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Decrease in Core Temperature as an Indication of Cholinergic Overdrive during Amitriptyline Withdrawal

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Introduction

Dilsaver et al. (1983a,b, 1984) observed that the withdrawal of tricyclic antidepressants (TCAs) results in the development of an array of symptoms that can be categorized to define four syndromes: (1) general somatic distress with flu-like symptomatology, (2) excessive, vivid dreaming and initial, middle, and terminal insomnia, (3) parkinsonism or akathisia, and (4) hypomania. The first three syndromes may be due to withdrawal-induced cholinergic overdrive at peripheral and central sites.

The hypothesis that TCA withdrawal produces cholinergic overdrive is supported by reports that antimuscarinic agents produce tolerance (Friedman et al. 1969), all TCAs block physiological (Dilsaver 1986) and biochemical responses mediated by muscarinic receptors (mAchRs) (Richelson and Dininetz-Romero 1977), and TCAs competitively displace mAchR receptor radioantagonists in vitro (Snyder and

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Yamamura 1977; Batra and Biorklund 1986). Finally, TCA withdrawal symptoms respond to centrally active antimuscarinic agents (Dilsaver et al. 1983a).

Dilsaver et al. (1987) recently demonstrated that chronic treatment with amitriptyline hydrochloride (AMI) results in supersensitivity to the hypothermic effects of the muscarinic agonist oxotremorine. The capacity of this TCA to produce this effect demonstrates dose dependence (Dilsaver and Snider 1987). However, these pharmacological paradigms deviate from the clinical situation. In human subjects, the development of TCA withdrawal symptoms presumably results in cholinergic rebound, the symptomatic effects of which are evident without the administration of a cholinomimetic agent. We recently conducted two experiments in which we treated rats with AMI, 10 mg/kg twice daily, for 7–21 days and then measured the fall in core temperature relative to baseline (prior to the first injection of AMI) 12 or 18 hr after the previous injection of AMI.

Methods

Experiment 1

Eight adult male Sprague-Dawley rats (11 weeks old) received AMI, 10 mg/kg ip, at 9:00 AM and 5:00 PM. Core temperature of each animal was telemetrically measured before and after 1 and 3 weeks of treatment with AMI using the Model VM Mini-Mitter (Mini-Mitter Corp., Sun River, OR). The second and third measurements were made 18 hr after the previous dose of AMI. Core temperature was measured 1 and 3 weeks after treatment. The reliability and validity of temperature measurements using this device was described elsewhere (Tocco-Bradley et al. 1985). Animals were injected with methylscopolamine nitrate, 1 mg/kg ip, 30 min prior to the measurement of core temperature to block peripheral cholinergic effects.

Experiment 2

Core temperature was measured in up to 12 adult male Sprague-Dawley rats (age circa 8 weeks) prior to and after 14, 15, and 16 days of treatment with AMI, 10 mg/kg at ~12-hr intervals. Methylscopolamine nitrate, 1 mg/kg ip, was administered 30 min prior to the measurement of baseline temperature. Baseline temperature was measured once again after 17 days of treatment. However, this measurement was preceded by the administration of scopolamine hydrobromide, 2.0 mg/kg ip. The actual number of animals yielding useful data varied due to occasional Mini-Mitter failure. Instrument failure is generally the consequence of poor contact between a battery inside the device and a connecting wire. It is not uncommon for these two elements to spontaneously reunite and the instrument to begin transmitting. Thus, we have data on 10, 12, 10, and 10 animals after 14, 15, 16, and 17 days of treatment.

Statistical Analysis

Data were analyzed using EPISTAT, a statistical package, on an IBM PC. Significance was assessed using Student's paired t-test. Measures of variance refer to the standard error of the mean (SEM).

Results

Experiment 1

Mean baseline core temperature prior to treatment with AMI was 36.6 ± 0.13°C versus 36.0 ± 0.27°C after 1 week ($p < 0.001$, $t = 5.44$, df = 7) and 35.8 ± 0.25°C ($p < 0.035$, $t = 2.71$, df = 7) after 3 weeks of treatment.

Experiment 2

Mean baseline temperature prior to treatment with AMI was 36.8 ± 0.05°C. After 14 days of treatment, mean baseline temperature was 36.4 ± 0.13°C ($p < 0.006, t = 3.61$, df = 9). Mean baseline temperature of those animals receiving 15 and 16 days of treatment was 36.4 ± 0.13°C ($p < 0.006, t = 3.43$, df = 11) and 36.4 ± 0.19°C ($p < 0.09$, $t = 1.88$, df = 10), respectively.

The mean baseline temperature of those an-

imals challenged with scopolamine at baseline was 36.7 ± 0.07°C versus 36.7 ± 0.17°C afterwards (NS, $t = 0.00$, df = 9).

Discussion

Core temperature was significantly decreased after 7, 14, and 21 days in Experiment 1 and after 15 days of treatment in Experiment 2. Furthermore, the decrease in core temperature on day 16 in Experiment 2 constituted a trend toward significance. The fact that pretreatment with scopolamine completely eliminated the difference between the pretreatment and posttreatment baseline temperatures suggests that a 12–18 hr lapse between injections of AMI may promote the development of a mild cholinergic overdrive state that is sufficient to produce a decrease in core temperature.

The data suggest that a spontaneous reduction in core temperature provides an indication of AMI withdrawal-induced cholinergic overdrive. The data are also consistent with the capacity of AMI to supersensitize a central muscarinic mechanism (Dilsaver et al. 1987), and the association between its withdrawal and the occurrence of symptoms is suggestive of cholinergic rebound (Dilsaver et al. 1983a,b; Dilsaver and Greden 1984).

Our data raise the question of the effect of AMI on core temperature. Lee et al. (1977) studied the effect of a single injection of AMI on rectal temperature. Analysis disclosed a significant decrease lasting 3–4 hr for AMI, 20 and 50 mg/kg, but not for 10 mg/kg. Pawlowski (1983) observed that AMI, 10 mg/kg ip, did not alter basal temperature. Other reports of the effect of AMI on core temperature relate to special circumstances or unusually high doses. In summary, there is evidence that doses of AMI much higher than 10 mg/kg lower core temperature. However, the dose employed in the experiments presented here is not known to decrease core temperature. Thus, the effect reported here is most likely due to effects of drug withdrawal.

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