

PHENELZINE PRODUCES SUBSENSITIVITY TO NICOTINE

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Abstract

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1. The authors attempted to detect a possible effect of treatment with phenelzine on a physiological response to nicotine in the rat.
2. Positive findings in an animal model suggest the feasibility of more complicated experiments in animals and the possibility of studies involving human subjects.
3. Treatment of Sprague Dawley rats (n = 10) with phenelzine sulfate (15.0 mg/kg ip) every 48 hours for 14 days was associated with a 73.3% decrease in the hypothermic response to nicotine.
4. Treatment with phenelzine did not enhance the rate of elimination of nicotine.
5. The authors discuss a possible relationship between changes in nicotinic mechanisms and the therapeutic actions of drugs used to treat affective illness.

Keywords: affective disorders, cholinergic, depression, monoamine oxidase, monoamine oxidase inhibitors, nicotine, phenelzine, receptors, thermoregulation

Abbreviations: high pressure liquid chromatography (HPLC); intra-peritoneal (ip); standard error of the mean (SEM); ultraviolet (UV)

Introduction

There is great deal of interest in the relationship between smoking and depression (Breslau et al., 1991; Churchill et al., 1989; Covey et. al., 1990; Dilsaver et al., 1990; Glassman et al., 1988, 1990). Subjects participating in the National Institute of Mental Health sponsored Epidemiologic Catchment Area (ECA) Study who had a history of major depression were significantly more likely to have had a history of regularly smoking than those individuals with and without another psychiatric disorder. Data from this study also indicated that individuals who were depressed were less successful in their efforts to stop smoking than non-affectively ill subjects. Breslau and Kilby (1991) recently reported that the probability of participants in the study who smoked would have onset of their first episode of major depression during a 14 month follow-up interval was much higher than expected by chance. These data have created interest in the interaction of drugs used to treat depression with

nicotinic cholinergic mechanisms.

Measurement of the thermic response to nicotine before, in the course of, and following chronic treatment is used to screen agents for possible effects on a nicotinic mechanism. We used this strategy to test the hypothesis that treatment with phenelzine has nicotinic effects. This drug is a non-specific and irreversible inhibitor of monoamine oxidase. Agents with this property are effective antidepressants (Liebowitz *et al.*, 1984; Paykel, 1989). The monoamine oxidase inhibitors, in contrast to the tricyclic antidepressants, do not bind to muscarinic (Goldman and Ericson, 1983; Snyder and Yamamura, 1977; Tollefson *et al.*, 1982) or nicotinic acetylcholine receptors (Schofield *et al.*, 1981; Shaker *et al.*, 1981). These findings have kindled interest in the interaction between drugs used to treat affective illness and nicotinic cholinergic mechanisms.

The data presented indicate that treatment with phenelzine blunts sensitivity to nicotine.

Materials and Methods

Change in core body temperature in response to the ip injection of 1.0 mg/kg of nicotine (base) before and following 7 and 14 days of treatment with phenelzine sulfate was measured in Experiment 1. This procedure has proved useful and reliable in screening the effects of drugs (Dilsaver and Davidson, 1987 a,b; Dilsaver and Hariharan, 1989 a,b; Dilsaver and Hariharan, 1988; Dilsaver and Majchrzak, 1990; Dilsaver *et al.*, 1987, 1988, 1989; Majchrzak and Dilsaver 1990), drug withdrawal (Dilsaver and Majchrzak, 1987), chronic stress (Dilsaver 1988c; Dilsaver *et al.*, 1986, 1990; Peck *et al.*, 1991) and treatment with bright light (Dilsaver 1988a, 1990a; Dilsaver and Majchrzak, 1988; Overstreet *et al.*, 1990 a,b) on muscarinic and nicotinic cholinergic mechanisms (Dilsaver and Alessi, 1988 for a review of the method).

The rats used in Experiment 1 continued to receive the same dose of phenelzine sulfate every 48 hours for an additional week. Experiment #2 involved the measurement of the plasma concentrations of nicotine and cotinine in these animals 30 minutes after the ip injection of 1.0 mg/kg of nicotine on day 21 of the study. Nicotine and cotinine levels were also measured under identical conditions in a saline treated control group.

Animals

Ten (10) adult male Sprague Dawley rats were treated with phenelzine. Their mean mass (\pm SEM) was 265.8 ± 8.5 g at the start of the study. The mean mass of the 8 saline control animals used in Experiment 2 was 267.5 ± 2.5 g. The animals were purchased from Harlan Laboratories (Indianapolis, IN). Care was provided by the University of Michigan Laboratory Animal Medicine.

Pharmaceuticals

Phenelzine sulfate, nicotine (base) and cotinine were purchased from Sigma

Chemical Company (St. Louis, MO, U.S.A). All references to concentrations or doses of nicotine and phenelzine refer to the base and salt forms respectively.

Nicotine Challenges

All challenges with nicotine started at 12:00 pm. Core temperature was measured immediately before the ip injection of 1.0 mg/kg of nicotine and at 10 minute intervals thereafter for 120 minutes. Challenges 2 and 3 occurred on the 7th and 15th days of treatment with phenelzine, respectively.

The Administration of Phenelzine

Phenelzine was given by ip injection at 4:00 pm every 48 hours. The dose of phenelzine was 15 mg/kg through the entire period of treatment. The second challenge with nicotine followed the injections of phenelzine Days 2, 4, and 6 of the experiment. The injection of nicotine followed the dose of phenelzine given on Day 6 by 20 hours. The third challenge with nicotine followed additional injections of phenelzine on Days 8, 10, 12 and 14 of the experiment. Nicotine was injected 20 hours following the dose of phenelzine given on the 14th day of the study.

Experimental Procedure

Experiment 1

Core temperature was measured using biotelemetry. The method is described below. The first measurement of temperature is referred to as the animal's "baseline." This is also referred to as the core temperature at time (t) = 0. Baseline core temperature was measured prior to touching the animal. This is noteworthy as merely handling the rat rapidly produces hyperthermia (Dilsaver and Majchrzak, 1990; Dilsaver et al., 1992).

Temperature at each of the 12 time points following t = 0 was transformed into a unit of thermic response by subtracting core temperature at t = 0. Thus, a negative number is obtained if core temperature decreases. The average of these 12 measurements is the mean thermic response of an individual rat. Significance of change in the thermic response of individual animals to nicotine was determined by pairing the thermic response of that animal at each of the 12 time points before and after 7 and 14 days of treatment. The mean thermic response of each animal was then used to determine whether the change in thermic response of the sample was significant.

Experiment 2

The effect of treatment with phenelzine on the rate of elimination of nicotine was measured by injecting 1.0 mg/kg of nicotine into the phenelzine (n = 10) and saline (n = 8) treated rats. The experimental and control groups received ip injections of 15.0 mg/kg (1.0 ml/kg) of phenelzine and normal saline (1 ml/kg), respectively, on Days 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 of the study.

Nicotine was injected the morning of the 21st day of the study. Blood was drawn by cardiac puncture and placed into heparinized tubes 30 minutes following the injection of nicotine. Plasma was then frozen until the concentration of nicotine and cotinine were measured using an HPLC assay with a UV detector (Hariharan *et al.*, 1988).

Measurement of Core Temperature

Core temperature was measured using the Model VM Mini-Mitter (Mini-Mitter Corp., Sun River, OR). This instrument consists of a thermosensor and radio-transmitter which emits AM waves at a rate directly proportional to temperature. Each Mini-Mitter is encased in a waterproof substance (Kerr Sticky Wax^R) and is capable of reliable operation for more than four months at the normal core temperature of the rat.

The Mini-Mitter is calibrated each time the casing is broken. The procedure used to calibrate the Mini-Mitter requires measurement of the rate of emission of AM waves at three or more temperatures in a temperature controlled water bath (Precision Instruments, 50). These data are used to calculate a linear regression equation. The equation is then transformed so that "y" (the dependent variable) is temperature and "x" (the independent variable) is the time required to emit a fixed number of AM waves. The Mini-Mitter is then implanted into the peritoneal cavity using ether as a general anesthetic or the combination of ketamine and a local anesthetic (xylazine). The animals are allowed at least 5 days to recover from the implantation procedure.

The Mini-Mitter yields reliable and valid results when used in psychopharmacological studies in which the magnitude of effect is of the order relevant to this report (Dilsaver *et al.*, 1990).

Table 1 highlights the time course of the events.

Table 1
Time Course of the Events

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1. The telemetric thermosensors (Mini-Mitters) are calibrated.
 2. The thermosensors are implanted into the peritoneal cavity.
 3. The animals are allowed 5 or more days to recover from the implantation procedure.

Day 1 of the Study

4. The animals are challenged with 1.0 mg/kg of nicotine (base) by ip injection at 12:00 pm. This challenge provides the pretreatment response of each rat to nicotine.

Days 2, 4 and 6

5. The experimental and control groups receive 15.0 mg/kg (volume = 1 ml/kg) of phenelzine sulfate and 1.0 ml/kg saline, respectively by ip injection at 4:00 pm.

Day 7

6. The animals in the experimental group are challenged with nicotine at 12:00 pm on Day 7. The fourth dose of phenelzine or saline is given about 4 hours following the injection of nicotine.

Days 8, 10, 12 and 14

7. Doses of phenelzine sulfate or saline are administered.

Day 15

8. The animals are challenged with nicotine for the third time.

Day 16, 18, and 20

9. Doses of phenelzine sulfate or saline are administered.

Day 21

10. Animals in both the experimental and control groups receive an ip injection of 1.0 mg of nicotine (base). Blood is collected by cardiac puncture 30 minutes later and injected into heparinized tubes. Aliquots of plasma are then frozen until an HPLC assay with UV detection is used to measure the concentrations of
n i c o t i n e a n d c o t i n i n e .

Assay of Nicotine

Plasma levels of nicotine and cotinine were measured using an HPLC assay coupled to UV detector. 2-phenylimidazole (Alrich) was used as an internal standard. The mobile phase consisted of 30 mM citrate buffer, 7% acetonitrile and 2mM sodium heptanesulfonate at a PH of 5.0. A C-18 column (Shandon, State College, PA) with a length of 150 mm and diameter of 2 mm was used. Evaporation of the organic phase was quickened by a flow of nitrogen gas. The residue was then reconstituted with 5 microliters of the mobile phase. Twenty microliters was then injected into the column. The sensitivity of the assay is 1 and 2 ng/ml for nicotine and cotinine, respectively. The assay yields linear results from 0 to 600 ng/ml for both analysates. All the reagents in the assay are HPLC grade (Hariharan, et al., 1988).

Statistical Analysis

All data in Experiment 1 were subject to analysis using Student's paired t-test. Data in Experiment 2 were analyzed using Student's two sample t-test. All measures of variance in the text refer to the SEM.

Results**Experiment 1**

Table 2 summarizes the results of this experiment. Nine of the 10 rats exhibited blunting of their thermic response to nicotine at $p < 0.005$ on Day 15. Thus, the effect of treatment with the monoamine oxidase inhibitor was not restricted to a few animals.

The mean thermic response of the sample prior to treatment with phenelzine was $-1.5 \pm 0.2^{\circ}\text{C}$. The mean response was $-1.2 \pm 0.2^{\circ}\text{C}$ after 7 days of treatment (i.e., three doses of phenelzine sulfate). The mean thermic response then decreased to $-0.4 \pm 0.1^{\circ}\text{C}$. ($df = 9$, $t = 3.93$, $p < 0.0035$) following 14 days of treatment (i.e., after 7 doses of phenelzine sulfate). The raw data are presented in Table 2. Figure 1 presents the results of the study.

Table 2

Summary of The Results of Experiment 2

Presentation of Data Entering into the Analysis for Experiment 1

Rat#	Mean Core Temperature	Response to Nicotine at Baseline	Response to Nicotine after 14 days Treatment
1.	37.5°C	-2.0°	- 1 . 2 ° C
2.	36.5	-1.0	-0.4
3.	36.7	-0.6	-1.4
4.	37.0	-1.5	-0.4
5.	37.5	-1.3	-0.6
6.	36.5	-1.9	-0.7
7.	36.2	-1.2	-0.3
8.	38.1	-1.9	-0.7
9.	37.0	-2.4	-0.1
10.	36.9	-1.5	-0.3
Mean + SEM	37.0 ± 0.2°C	-1.5 ± 0.2°C	-0.4 ± 0.1°C

Nine (9) of the 10 rats exhibited significant blunting of the thermic response to nicotine following 14 days of treatment. The exception was rat 3. All numbers rounded to nearest 1/10.

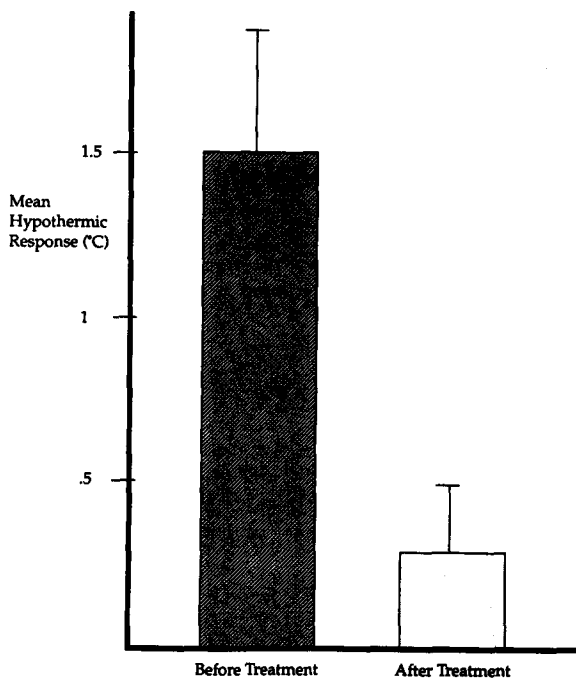


Fig 1. Mean ± SEM thermic response of 10 Sprague Dawley rats to 1.0 mg/kg of nicotine (base) before and after a 14 day course of treatment with 15.0 mg/kg phenelzine sulfate by ip injection every 48 hours. The change is significant at $p < 0.0035$.

Experiment 2

Nicotine levels in the experimental and control groups were 447 ± 27 ng/ml and 394 ± 9.0 ng/ml. ($df = 16$, $t = 1.15$, $p > 0.2$), respectively. The corresponding levels of cotinine were 230 ± 21 ng/ml and 289 ± 40 ng/ml ($df = 16$, $t = 1.47$, $p > 0.10$), respectively. Neither difference was significant.

Table 3 summarizes the results of the experiment.

Table 3
Differences in Nicotine and Cotinine Levels in Phenelzine and Saline Treated Rats.

	Mean level of nicotine 30 minutes after its injection (1 mg/kg ip)	Mean level of cotinine 30 minutes after the injection of nicotine
Treatment with Phenelzine every 48 hours for 21 days (10 doses)	447 ± 27 ng/ml	230 ± 21 ng/ml
Treatment with saline every 48 hours for 21 days (10 doses)	394 ± 9.0 ng/ml	289 ± 40 ng/ml
Absolute value of % Difference in concentration of nicotine (phenelzine relative to saline group)	11.9% (ns)	25.7% (ns)

The rate of elimination of nicotine did not differ between groups. The percent (%) difference = absolute value of [(level of nicotine or cotinine in the phenelzine group) - (the level of nicotine or cotinine in the saline group) divided by the levels of nicotine or cotinine in the phenelzine group] (100).

Discussion

Treatment with phenelzine produced time-dependent subsensitivity to the thermic effect of nicotine. Thermic responsiveness decreased by 20 and 73% following 7 and 14 days of treatment, respectively. This strongly suggests that an acute effect of the monoamine oxidase inhibitor does not account for the findings. Experiment 2 indicates that the animals receiving phenelzine and saline every 48 hours for 21 days had similar plasma nicotine and cotinine levels 30 minutes after the ip injection of 1.0 mg/kg of nicotine (base). This suggests that decreased responsiveness to nicotine is not due to an increase in its rate of elimination.

The injection of nicotine at a dose of 1.0 mg/kg ip at 7 day intervals does not produce a carryover effect (Dilsaver et al, 1988). It is therefore probable that decreased sensitivity to nicotine is due to a pharmacodynamic effect of treatment with phenelzine.

Cholinergic Properties of Drugs Used to Treat Affective Disorders

Jaffe and Sharpless (1968) and Friedman et al. (1969) demonstrated that chronic treatment with an antimuscarinic agent produces supersensitivity to a muscarinic

receptor agonist in an animal model. Muscarinic receptor antagonists were subsequently demonstrated to produce upregulation of muscarinic receptors (Dilsaver 1988b; Shifrin and Klein, 1980; Simian and Klein, 1979; Taylor *et al.*, 1979; Yamada *et al.*, 1983).

The affinities of peripheral and central muscarinic receptors for many pharmacological treatments for depression have been measured (Blackwell *et al.*, 1978; Goldman and Erickson, 1983; Rehavi *et al.*, 1980 Richelson and Dinninetz-Romero, 1977; Snyder and Yamamura, 1977; Szabdi *et al.*, 1972; Tollefson *et al.*, 1982). The tricyclic antidepressants specifically bind to these receptors. Chronic treatment with these drugs produces compensatory biochemical and physiological changes in both the rat and human subjects (Dilsaver 1989; Dilsaver and Greden, 1983 and 1984; Dilsaver and Davidson, 1988; Dilsaver *et al.*, 1983 a,b, 1987; Nomura *et al.*, 1982 a,b). These changes constitute chemically induced denervation supersensitivity. It is manifested by enhanced responsiveness to acetylcholine and muscarinic receptor agonists.

Phenelzine is devoid of affinity for the muscarinic receptors (Snyder and Yamamura, 1977). The antimuscarinic-like side-effects produced by this drug are likely due to its actions on noradrenergic systems (Dilsaver 1986 a,b,c; Dilsaver and Coffman, 1989). Isoproterenol is an example of a drug devoid of direct effects on muscarinic receptors but which can appear to have adrenergic properties. Treatment with this beta-blocker increases the density of muscarinic receptors and the acetylcholine-mediated activation of ornithine carboxylase in the myocardium of the rat (Nomura *et al.*, 1982b) by virtue of its interaction with adrenergic neurons.

Somatic Treatments Blunting the Thermic Response to Nicotine

The nicotinic properties of somatic treatments for depression have received very little attention. All of the articles included in the MEDLINE database from 1986 to January 1992 are cited in this report. Fluoxetine (Dilsaver and Davidson, 1987a), desipramine (Dilsaver *et al.*, 1989) and bright artificial light (Dilsaver 1988a, 1990a) also produce subsensitivity to nicotine in the rat. In contrast, lithium (Dilsaver and Hariharan, 1989b) and amitriptyline (Dilsaver *et al.*, 1988) enhance the rat's thermic response to nicotine (see Dilsaver and Hariharan, 1989a for a review). These seemingly incompatible findings can be reconciled.

The observation that various treatments for affective illness affect the function of nicotinic mechanisms is compatible with the aminergic theories of its etiology. The nicotinic effects of somatic treatments for the disorders of mood may either be causally or indirectly related to events critical to their mechanism of action. Nicotine promotes the release of norepinephrine in the hypothalamus (Westfall, 1973) and of dopamine within the nigrostriatal and mesolimbic systems (Anderson *et al.*, 1981). Treatments which mobilize nicotinic mechanisms might secondarily activate defective aminergic systems. A treatment which enhances the activity of aminergic mechanisms might induce compensatory subsensitization of those nicotinic mechanisms with which it interacts in order to preserve homeostasis.

Relationship between Dose of Nicotine and Effect

The study reported here employed a single dose of nicotine in a repeated measures

design. Nicotine rapidly produces tolerance. The use of independent multiple samples is more conducive to studying the effects of multiple doses on an endpoint. The measurement of the relationship of dose of nicotine to thermic change before and after treatment with phenelzine and other agents of interest would be a logical step in an effort to demonstrate that these treatments alter sensitivity to nicotine.

Temperature is an ideal endpoint for this type of study. It is easily measured and is contaminated by minimal variance. The available data suggest that phenelzine, fluoxetine, bright light, and desipramine will produce a right shift in the dose-effect curve (indicating that a higher dose of nicotine is required to produce a given hypothermic response to nicotine). Amitriptyline and lithium, should produce a left-shift in the curve. These points are illustrated in Fig. 2.

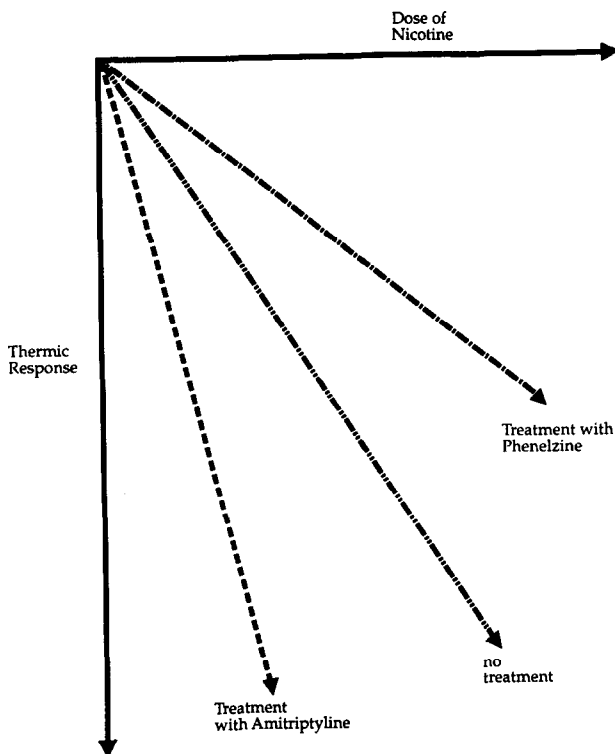


Fig. 2 Effects of chronic treatments with amitriptyline and phenelzine. The Chronic administration of all six somatic treatments for the affective disorders (amitriptyline, desipramine, fluoxetine, lithium, bright light and phenelzine) studied to date dramatically alter the thermic response to nicotine. A single dose of nicotine was used in this and all previously published reports on this topic. Studies designed to detect a possible relationship between dose of nicotine and thermic response (dose-response studies) have yet to be conducted. Figure 2 illustrates the hypothetical results of a study of this type. It indicates that chronic treatment with amitriptyline and phenelzine increase and decrease by the left shift of the dose-response curve for the group treated with amitriptyline and the right shift of the dose-response curve of the group treated with phenelzine, relative to the group of receiving no treatment.

Studies in Human Subjects

Nicotinic effects of phenelzine are not likely to be related to its mechanism of action if depressed patients in whom it is efficacious do not exhibit altered responsiveness to nicotine. Studies indicating a time-dependent change (such as that reported here) could prove quite important.

The effects of acute and chronic treatment with phenelzine and other drugs used to treat disorders of mood on the responsiveness of human subjects to nicotine can be measured. The effect of intravenous doses of nicotine (Benowitz and Jacob, 1990; Newhouse *et al.*, 1988) on subjective state, neuroendocrine parameters and body temperature can be measured before and in the course of treatment. Studies of this type are necessary in order to determine whether the finding reported here may have relevance to the mechanism of action of phenelzine.

Limitations of the Use of a Physiological Endpoint

Documentation that a given type of experimental intervention (e.g. drug treatment) consistently produces changes in a series of physiological endpoints is an excellent means of isolating a regularity in nature. Isolation of these regularities would have once been sufficient data to exercise influence over the way most scientists think. However, the history of science has proceeded from the study of events at the organismal to cellular and now molecular levels.

There is a floating concept in the scientific community of Kant's "noumenon" (Kant, 1781). Noumenon refers "the thing itself." It is reality. Kant emphasized that man merely grasps appearances of reality via the all too easily deceived senses. He labeled that which is perceived "phenomenon". The ideas of noumenon and phenomenon in the sciences are mutable. The isolation of regularities is of the very essence of the scientific process. However, the isolation of regularity in an intact animal is now merely phenomenon (Dilsaver 1990b). The observations reported here draw attention to underlying events which were identified by measuring a physiological endpoint. Basic biochemical and electrophysiological studies designed to characterize the interaction between muscarinic and nicotinic cholinergic mechanisms will be required to effect the move "from phenomenon to mechanism."

Conclusions

1. Treatment of the Sprague-Dawley rats with phenelzine sulfate, a non-selective monoamine oxidase inhibitor useful in the treatment of depression, resulted in subsensitivity to the hypothermic effect of nicotine.
2. The effect of treatment was robust. Nine (9) of the 10 rats exhibited significant decreases in their hypothermic responses to nicotine after 14 days of treatment. The sample exhibited a 73.3% reduction in its hypothermic response.
3. Treatment with phenelzine did not alter the pharmacokinetics of nicotine.
4. Fluoxetine, desipramine and bright artificial light all reduce the thermic response to nicotine. Desipramine retards the metabolism of nicotine yet affects decreased sensitivity to its hypothermic effect..

5. Amitriptyline and lithium enhance the thermic response to nicotine.
6. The authors suggest that at least some somatic treatments for affective illness may either directly or indirectly alter the function of nicotinic systems. The activation of these systems may enhance the function of aminergic mechanisms. Alternatively, the activation of aminergic mechanisms may produce compensatory subsensitivity of nicotinic systems.

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