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BRIEF COMMUNICATION

Chronic Restraint Stress Does Not Sensitize a Muscarinic Mechanism

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FLEMMER, D D AND S C DILSAVER *Chronic restraint stress does not sensitize a muscarinic mechanism* PHARMACOL BIOCHEM BEHAV **34**(1) 207–208, 1989 —Describing the neurobiological changes which may explain the link between chronic stressors and the epidemiological association of recurrent episodes of depression in patients with unipolar or bipolar illness is a goal of psychiatric research Disorders of mood may involve hyperactivity of central muscarinic mechanisms Chronic forced swim stress and footshock produce supersensitivity to a muscarinic agonist Chronic prolonged restraint is a severe stressor for the rat and activates the hypothalamic-pituitary-adrenal (HPA) axis This report presents data suggesting that this stressor does not, unlike forced swim stress and footshock, enhance sensitivity to the hypothermic effects of a muscarinic agonist

Acetylcholine Affective disorders Cholinergic Depression Muscarinic Oxotremorine Rats Receptors Stress

LINKING stressors with neurobiological changes which might explain the association of depression and adverse life events (16) is a task of psychiatric research Depression (2, 10, 19) and the response to stress (10–12) may involve the activation of central muscarinic mechanisms Chronic swim stress and footshock apparently render a central hypothalamic muscarinic mechanism (involved in the regulation of core temperature) supersensitive to a muscarinic agonist (3, 4, 7) Chronic swim stress also depletes brain biogenic amines (20). Activation of muscarinic mechanisms in combination with the impact of stressors on aminergic systems can explain many of their neurobiologic effects (1, 8, 9, 13)

We attempted to identify chronic stress paradigms which do not alter sensitivity to muscarinic agonists. Dilsaver and Davidson (5) reported that prolonged cold room stress does not alter the thermic response to oxotremorine We now report that two hours of daily restraint stress does not produce supersensitivity to oxotremorine Two hours of restraint is sufficient to activate the hypothalamic-pituitary-adrenal axis (9,13) and is regarded to be a severe stressor (14,15)

METHOD

The dependent variable is the mean hypothermic response produced by the intraperitoneal (IP) injection of oxotremorine, 0 25 mg/kg in adult male Sprague-Dawley rats (Harlan Laboratories, Indianapolis, IN) Oxotremorine (base) and methylscopolamine nitrate were obtained from Sigma Chemical Co (St Louis, MO). Systemically administered oxotremorine acts to alter temperature at the level of the hypothalamus (17,18). Core temperature was telemetrically measured using a hearing-aid-battery powered telemetric thermosensor (Mini-Mitter Corp , Sun River, OR) This device emits amplitude modulated radio waves at a rate proportional to temperature. A standard AM receiver can translate these emissions into pulses detectable with a digital frequency counter (Universal Instruments, New Haven, CT, Model 5001). The Mini-Mitter provides a reliable and valid method of measuring change in core temperature (6)

Twelve rats were subjected to daily restraint stress for 120 minutes between 7 00 a m. and 9·00 a m for 7 days in restrainers designed for animals weighing 200–250 g. These instruments were custom made for us at the University of Michigan, Mental Health Research Institute The restrainers are identical to those produced by Harvard rat.

The animals received methylscopolamine nitrate (a peripherally active antimuscarinic agent) 1 mg/kg IP 30 minutes prior to the injection of oxotremorine Core temperature was measured immediately prior to the injection of oxotremorine Oxotremorine, 0 25 mg/kg IP, was then injected and core temperature was measured every 10 minutes for 120 minutes following this All oxotremorine challenges started at 3 00 p m These challenges were conducted on the day prior to the first and the day following the last of 7 days of restraint stress

The mean thermic response of a given rat was calculated by adding the 12 deviations from core temperature of that animal prior to administering oxotremorine and dividing by 12 The mean change for each rat before and after chronic restraint stress was paired The data were analyzed using Student's paired *t*-test The standard error of the mean is used as the measure of variance

RESULTS

The mean mass of the 12 rats used in this study was 238 3 ± 7 0

g (8–9 weeks of age) The mean core body temperature of the sample prior to challenge with oxotremorine was 37 2±0 2°C and 37 4±0 2°C before and after chronic restraint stress, respectively The mean thermic response was −0 35±0 12°C and −0 36±0 13°C before and after subjection to chronic restraint stress (t=0 19, p>0 85)

DISCUSSION

Once-daily restraint stress for 120 minutes for 7 days had no effect on the thermic response to oxotremorine, 0 25 mg/kg IP The mean difference in hypothermic response before and after application of the forced stressor was only +0 01±0 09°C The restraint stress protocol we selected is a severe stressor (14,15) However, it is possible that longer restraint stress sessions per day, more sessions daily, daily restraint for more or less than 7 days, or another modification would have resulted in enhancement of the hypothermic response to oxotremorine

Our group has now completed its survey of the effect of forced stress on the thermic response to a muscarinic agonist Chronic cold room stress has no effect on the thermic response to oxotremorine (5) Forced swim stress (7) and inescapable footshock (4) powerfully supersensitize a muscarinic mechanism involved in the regulation of core temperature These experimental manipulations appear to be adequate for most stress research in this area

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