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Bright Light Blocks Amitriptyline-Induced Cholinoceptor Supersensitivity

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Introduction

Seasonal affective disorder (SAD) is a syndrome marked by recurrent depressions that generally occur in the fall or winter (Rosen-

thal et al., 1984). This syndrome reportedly responds to daily treatment with 2–6 hr of bright artificial light (Lewy et al. 1982; Rosenthal et al. 1984, 1986; James et al. 1985; Wehr et al. 1986). Neurobiological mechanisms accounting for the efficacy of this treatment remain unknown. Certain forms of affective illness may involve state-independent supersensitivity of central muscarinic mechanisms (Janowsky et al. 1972; Dilsaver 1986a–c). Amitriptyline and other heterocyclic antidepressants produce supersensitivity of a central muscarinic mechanism involved in the regulation of core temperature (Dilsaver et al. 1987; Dilsaver and Davidson 1987; Dilsaver

and Snider 1988). This article presents data indicating that 6 hr of bright artificial light daily blocks amitriptyline-induced supersensitivity of this mechanism.

Methods

The dependent variable in the experiments below is mean change in core temperature in response to oxotremorine, a muscarinic acetylcholine receptor (mAchR) agonist. Dilsaver and Alessi (1988) outlined the principles governing the use of core temperature in psychopharmacological research. Core temperature was measured using an intraperitoneally (ip) implanted telemetric thermosensor, the Model VM Mini-Mitter (Mini-Mitter Corp., Sun River, OR). These devices emit radio waves at an AM frequency at a rate directly proportional to core temperature. Temperature was measured every 10 min for 120 min following the injection of saline (1 ml/kg, ip) or oxotremorine (1 mg/kg) at 9:00 AM. The response to routine handling and the injection of saline is a mean thermic rise of 0.2–0.8°C (Dilsaver and Majchrzak 1988b). We routinely challenge animals with saline prior to administering an agonist. It may not be possible to interpret the thermic response of a sample to an agonist in the absence of knowledge of that sample's response to handling and the injection of placebo. For instance, a sample of 10 rats may exhibit a mean ($\pm$ SEM) thermic rise of 0.7 $\pm$ 0.2°C on response to handling and the injection of saline. The sample's mean change in core temperatures of 0 $\pm$ 0.2°C when injected with 0.05 mg/kg of oxotremorine would be significant in this instance. The rats used in the experiments reported below were challenged with saline 24 hr prior to the initial challenge with oxotremorine. Information regarding the reliability and validity of measurements using the Mini-Mitter is available elsewhere (Dilsaver and Majchrzak 1989).

Full-spectrum bright artificial light, 7400 lux, was emitted from a bank of eight 122-cm long Vita Lite tubes suspended 50 cm above the animals. This light unit (model 5599; Duro Test Corp., Bergen, NJ) is used to treat seasonal

depression (Lewy et al. 1982). Temperature under the light unit was 23–23.5°C. Oxotremorine challenges started at baseline and were preceded by the injection of methylscopolamine nitrate (1 mg/kg, ip). Methylscopolamine nitrate blocks the effects of muscarinic agonists on peripheral mAchRs. The quartanary amine group of methylscopolamine renders it lipid-insoluble, and it therefore does not effectively cross the blood–brain barrier. Thus, pretreatment with methylscopolamine allows one to isolate the effects of a treatment on central muscarinic mechanisms. Baseline temperature was examined 30 min after the injection of methylscopolamine. Oxotremorine (base), 1 mg/kg, ip, was then injected, and temperature was measured every 10 min for 120 min.

Mean change in core temperature (i.e., the average change at each of the 12 time points) was entered into an analysis using Student's paired t-test. Mean change at a given time point was calculated by subtracting the core temperature of a given rat at that time point (e.g., 36.0°C) from the temperature of that rat prior to the injection of oxotremorine (e.g., 37.0°C). Measures of variance in the text refer to the standard error of the mean (SEM).

Amitriptyline HCl, oxotremorine (base), and methylscopolamine nitrate were purchased from Sigma Chemical Company (St. Louis, MO). All drugs were prepared at a concentration that allowed us to inject 1 ml/kg of the solution.

Experimental Design

Experiment 1. Mini-Mitters were implanted into 10 adult, male Sprague-Dawley rats weighing 227.0 $\pm$ 8.4 g. The rats were allowed 5 days to recover from the surgical procedure. The thermic response to saline (1 ml/kg, ip) was measured prior to the first challenge with oxotremorine (1 mg/kg, ip). The rats were then treated with amitriptyline (15 mg/kg, ip) at 9:00 AM and 5:00 PM for 7 days. During this period, the animals were housed under standard conditions in which lights in the vivarium were automatically turned on and off at 6:00 AM and 6:00 PM, respectively. The rats

Table 1. Sequence of Steps for Experiments
1 and 2

1. Telemetric (hearing aid powered) thermosensors are
   calibrated (MiniMitters)
2. MiniMitters are implanted
3. The rats are given 5 days to recover
4. The mean thermic response to saline (1 mg/kg) is
   measured
5. Twenty-four hours later, the mean thermic response
   to oxotremorine (1 mg/kg) is measured
6. Treatment with amitriptyline (15 mg/kg ip) begins
   after the first oxotremorine challenge
7. Treatment with bright (Experiment 1) or dull
   (Experiment 2) light begins at 5:00 PM (on the day
   following the first oxotremorine challenge)
8. Seven days later, at 9:00 AM 19 hr after the previous
   dose (14th) of amitripyline, the second oxotremorine
   challenge is repeated
9. Treatment with amitriptyline continues for 7 more
   days
10. A third oxotremorine challenge starts at 9:00 AM, 19
    hr after the last dose (28th dose) of oxotremorine.
11. Mean thermic response for each challenge is
    calculated and data analyzed

    Mean thermic response = [core temperature of a rat 10, 20, 30,
. . . , 120 min after the injection of saline or oxotremorine] − [core
temperature of the same rat prior to the injection of saline or oxo-
tremorine].

were rechallenged with oxotremorine after a week
of treatment with amitriptyline. One week of
treatment with this tricyclic antidepressant pro-
duces dose-dependent supersensitivity to the hy-
pothermic effect of oxotremorine (Dilsaver et al.
1987; Dilsaver and Snider 1988). Enhancement
of the hypothermic response to oxotremorine
persists for at least 4 weeks after starting treat-
ment with amitriptyline (Dilsaver et al. 1987).
Bright artificial light was administered between
5:00 PM and 11:00 PM for 7 days following the
second oxotremorine challenge, based on our
original notion that prolonging the photoperiod
might contribute to its effects. We have since
learned that prolonging the photoperiod is not
important to mediating some effects of bright light.
For example, bright light given during part of the
photoperiod or during the entire photoperiod
subsensitizes rats to nicotine and oxotremorine
(Dilsaver 1988; Dilsaver and Flemmer 1988).
Treatment with amitriptyline continued during the
period during which bright light was given. The

sample was rechallenged with oxotremorine af-
ter 1 week of treatment with both amitriptyline
and bright artificial light. The oxotremorine chal-
lenges occurring in the course of treatment with
amitriptyline started 19 hr after the preceding in-
jection of the tricyclic.

Experiment 2. The objective of this experi-
ment was to illustrate that a simple manipulation
of the light/dark cycle using dull light (300 lux)
does not account for effects associated with bright
artificial light. Mini-Mitters were implanted into
10 adult, male Sprague-Dawley rats weighing
237.3 ± 3.6 g. The animals were allowed 5
days to recover from the implantation proce-
dures. The thermic response to saline was then
measured. The animals were subsequently chal-
lenged with oxotremorine. Treatment with ami-
triptyline (15 mg/kg ip) at 9:00 AM and 5:00 PM
followed. The thermic response to oxotremorine
was measured 7 days later. The rats were then
subjected to 300 lux light emitted from standard
fluorescent light units between 5:00 PM and 11:00
PM and were concurrently treated with amitrip-
tyline (15 mg/kg, ip) for 7 days. The sample
was otherwise subjected to the standard light/dark
cycle.

Table 1 outlines the sequence of steps in both
Experiments 1 and 2.

Results

Experiment 1

Mean core temperature at baseline (prior to the
saline challenge) was $38.1 \pm 0.42°C$. Table 2
summarizes the mean thermic response over the
12 points in time.

The sample exhibited a mean thermic re-
sponse to saline of $+0.2 \pm 0.10°C$. The mean
thermic response to oxotremorine prior to treat-
ment with amitriptyline was $-1.3 \pm 0.2°C$.
This differed from the thermic response to saline
at the 0.00003 level ($t = 7.02$, df $= 9$). All
10 animals exhibited enhancement of the hy-
pothermic response to oxotremorine after 1 week
of treatment with amitriptyline ($p = 0.0001$,
sign test). The mean thermic response to oxo-
tremorine after 1 week of treatment with ami-

Table 2. Experiment I: Mean Thermic Responses

Animal number	A Saline	B Oxotremorine challenge I	C Oxotremorine challenge 2	D Oxotremorine challenge 3
1	0.2 ± 0.1	−2.5 ± 0.4	−3.4 ± 0.4	−0.7 ± 0.2
2	0.3 ± 0.1	−1.0 ± 0.3	−2.3 ± 0.3	−0.9 ± 0.1
3	0.5 ± 0.1	−0.8 ± 0.2	−2.0 ± 0.3	−1.7 ± 0.3
4	0.1 ± 0.1	−0.3 ± 0.04	−2.7 ± 0.3	−1.8 ± 0.2
5	0.3 ± 0.1	−0.7 ± 0.2	−2.9 ± 0.3	−1.0 ± 0.2
6	0.1 ± 0.1	−1.2 ± 0.3	−1.9 ± 0.3	−0.8 ± 0.2
7	−0.1 ± 0.1	−2.3 ± 0.4	−2.2 ± 0.4	−1.7 ± 0.3
8	0.1 ± 0.1	−1.5 ± 0.2	−3.1 ± 0.4	−1.7 ± 0.2
9	0.4 ± 0.1	−1.3 ± 0.4	−3.4 ± 0.5	±1.5 ± 0.2
10	0.3 ± 0.1	−1.3 ± 0.3	−2.0 ± 0.3	−1.0 ± 0.2
Mean	+0.2 ± 0.10	−1.3 ± 0.20	−2.6 ± 0.20	−1.3 ± 0.10

This table presents the thermic response of each animal in Experiment 1 to saline (1 mg/kg, ip) and to oxotremorine (1 mg/kg, ip) prior to treatment with amitriptyline (Challenge 1), after 1 week of treatment with amitytriptyline (15 mg/kg, ip, at 9:00 AM and 5:00 PM daily) (Challenge 2), and after 1 week of concurrent treatment with full-spectrum, bright artificial light (between 5:00 and 11:00 PM) and amitriptyline (15 mg/kg, ip, at 9:00 AM and 5:00 PM daily) (Challenge 3). Each entry is the mean of 12 measurements of change in core temperature relative to the rat's core temperature immediately prior to the injection of saline or oxotremorine. Please see the Results section for probability statements.

triptyline was −2.6 ± 0.2°C. This differed from the thermic response to oxotremorine prior to treatment with amitriptyline ($p < 0.0006$, $t = 5.21$, df = 9). The sample exhibited the identical thermic response to oxotremorine (−1.3 ± 0.10°C) after 1 week of treatment with bright artificial light that it displayed prior to the administration of amitriptyline, despite continued treatment with this agent. Figure 1 illustrates the results of this experiment.

Experiment 2

The mean core temperature of the animals in this experiment at baseline was 37.3 ± 0.03°C prior to injection with saline. The sample exhibited a mean thermic response to saline of +0.36 ± 0.6°C. The mean thermic response to oxotremorine prior to treatment with amitriptyline was −0.90 ± 0.07°C. This differed from the thermic response to saline ($p < 0.0001$, $t = 12.6$, df = 9). The mean thermic response after 1 week of treatment with amitriptyline was −1.36 ± 0.15°C. This differed from the response to oxotremorine prior to treatment with amitriptyline ($p < 0.0003$, $t = 6.10$, df = 9). The sample exhibited a mean thermic response of −1.42 ± 0.12 after an additional week of treatment with amitriptyline, during which it was exposed to 300 lux light between 5:00 PM and 11:00 PM. This did not differ from the response to oxotremorine
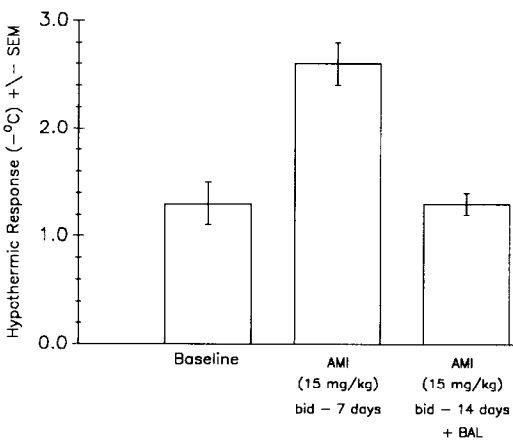

Figure 1. Six hours of bright light daily blocks the capacity of amitriptyline to produce supersensitivity to oxotremorine.
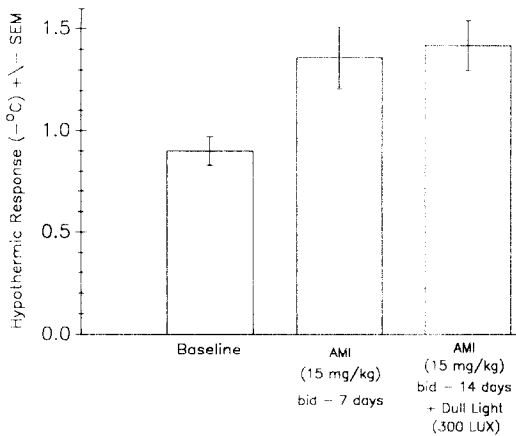
Figure 2. Dull light does not produce subsensitivity to oxotremorine.

after 1 week of treatment with amitriptyline ($p > 0.6$, $t = 0.64$, df $= 9$). Figure 2 illustrates the results of Experiment 2.

Discussion

The data presented indicate that concurrent treatment with bright artificial (7400 lux), but not dull (300 lux), light counteracts the capacity of amitriptyline to produce supersensitivity to the thermic effect of oxotremorine. This suggests that light intensity is a critical variable. All 10 animals in Experiment 1 exhibited an increase in the hypothermic response to oxotremorine after 1 week of treatment with amitriptyline. Similarly, all 10 animals in this experiment exhibited blunting of the thermic effects of oxotremorine after 1 week of concurrent treatment with oxotremorine and bright artificial light ($p = 0.0001$, sign test). This strongly suggests that bright light potently affects the muscarinic mechanism supersensitized by amitriptyline.

Janowsky et al. (1972) proposed that depressive disorders are related to a defect in central muscarinic mechanisms. Sitaram et al. (1980) observed that euthymic affective disorder patients exhibit accelerated onset of rapid eye movement (REM) sleep in response to the infusion of arecoline (an mAchR agonist) relative

to normal subjects. This indicates that at least some forms of affective illness involve state-independent supersensitivity of a central muscarinic mechanism. Bright artificial light is the first treatment for a depressive disorder discovered to produce subsensitivity of a central muscarinic cholinergic mechanism.

Several aspects of this study require comment. The albino rat is useful in conducting preliminary experiments designed to assess the effects of bright light on neurotransmitter systems, but it is not the ideal animal for research in this area. A pigmented diurnal species will eventually have to be used in these studies. The albino rat may experience irreversible neuroanatomic retinal changes when chronically exposed to bright light. We emphasize, however, that although this may occur, albino rats exposed to bright light at an intensity of 7400 lux for 24 hr a day for 7 consecutive days return to their baseline level of sensitivity to clonidine when returned to standard vivarium conditions (Dilsaver and Majchrzak 1988). This argues against the possibility that a neuroanatomic effect on the retina accounts for the findings we have reported (Dilsaver 1988; Dilsaver and Flemmer 1988).

The time fragment of the 24-hr day over which one administers bright light to either a diurnal or nocturnal species would be physiologically important (Lewy et al. 1983, 1984, 1985; Lewy and Sack 1987). Bright light can either phase delay or phase advance an endogenous pacemaker ("master clock"), depending on the time it is administered. During the first half of subjective night (as in the study reported here), bright light produces a phase delay. A pulse of bright light of identical intensity and duration will produce a phase advance when given during the second half of subjective night. We have reported that the constant administration of bright light (Dilsaver and Majchrzak 1987) or its administration during a fragment of the regular photoperiod (Flemmer and Dilsaver 1988) all produce subsensitivity of a central muscarinic mechanism. Thus, whether the animals are free-running (as occurs when bright light is given

constantly), circadian phase is supposedly not altered (as occurs when bright light is given during the regular photoperiod) or delayed (in the study reported here) we obtain the same basic result.

Finally, with respect to the phasic effects of light, it is important to note that the issue is not whether or not 300 lux light is a physiologically significant stimulus in the albino rat. It unequivocally is! Abruptly removing a stimulus of 300 lux light by turning the lights in a vivarium off leads to a dramatic increase in motor activity in less than 1 min and a rise in body temperature. Turning the lights on during the dark phase leads to a dramatic (but slower occurring) decrease in motor activity. The crucial issue is whether or not 300 lux and 7400 lux light have equivalent phasic effects on an endogenous pacemaker that might affect mAchR sensitivity. This study was not designed to answer this particular question.

The possibility that exposure to bright light stresses the rat must be considered. We doubt that it does. First, the animals do not behave as if they are stressed. Second, forced swim stress (Dilsaver et al. 1986; Dilsaver 1988b) and inescapable footshock (Dilsaver and Alessi 1987) enhance the sensitivity of a central muscarinic mechanism involved in the regulation of core temperature. Data from other laboratories also indicate that stressors activate muscarinic mechanisms (for a review of this literature, please see Dilsaver 1988). Thus, the effect of bright light reported here is the opposite of that associated with stressors.

Why amitriptyline produces supersensitivity to muscarinic agonists, given that it is an antidepressant, puzzles some thoughtful psychiatrists who have attempted to reconcile this fact with the muscarinic cholinergic system hypothesis of depression. Amitriptyline is an mAchR antagonist (i.e., it blocks the access to acetylcholine to the mAchR). It produces signs and symptoms of mAchR blockade (Atkinson and Landinsky 1972; Richelson and Dininetz-Romero 1977; Szabadi et al. 1980; Petersen and Richelson, 1982).Drugs blocking the access of acetylcholine to the mAchR compel compensatory changes in cholinoceptive

neurons. These changes include mAchR up-regulation (for a review of this literature, please see Dilsaver 1986a) and the enhancement of sensitivity to acetylcholine and muscarinic agonists (Jaffe and Sharpless 1968; Friedman et al. 1969; Innes and Nickerson 1975; Jaffe 1980). Amitriptyline, just as classical mAchR antagonists do, produces up-regulation of mAchRs in the rodent brain (Rehavi et al. 1980; Goldman and Erickson 1983) and supersensitivity to a muscarinic agonist (Dilsaver et al. 1987; Dilsaver and Snider 1988). Desipramine similarly produces mAchR up-regulation in the myocardium of rats (Nomura et al. 1982, 1983) and supersensitivity to a muscarinic agonist (Dilsaver and Davidson 1987). It is important to note that the antimuscarinic effects of the tricyclics are now regarded as being related to their side effect profile, but unrelated to their antidepressant properties. Amitriptyline is not an antidepressant because it is a mAchR antagonist—it is an antidepressant despite this property! As it has this property, it potently produces supersensitivity to a muscarinic agonist. Many outstanding antidepressants either lack or have minimal affinity for the mAchR (Snyder and Yamamura 1977; Blackwell et al. 1978; Tollefson et al. 1982; Richelson and Nelson 1984).

Conclusion

Data presented in this article indicate that bright artificial, but not dull light blocks the capacity of amitriptyline to produce supersensitivity of a central muscarinic mechanism. These data are *consistent* with the hypothesis that the depressed state is accompanied by supersensitivity of a central muscarinic mechanism and that a treatment subsensitizing it has antidepressant properties.

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