

BRIGHT ARTIFICIAL LIGHT PRODUCES SUBSENSITIVITY TO NICOTINE

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Summary

Bright artificial light is a treatment for seasonal depression. Eleven (11) rats were exposed to bright artificial light (11,500 lux) for two consecutive weeks. The thermic response to nicotine was measured prior to light exposure and after one and two weeks of treatment. The thermic response to nicotine at baseline was $-1.69 \pm 0.25^{\circ}\text{C}$ (mean \pm SEM). The thermic response to nicotine was $-0.66 \pm 0.12^{\circ}\text{C}$ ($p < 0.002$) after one and $+0.31 \pm 0.14^{\circ}\text{C}$ ($p < 0.000025$) after two weeks of light exposure. The change in temperature was different between weeks one and two ($p < 0.000025$). The exposure of animals to constant light at an intensity of 300 lux did not blunt the hypothermic response to nicotine. These findings suggest that bright artificial light, like other antidepressant treatments, produces subsensitivity of a nicotinic mechanism involved in the regulation of core temperature.

Seasonal affective disorder (SAD) is a recently described syndrome characterized by recurrent depressions which occur at the same time each year (1). This syndrome responds to daily treatment with two-six hours of bright artificial light (1-5). A mechanism accounting for the efficacy of this treatment or an effect linking it with other forms of antidepressant treatment has not been identified. Phenelzine (6), desipramine (6), and fluoxetine (7) produced subsensitivity to the hypothermic effects of nicotine. Thus, we sought to determine whether exposure to bright artificial light alters the hypothermic response to nicotine in rats subjected to artificial light at an intensity of 11,500 lux for two weeks.

Materials and Methods

Experiment 1: This experiment involved 11 adult, male Sprague-Dawley rats weighting 312.7 ± 7.8 g (mean \pm SEM). The hypothermic response to nicotine (base), 1 mg/kg ip, was measured at 10 minute intervals for 120 minutes at baseline (i.e., prior to exposure to bright artificial light), after one and two weeks of treatment, and one and two weeks after withdrawal.

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Core temperature was measured using intraperitoneally implanted Model VM Mini-Mitters (Mini-Mitter Co., Sun River, OR). These telemetric thermosensors emit radio waves, detectable with a standard AM receiver, at a rate directly proportional to temperature. The animals were allowed five days to recover from the surgical procedure prior to starting the study. The reliability and validity of this method of measuring temperature is described elsewhere (8).

Bright artificial light consisted of 11,500 lux full-spectrum light emitted 24 hours/day for 14 days from a bank of eight 122 cm long Vitalight tubes suspended 50 cm above the animals. This unit (Duro Test Co., North Bergen, NJ, Model 5599) is used to treat patients with SAD. Temperature under the unit was 23°C.

Experiment 2: Experiment 2 involved the use of 10 adult male Sprague-Dawley rats weighting 248.0 ± 14.9 g. This involved the exposure of animals to standard fluorescent light at an intensity of 300 lux 24 hours a day for 14 days. This was designed to show that changes in circadian rhythm due to light exposure do not account for a change in sensitivity to nicotine.

Experiment 3: A control experiment was designed to assess whether multiple injections of nicotine, at the dose and frequency of administration used in this article, might produce detectable carryover effects. Model VM Mini-mitters were implanted into 8 adult, male Sprague-Dawley rats (mean weight \pm SEM = 303 ± 9.4 g). The animals were allowed 5 days to recover. The animals then received nicotine (base), 1 mg/kg ip, every 7 days for 21 days. Core temperature was measured every 10 minutes for 120 minutes after the first (baseline) and fourth injections of nicotine.

Baseline core temperature for a given nicotine challenge is defined as the core temperature immediately prior to the injection of nicotine ($t = 0$). The mean thermic response of each individual animal was determined by pairing the core temperature at $t = 0$ with the core temperature 10, 20, 30, ..., 120 minutes after the administration of nicotine. These multiple measurements allow us to make probability statements about the thermic responsiveness of each individual animal relative to the "prelight treatment phase," after one or two weeks of bright light exposure or after two weeks as opposed to one week of light treatment. The mean hypothermic response of each animal at each point in the study was entered into an analysis to determine the level of significance of the sample's thermic response. Student's paired t-tests were used for this purpose. All measures of variance in the text refer to the standard error of the mean (SEM).

Results

Experiment 1: Table I summarizes the individual responses of all 11 animals. Eight (8) animals demonstrated significant blunting of the hypothermic response, and two demonstrated a trend toward a significant decrease after one week of bright light exposure. All 11 animals exhibited blunting of the response at the 0.0003 level or less after two weeks of treatment. Moreover, 10 animals exhibited significantly greater blunting of the hypothermic response after two weeks of light exposure than after one week of treatment. Interestingly, 8 of the 11 animals actually showed a mean increase in core temperature in response to nicotine (rather than a hypothermic response) after two weeks of light treatment.

The core temperature at $t = 0$ of the sample prior to exposure to bright artificial light, after one and two weeks of treatment and one and two weeks of withdrawal, was $36.7 \pm 0.18^\circ\text{C}$, $37.5 \pm 0.13^\circ\text{C}$, $37.0 \pm 0.17^\circ\text{C}$, $36.7 \pm 0.16^\circ\text{C}$, and $37.0 \pm 0.16^\circ\text{C}$, respectively. The mean thermic response of the sample was -1.69

TABLE I

Animal #	A		B		C		D		E		F		G	
	Mean Hypothermic Response at Baseline	Hypothermic Response Week One of Light	Hypothermic Response Week One of Light	Hypothermic Response Week Two of Light	p < Baseline vs Week One of Light	p < Baseline vs Week Two of Light	Hypothermic Response Week One of Light	Hypothermic Response Week Two of Light	p < Baseline vs Week One of Light	p < Baseline vs Week Two of Light	Week One of Light	Week Two of Light	Week One of Light Minus Week Two of Light	p <
1	-1.04 ± 0.16	-1.18 ± 0.08	-1.18 ± 0.08	+0.17 ± 0.10	n.s.	0.000001	+0.17 ± 0.10	+0.17 ± 0.10	0.000001	0.000001	-1.35 ± 0.10	-1.35 ± 0.10	-1.35 ± 0.10	0.000001
2	-1.47 ± 0.15	-0.38 ± 0.08	-0.38 ± 0.08	0 ± 0.07	0.000009	0.000003	0 ± 0.07	0 ± 0.07	0.000003	0.000003	-1.39 ± 0.07	-1.39 ± 0.07	-1.39 ± 0.07	0.00004
3	-1.39 ± 0.06	-0.83 ± 0.09	-0.83 ± 0.09	-0.25 ± 0.05	0.00002	0.000001	-0.25 ± 0.05	-0.25 ± 0.05	0.000001	0.000002	-0.58 ± 0.08	-0.58 ± 0.08	-0.58 ± 0.08	0.00002
4	-1.16 ± 0.20	0 ± 0.11	0 ± 0.11	+0.29 ± 0.13	0.00005	0.000002	+0.29 ± 0.13	+0.29 ± 0.13	0.000002	0.000005	-0.28 ± 0.16	-0.28 ± 0.16	-0.28 ± 0.16	n.s.
5	-1.97 ± 0.35	-0.31 ± 0.07	-0.31 ± 0.07	+0.61 ± 0.06	0.0003	0.000025	+0.61 ± 0.06	+0.61 ± 0.06	0.000025	0.000005	-0.92 ± 0.11	-0.92 ± 0.11	-0.92 ± 0.11	0.000005
6	-0.63 ± 0.24	-0.13 ± 0.11	-0.13 ± 0.11	+0.57 ± 0.12	0.10	0.0003	+0.57 ± 0.12	+0.57 ± 0.12	0.0003	0.00009	-0.70 ± 0.09	-0.70 ± 0.09	-0.70 ± 0.09	0.00009
7	-2.01 ± 0.25	-1.17 ± 0.11	-1.17 ± 0.11	+1.29 ± 0.07	0.005	0.000001	+1.29 ± 0.07	+1.29 ± 0.07	0.000001	0.000001	-2.47 ± 0.11	-2.47 ± 0.11	-2.47 ± 0.11	0.000001
8	-2.12 ± 0.22	-0.70 ± 0.07	-0.70 ± 0.07	+0.19 ± 0.08	0.000015	0.000003	+0.19 ± 0.08	+0.19 ± 0.08	0.000003	0.00001	-0.89 ± 0.12	-0.89 ± 0.12	-0.89 ± 0.12	0.00001
9	-1.15 ± 0.22	-0.75 ± 0.04	-0.75 ± 0.04	+0.15 ± 0.06	0.10	0.0003	+0.15 ± 0.06	+0.15 ± 0.06	0.0003	0.000001	-0.90 ± 0.08	-0.90 ± 0.08	-0.90 ± 0.08	0.000001
10	-1.85 ± 0.27	-1.00 ± 0.04	-1.00 ± 0.04	-0.10 ± 0.15	0.02	0.000002	-0.10 ± 0.15	-0.10 ± 0.15	0.000002	0.000009	-0.96 ± 0.15	-0.96 ± 0.15	-0.96 ± 0.15	0.00009
11	-3.78 ± 0.38	-0.85 ± 0.09	-0.85 ± 0.09	+0.10 ± 0.33	0.00001	0.0002	+0.10 ± 0.33	+0.10 ± 0.33	0.0002	0.04	-0.95 ± 0.39	-0.95 ± 0.39	-0.95 ± 0.39	0.04

This table lists [1] the mean hypothermic response ± SEM for each of the 11 animals at baseline (prior to light treatment) - (Column A); [2] the mean hypothermic responses for each animal after one (Column B) and two (Column D) weeks of light treatment; [3] the level of significance of the difference between the baseline hypothermic response and the response after one (Column C) and two (Column E) weeks of treatment; [4] and the difference between the mean hypothermic response after one and two weeks of treatment (Column F) and the level of significance of this difference (Column G). Positive numbers in column D indicate an actual increase in core temperature (rather than the expected hypothermic response). Core temperature was measured every 10 minutes for 120 minutes following the injection of nicotine, 1 mg/kg ip. Please see the second paragraph of the results section for statistical data pertaining to the sample.

$\pm 0.25^{\circ}\text{C}$ at baseline and $-0.66 \pm 0.12^{\circ}\text{C}$ ($p < 0.0002$, $t = 4.24$, $df = 10$) and $+0.32 \pm 0.14^{\circ}\text{C}$ ($p < 0.00003$, $t = 7.35$, $df = 10$) after one and two weeks of treatment, respectively. The difference in thermic responsiveness, was also significantly different between weeks one and two ($p < 0.0003$, $t = 5.57$, $df = 10$). The thermic response one week after discontinuing treatment was $-0.26 \pm 0.11^{\circ}\text{C}$. This differed both from baseline ($p < 0.00006$, $t = 6.75$, $df = 10$) and the response after two weeks of phototherapy ($p < 0.015$, $t = 3.11$, $df = 10$). The thermic response two weeks after discontinuing light was $-0.56 \pm 0.17^{\circ}\text{C}$. This is different from the response after two weeks of treatment at $\alpha < 0.0015$ ($t = 4.33$, $df = 10$). Thus, there was a significant tendency for the animals to respond to the withdrawal of bright artificial light by becoming more sensitive to nicotine.

Experiment 2: Mean core temperature at $t = 0$ prior to challenge with saline and the baseline challenge with nicotine was $37.2 \pm 0.32^{\circ}\text{C}$ and $37.1 \pm 0.25^{\circ}\text{C}$. Mean core temperature prior to nicotine challenges 2 and 3 (i.e., after one and two weeks of exposure to 300 lux light) was $36.9 \pm 0.28^{\circ}\text{C}$ and $36.6 \pm 0.30^{\circ}\text{C}$, respectively. The mean thermic response of the sample to saline (1 ml/kg ip was $+0.30 \pm 0.10^{\circ}\text{C}$ ($p < 0.02$, $t = 3.11$, $df = 9$). The mean thermic response of the sample to nicotine was $-1.0 \pm 0.11^{\circ}\text{C}$ at baseline. This differed from the response to saline at $\alpha < 0.000001$ ($t = 13.63$, $df = 9$). The mean thermic responses to nicotine after one, $-0.9 \pm 0.11^{\circ}\text{C}$ ($p > 0.80$, $t = 0.24$, $df = 9$), and two, $-1.1 \pm 0.07^{\circ}\text{C}$ ($p > 0.30$, $t = 1.09$, $df = 9$), weeks of light treatment did not differ from baseline.

Experiment 3: Mean core temperature at baseline was $37.5 \pm 0.60^{\circ}\text{C}$. The mean thermic response to nicotine, 1 mg/kg ip, was $-1.37 \pm 0.23^{\circ}\text{C}$ ($n = 8$) when the sample was first challenged and $-1.32 \pm 0.20^{\circ}\text{C}$ ($n = 8$) after the fourth challenge ($p > .50$, $t = 0.67$, $df = 7$). Thus, multiple injections did not produce subsensitivity to subsequent challenges.

Discussion

The data presented in this article indicate that bright artificial light (11,500 lux) but not standard fluorescent light (300 lux) potentially produces subsensitivity of a nicotinic cholinergic mechanism involved in the regulation of core temperature. The potential importance of this finding is highlighted by data indicating that antidepressants such as fluoxetine (7), desipramine (6), and phenelzine (6) also produce subsensitivity to nicotine.

Chronic treatment with bright artificial light, 11,500 lux, produced subsensitivity to the hypothermic effects of nicotine, but light at an intensity of 300 lux did not. This suggests that light intensity is a critical variable. Further, this observation argues against the hypothesis that the effects we measured result from alterations in circadian rhythms consequent to constant light exposure. The intensity of light in the rat cages in our vivarium is exactly 300 lux. Sprague-Dawley rats demonstrate clear-cut circadian changes in motor activity and core temperature in response to turning the lights in the vivarium on or off. Thus, we propose that the results presented in this article are due to the effects of bright artificial light rather than light itself. Further, the documentation that multiple injections of nicotine, 1 mg/kg ip, every 7 days for 21 days (i.e., 4 doses) does not alter the hypothermic response also suggests that the outcome is not an artifact of the experimental design.

Janowsky et al. (9) proposed that depressive disorders are related to a defect in cholinergic mechanisms. Specifically, the depressed state in some individuals may be characterized by cholinergic overdrive. Sitaram et al. (10) observed that euthymic patients exhibit accelerated onset of REM sleep relative

to normal subjects in response to cholinomimetic challenge. This indicates that at least certain forms of affective illness involve state independent supersensitivity of a central muscarinic mechanism. These and other data supporting the cholinergic hypothesis of depression were recently summarized (11,12). It is, however, essential to emphasize that the relative roles of nicotinic and muscarinic cholinergic mechanisms in the pathophysiology of affective disorders is not known. Further, the classic form of the cholinergic hypothesis focuses exclusively on muscarinic mechanisms.

There are indeed sites in the mammalian brain which bind [³H] nicotine (13), α -bungarotoxin (14), and neosurugatorin (15), but a receptor with the structural properties characterizing the peripheral nicotinic receptor has not been identified. Two possibilities exist. Nicotinic and muscarinic agonists may act at sites which have mixed nicotinic-muscarinic responsiveness. This suggests that subsensitivity to nicotine would be accompanied by subsensitivity to muscarinic agonists. We currently are evaluating this possibility. It is also possible that the development of subsensitivity to nicotine is an epiphenomenon. Activation of nicotinic sites releases norepinephrine in the hypothalamus (16) and dopamine within the mesolimbic and nigrostriatal tracts (17). Should treatment with bright artificial light enhance the sensitivity of catecholaminergic mechanisms, a compensatory response may be subsensitization of those nicotinic mechanisms capable of activating them.

Patients with SAD are generally treated with full-spectrum light at an intensity of 2,500 lux. There are distinct advantages to using brighter light in a preliminary study. Our objective was to determine whether bright light as opposed to standard room lighting affects subsensitivity to nicotine. The higher the "dose," one might suppose, the lower the probability of a Type II error ("bright artificial light does not produce subsensitivity to the thermic effects of nicotine"). It is now known that treatment with full-spectrum light at an intensity of 11,500 lux results in decreased sensitivity to nicotine. Thus, it would now be reasonable to evaluate the effects of various intensities of illumination and the effects of administering light for circumscribed periods of time during the day.

The light unit we used delivers light at an intensity of 2,500 lux when it is 122 cm from the face of patient. In order to deliver light at an intensity of 11,500 lux, we suspended the unit 50 cm above the animals. A patient does not experience discomfort when the unit is placed this distance from the face. It would, therefore, be feasible to use a higher "dose" or brighter light should studies suggest that an intensity of illumination greater than 2,500 lux is preferable.

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