Tricyclic antidepressants (TCAs) bind to muscarinic cholinergic receptors (mAChRs) and produce biochemical and physiological evidence of the blockade of muscarinic mechanisms. Supersensitization of these mechanisms is a regularly occurring effect of agents that directly block access of acetylcholine to the postsynaptic mAChR or inhibit its release from presynaptic cholinergic neurons. Treatment with amitriptyline (AMI) 10 mg/kg i.p. twice daily for 7 days or more enhances sensitivity to the hypothermic effects of oxotremorine. Although the muscarinic effects of TCAs have been investigated, the influences of these and other antidepressants on parameters influenced by nicotinic mechanisms have received minimal attention.

The effects of antidepressants on nicotinic mechanisms has not been the subject of systematic study. However, Schofield et al. presented evidence that a TCA binds to the ionic channel of the nicotinic receptor (nAChR). We studied the effects of AMI, desipramine (DMI), phenelzine, and bright artificial light on a nicotinic mechanism involved in the regulation of core temperature.

Methods

Core temperature was telemetrically measured using the Model VM Mini-Mitter. The devices were implanted into the peritoneal cavity. A transistor radio served as a receiver.

The initial nicotine challenge occurred prior to treatment with an antidepressant. Subsequent challenges occurred the morning after the previous evening's dose of antidepressant or in the course of treatment with bright light. Temperature was measured prior to and every 10 min after the injection of nicotine 1 mg/kg i.p. Baseline temperature for a given challenge was defined as the temperature immediately prior to the injection of nicotine.

Amitriptyline HCl, DMI HCl, phenelzine sulfate, and nicotine (base) were purchased from Sigma Chemical Company. Fluoxetine HCl was obtained from Lilly Pharmaceuticals. Doses of nicotine refer to the base form. Doses of the antidepressants refer to the salt. Agents were administered intraperitoneally on a milligram per-kilogram basis.
Plasma levels of nicotine and cotinine were determined by a high performance liquid chromatography (HPLC) method using an ultraviolet detector (262 nm) with 2-phenylimidazole as an internal standard. Details of the assay are reported elsewhere.\textsuperscript{6}

Data were analyzed using Student’s paired \textit{t} test. Measures of variance refer to the standard error of the mean (SEM).

\section*{Results}

\subsection*{Amitriptyline}

One week of treatment with AMI 10 mg/kg i.p. at 9 a.m. and 9 p.m. was associated with an increase in the mean maximum hypothermic response of $1.21 \pm 0.12^\circ C$ ($p < 0.001$, $n = 10$). The mean maximum hypothermic response ($1.31 \pm 0.23^\circ C$) remained elevated 1 week ($p < 0.001$) and 2 weeks ($1.00 \pm 0.35^\circ C$; $p < 0.02$) after the discontinuation of AMI. The mean reduction in core temperature after 7 days of treatment with AMI relative to the pre-AMI baseline was $0.46 \pm 0.15^\circ C$ ($p < 0.02$), after 7.5 days of abstinence $0.54 \pm 0.2^\circ C$ ($p < 0.05$), and after 14.5 days of abstinence $0.19 \pm 0.19^\circ C$. These results were confirmed in a second experiment.\textsuperscript{7}

\subsection*{Fluoxetine}

Prior to the first nicotine challenge these animals were challenged with saline 1 ml/kg i.p. The thermic response to saline was $0.22 \pm 0.10^\circ C$. The sample ($n = 9$) exhibited a change in core temperature of $-1.41 \pm 0.24^\circ C$ in response to the first nicotine challenge. The thermic response to nicotine after 1 week of treatment with fluoxetine 10 mg/kg i.p. at 9 a.m. and 5 p.m. was $-0.44 \pm 0.26^\circ C$ ($p < 0.002$). The thermic response to nicotine was $0.16 \pm 0.14^\circ C$ after 2 weeks of treatment. This response did not differ from that of saline ($p > 0.70$). The thermic response to nicotine after 1 week of withdrawal from fluoxetine was $-0.91 \pm 0.25^\circ C$, which did not differ from baseline ($p > 0.15$).

\subsection*{Desipramine}

The mean thermic response to saline was $+0.23 \pm 0.12^\circ C$ ($n = 12$). The sample exhibited a change in core temperature of $-1.43 \pm 0.18^\circ C$ in response to the first nicotine challenge. This difference was highly significant from the response to saline ($p < 0.00003$). After 1 week of treatment the sample exhibited a thermic response of $-0.58 \pm 0.22^\circ C$. This response differed from that at baseline ($p < 0.015$). After 2 weeks of treatment the sample exhibited a decrease in temperature of $-0.8 \pm 0.21^\circ C$, which also differed from the baseline response ($p < 0.005$). The thermic response to nicotine did not differ after 1 and 2 weeks of treatment ($p > 0.35$).

We assessed the possibility that DMI might accelerate the metabolism of nicotine. Rats were treated with saline 1 mg/kg i.p. twice daily or DMI 10 ml/kg i.p. twice daily. The animals received nicotine (base) 1 mg/kg i.p. 19–20 h after the last dose of saline ($n = 10$) or DMI ($n = 10$). Blood was collected by cardiac puncture 30 min after the injection. The mean nicotine levels in the DMI and control groups were $318.2 \pm 10.4$ and $220.3 \pm 14.0$ ng/ml, respectively ($p < 0.00003$). Thus the animals treated with DMI had higher levels of nicotine. The mean cotinine levels