior to the first, second, and third challenges with clonidine was 37.4 ± 0.09, 37.2 ± 0.09, and 37.2 ± 0.09°C, respectively. The mean hypothermic response at $t = 60$ was −1.23 ± 0.15, −1.11 ± 0.12, and −0.77 ± 0.19°C prior to and after 7 and 14 days of treatment, respectively. The mean hypothermic response at $t = 120$ was −1.01 ± 0.15, −0.66 ± 0.11, and −0.29 ± 0.16°C prior to and after 7 and 14 days of treatment, respectively.

Hypothermic response decreased as a function of the duration of treatment, $F(2, 30) = 4.33$, $p = 0.02$. There was not a relationship (interaction) between hypothermic response at $t = 60$ and 120 min, $F(2, 30) = 0.38$, n.s. Hypothermic response was less at $t = 60$ than at $t = 120$ regardless of treatment status, $F(2, 30) = 4.33$, $p < 0.0001$.

Hypothermic response at $t = 60$. The decrease in hypothermic response was not significant after 7 days of treatment, $t(10) = 1.26$, n.s. The decrease was significant after 14 days of treatment, $t(10) = 3.42$, $p < 0.05$. Hypothermic response decreased significantly between days 7 and 14 of treatment, $t(10) = 3.16$, $p < 0.05$.

Hypothermic response at $t = 120$. The decrease in hypothermic response was significant after both 7, $t(10) = 3.17$, $p < 0.05$, and 14 days of treatment, $t(10) = 3.28$, $p < 0.05$. The response decreased significantly between days 7 and 14 of treatment, $t(10) = 3.42$, $p < 0.05$.

Figure 1 pictorially presents the results of this experiment.

DISCUSSION

The 12 subjects in Experiment 1 remained healthy and consumed the projected quantity of chow. Mean daily consumption was the same before and during treatment with valproate. Steady-state serum valproate levels were in the range used to treat patients with mania.

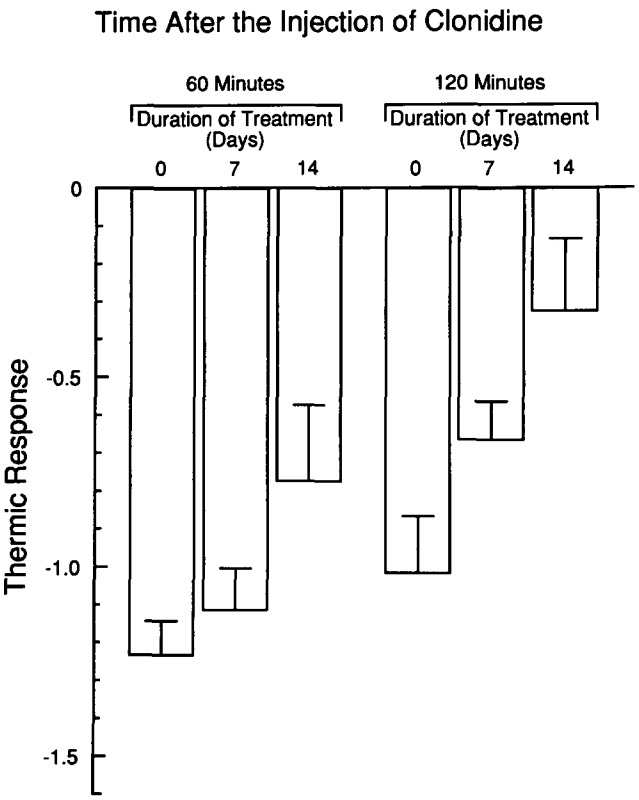

FIG. 1. Mean hypothermic response (± SEM) of subjects 60 and 120 min after injection of clonidine for the first (before treatment), second (after 7 days of treatment), and third (after 14 days of treatment) challenges with clonidine.

The 11 subjects in Experiment 2 exhibited a reduction in their hypothermic response to clonidine as a function of time. The daily dose of valproate was higher during the second than first week of treatment. It is possible that the reduction in hypothermic response following the second week of treatment was due to the either the increase in the daily dose or duration of treatment with valproate, or both of these factors. The effect of both dose and length of treatment should be assessed in studies carried out in the future.

The studies published to date indicate that the somatic treatments for affective disorders decrease sensitivity to clonidine (2,4,5,9-12,21-23). This change may be related to the efficacy of these treatments (2,4,5,9-12,21-23). Lithium (9, 23) and electroconvulsive therapy (19), highly effective treatments for mania, desensitize the α_2-autoreceptor. The results presented here suggest that valproate does the same.

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