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Neonatal Scopolamine or Antidepressant Treatment: Effect on Development of Hamster Circadian Rhythms

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KLEMFUSS, H. AND J. C. GILLIN. *Neonatal scopolamine or antidepressant treatment: Effect on development of hamster circadian rhythms.* PHARMACOL BIOCHEM BEHAV **59**(2) 369–373, 1998.—Chronic treatment of young rodents with drugs altering monoamine metabolism has been reported to produce lasting effects on behavior that resemble human affective disorders. To test the generality of this finding, scopolamine, imipramine, or clomipramine was injected daily between the ages of 8 and 21 days in golden hamsters. Wheel-running rhythms were monitored continuously from the age of 4 to 20 weeks of age to test the hypothesis that neonatal treatments would lower the amplitude of biological activity rhythms in adults. Of these three neonatal treatments only scopolamine altered running rhythms, significantly increasing the amplitude of running rhythms in adult hamsters under both entrained and free-running conditions. Hamsters treated neonatally with scopolamine were also more sensitive to the hypothermic effects of the muscarinic agonist, oxotremorine, as adults. These data indicate that neonatal exposure to cholinergic receptor blockade may produce long-lasting changes in biological rhythm characteristics related to upregulation of muscarinic receptors. © 1998 Elsevier Science Inc.

Circadian Rhythms Affective disorders Muscarinic Depression Imipramine Chlorimipramine Scopolamine

REPEATED injection of neonatal rats with the tricyclic antidepressant drug clomipramine (CMI) has been reported to produce, in adults, decrements in sexual, aggressive, and hedonistic behaviors, and increases in rapid eye movement (REM) sleep. This syndrome resembles human endogenous depression (16,36,37). Increased immobility in the forced swim test is also consistent with a depressogenic effect of neonatal CMI treatment (32). Some of these signs are reversed by treatment of adults with imipramine or REM sleep deprivation (36). CMI is a serotonin reuptake blocker, although a metabolite of CMI, desmethylcloripramine, also blocks norepinephrine reuptake (23). Neonatal treatment with CMI apparently downregulates serotonin-sensitive receptors, reflected in decreased firing rate of serotonergic neurons in the dorsal raphe nuclei of anesthetized adults (40). However, neonatal CMI treatment is also associated with an enhanced hypothermic response to acute challenge with oxotremorine, a cholinergic agonist, indicating that cholinergic mechanisms may also be affected (19). Perhaps the most interesting aspect of this model is that similar syndromes are produced with neonatal administration of other antidepressants as well, including zimelidine and the norepinephrine-selective antidepressant desipramine (8,9,23).

Although functional deficits of noradrenergic and serotonergic neurotransmission are prominent in the pathophysiology of affective disorders (5,20), Janowsky suggested that depression results from a relative excess of cholinergic to aminergic neurotransmission (10). In the context of this cholinergic–aminergic hypotheses of depression, it would be useful to compare treatments that may produce a permanent decline in serotonergic action to treatments that may produce a permanent upregulation of cholinergic action. Overstreet and colleagues have developed a genetic line of rats selected for hyperresponsivity to an acetylcholinesterase inhibitor (18). These Flinders Sensitive Line (FSL) rats exhibit increased REM, hypoactivity, anhedonia, and other signs of clinical depression (18,27). It is thought that these changes relate to increased density of muscarinic receptors in the hippocampus and striatum in FSL rats (27). Therefore, the behavioral effects of down-

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regulated monoaminergic receptors and upregulated muscarinic receptors appear to converge on producing signs associated with human affective disorders.

Vogel et al. (34,38) have argued that most clinically useful antidepressants suppress REM sleep, and that it is this REM suppression that is responsible for both the beneficial actions of antidepressants and the effects of neonatal tricyclic injection. They also observed that the muscarinic receptor blocker, scopolamine (**SCOP**), is one of the few drugs not generally classified as an antidepressant that is known to suppress REM sleep (6,7,29,33). Thus, it would be reasonable to hypothesize that neonatal SCOP treatment may produce a cholinergic model of depression mirroring the CMI model. However, one previous study in rats reported that neonatal treatment with SCOP did not decrease sexual behavior or increase immobility time in the forced swim test, which are proposed as animal analogs of depression. Conversely, SCOP treatment increased the number of ejaculations in adult male rats (31).

Disturbances in circadian phase regulation may be present in mood disorders (14,39). Cholinergic supersensitivity has also been associated with circadian phase disturbances in animals. Hypercholinergic FSL rats have been reported to show shortened REM latency (27), and alterations in the phase position and period of daily rhythms of body temperature (25) and drinking (26). Strain differences in the waveform of the body temperature rhythm have been noted, but the phase differences have not been a consistent finding (26). Changes in the waveform of the temperature rhythm may reflect alterations in amplitude, although cosinor amplitude was not significantly different in FSL and control rats (25). Amplitude of biological rhythms may be an important factor in depressive illness. Depressive disorders have been associated with reduced hormonal and temperature rhythm amplitude (21, 24,28), and amplitudes are increased during remission (28).

The purpose of the present study was to examine the effects of neonatal scopolamine treatment on the amplitude of the circadian wheel-running rhythm, and to compare these effects to those of neonatal clomipramine and imipramine. Although previous studies of antidepressant treatment of neonates have been done in rats, we elected to study hamsters because their circadian rhythm of wheel-running is generally more consistent. In a preliminary study we found that neonatal scopolamine treatment of hamsters produced a significant decrease in circadian rhythm amplitude in juvenile hamsters of 6 weeks of age (13). However, that study did not follow hamsters to adult. Therefore, we sought to replicate the amplitude finding from the preliminary study, and expand the study to include tricyclic antidepressants and adult animals.

METHOD

Adult female and male golden (Syrian) hamsters weighing 110–120 g were purchased from Sasco (Omaha, NE). Females were housed singly in shoebox cages under a 14 L:10D schedule (lights on 0600–2000 h). After several weeks adaptation, a breeder male was placed in each female's cage for 5 days. The male was then removed, and females were disturbed as little as possible for the next 3 weeks. Six females gave birth to litters of 9–15 pups with 2 days of each other. At age 4 days pups were reallocated so that each dam had a litter of 12 pups, of which 2 were her own. At age 8 days males were randomly assigned to one of four drug treatments: SCOP (scopolamine HCl, 3 mg/kg), IMI (imipramine HCl, 15 mg/kg), CMI (clomipramine HCl, 15 mg/kg), or vehicle CON (normal saline). These doses were based on literature review and pilot studies to produce behavioral effects without toxicity. Females were not used in this study. Drug or vehicle were injected subcutaneously between the shoulderblades in a volume of 1 μl/g, between 1700–1800 h every day between 8 and 21 days of age.

After the 2 weeks of daily injections, 36 treated male hamsters (nine/treatment group) were separated from the mother and housed in group cages. One week later each injected hamster was transferred to an individual cage containing a running wheel, housed in a ventilated light-tight cabinet, with the same 14L:10D light regimen (light about 30 lx, dark <0.1 lx). Starting at age 15 weeks, lights remained on continuously until the end of the experiment.

Running wheel revolutions were recorded in 5-min epochs by computer, and analyzed in 2-week batches of data collected at 3-week intervals; i.e., data were collected for weeks 4–5, 7–8, 10–11, 13–14, and 16–17 of age. Cage cleaning and other procedures were carried out in the nonanalyzed weeks. Wheel-running data were analyzed using several different procedures. Using the cosinor procedure, which fits a sine wave with a period of 24 h to the raw data using least squares regression,we measured the mesor (daily mean) and peak-to-trough range (cosinor amplitude) of the fitted sine wave (17). Although commonly used for describing amplitude of synchronized biological rhythms, cosinor is most useful for data that approximate a sine wave. Harmonic analysis, a derivative of the cosinor procedure, has advantages for describing nonsinusoidal data (11), and was the primary amplitude measurement employed. In this analysis, we derive the complex waveform described by a sine wave with a period of 24 h plus a set of nine true harmonic frequencies, which produces the best approximation to the raw data as determined by least-squares regression. This technique generates an estimate of rhythm amplitude (power^{-2}) that is relatively independent of the shape of the waveform (11,12). We also used an iterative version of harmonic analysis to estimate period and amplitude of nonsynchronized rhythms, during the interval when hamsters were free-running in constant light (weeks 16–17). The phase of activity onset of the entrained activity rhythm was estimated using the onset periodogram program (11,12). Data from one SCOP-treated hamster were dropped because his harmonic amplitude decreased overnight from 29.0 revolutions/min to 0.4 revolution/min, following an unplanned confrontation with another hamster. His running-wheel amplitude remained low for several weeks, then spontaneously returned to preconfrontation levels.

At age 18 weeks, each hamster was subjected to an oxotremorine challenge to identify cholinergic receptor sensitivity, following methods based on Overstreet (18). After taking a baseline rectal temperature (Yellow Springs Instruments), hamsters were weighed, pretreated with 2 mg/kg scopolamine methyl bromide subcutaneously, and placed in an individual holding cage. Scopolamine methyl bromide does not cross the blood–brain barrier, and blocks the peripheral side effects of oxotremorine. Fifteen minutes later each was injected with 200 μg/kg oxotremorine intraperitoneally. Because this experiment was carried out in constant light (free-run) conditions, oxotremorine injections were given 4 h prior to the expected time of activity onset, as estimated from the tau and phase measurements made during the previous 2 weeks. Rectal temperature was recorded 30 minutes after injection, and then animals were returned to the home running-wheel cage.

Statistical analyses were carried out using SPSS. Repeated measures analysis of variance (ANOVA) was used to evaluate time-related effects of neonatal treatment, with age as a within-subjects variable, at the four time points under light-synchronized conditions. Effects of neonatal treatments on

running activity under constant light conditions (week 16–17) and on body temperature response to oxotremorine, were evaluated using oneway ANOVA. In the event of a significant *F* ratio, ANOVA with planned comparisons or Dunnett's test were used to localize effects. All results in the text and tables are expressed as mean ± SD.

RESULTS

Harmonic Amplitude

There were significant effects of age, $F(4,32) = 26.75$, $p < 0.001$, and also interactions between age and neonatal treatment, $F(12,32) = 2.01$, $p < 0.05$, on the harmonic amplitude of running wheel rhythms. As has been previously described (13), hamsters pretreated with SCOP as neonates showed significant lower harmonic amplitude of wheel-running rhythms as juveniles (weeks 4–5 of age; $p < 0.05$, planned comparison SCOP vs. CON). Figure 1 shows that the amplitude of wheel-running increased as animals matured. This increase in amplitude was particularly clear in the SCOP-treated animals, so that by the age of 7–8 weeks amplitude was significantly larger in the SCOP-pretreated hamsters than in controls. Increased rhythm amplitude in SCOP animals persisted when the lighting condition was changed to constant light (week 16–17). In contrast to the effects of neonatal SCOP treatment, neonatal treatment with IMI did not significantly affect rhythm amplitude, compared to saline control. Animals treated with CMI as neonates did show increased amplitude of running rhythms, but this effect was only statistically significant at the week 10–11 time point.

Mesor and Cosinor Amplitude

Both mesor and cosinor amplitude showed unambiguous effects of maturation, $F(4,32) > 19$, $p < 0.001$, but although treatment effects on mesor and cosinor amplitude were in the same direction as effects on harmonic amplitude (Tables 1 and 2), they did not reach statistical significance, $F(12,32) < 1.7$, $p > 0.075$. Harmonic amplitude, when expressed as a function of mesor (amplitude/mesor or amplitude-mesor) also did not reach statistical significance.

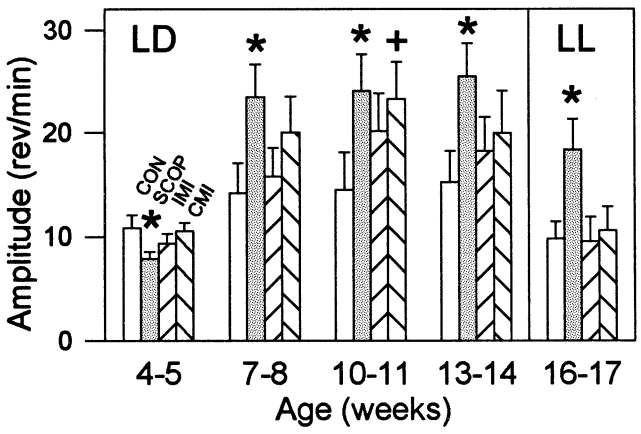

FIG. 1. Time course of change in the amplitude of the wheel-running rhythm after neonatal treatment of hamsters with SCOP (scopolamine 3 mg/kg/day; shaded bars), IMI (imipramine 15 mg/kg/day; rising diagonal), CMI (clomipramine 15 mg/kg/day; falling diagonal), or CON (vehicle control; empty bars). $^{*}p < 0.01$ vs. vehicle control; $^{+}p < 0.05$ vs. vehicle. $n = 8$–9/group.

TABLE 1

EFFECTS OF TREATMENTS ON MESOR

	Weeks 4–5	Weeks 7–8	Weeks 10–11	Weeks 13–14	Constant Light
CON	5.5 ± 2.0	6.4 ± 3.6	6.5 ± 4.7	6.7 ± 4.0	4.1 ± 2.5
SCOP	3.9 ± 1.0	9.8 ± 3.7	10.0 ± 4.2	10.5 ± 3.9	7.2 ± 3.8
IMI	4.7 ± 1.3	7.2 ± 3.2	8.5 ± 4.0	7.3 ± 3.8	4.1 ± 3.8
CMI	5.5 ± 1.1	9.4 ± 4.3	10.5 ± 4.8	8.9 ± 5.1	4.5 ± 3.1

Mean wheel revolutions/min ± SD, as calculated by cosinor.

Rhythm Phase and Period

No neonatal treatment affected the entrained phase of running onset at any time point measured (Table 3). Similarly, the period of the wheel-running rhythm in constant light was not affected by neonatal pretreatment (CON: 24.03 ± .12 h; SCOP: 24.04 ± .13 h; IMI: 23.99 ± .21 h; CMI: 24.09 ± .16 h).

Oxotremorine Challenge

Baseline body temperatures were not different between groups (CON: 36.7 ± 0.9° SD; SCOP 36.7 ± 1.2°; IMI: 36.6 ± 0.3°; CMI 36.8 ± 1.0°). Thirty minutes after oxotremorine administration, the average temperature decreased by about 1.1°C in neonatal SCOP-treated animals, which just reached statistical significance using one-tailed ANOVA with planned comparisons (Fig. 2).

Other Effects of Treatments

Neonatal hamsters tolerated the injections well, although animals receiving either IMI or CMI developed noticeable skin adhesions that covered the entire back by the conclusion of the injection protocol. Although skin adhesions remained palpable for at least 1 month, they did not appear to interfere with running, because total wheel running was not different between controls, scopolamine-treated, or tricyclic-treated hamsters (Table 1).

DISCUSSION

These data show that brief treatment of neonates with a muscarinic receptor blocker can produce lasting effects on circadian rhythm amplitude in the hamster. These effects may be associated with increased sensitivity of muscarinic receptors, because adult hamsters treated neonatally with SCOP demonstrated an increased hypothermic response to the muscarinic agonist oxotremorine, compared to hamsters given control or tricyclic treatment. At least some of the altered muscarinic

TABLE 2

EFFECTS OF TREATMENTS ON AMPLITUDE AS DETERMINED BY THE COSINOR METHOD

	Weeks 4–5	Weeks 7–8	Weeks 10–11	Weeks 13–14	Constant Light
CON	7.1 ± 3.2	9.6 ± 6.4	9.8 ± 8.2	10.7 ± 6.9	6.7 ± 3.2
SCOP	5.3 ± 1.4	16.5 ± 6.3	17.0 ± 7.3	17.7 ± 6.8	12.1 ± 6.6
IMI	6.1 ± 2.2	11.1 ± 5.9	13.5 ± 7.8	12.1 ± 6.8	6.3 ± 5.2
CMI	6.9 ± 1.7	14.4 ± 7.9	16.6 ± 8.4	14.1 ± 9.1	6.7 ± 4.7

Mean cosinor amplitude, in wheel revolutions/min, ± SD.

TABLE 3
EFFECTS OF TREATMENT ON ENTRAINED PHASE

	Weeks 4–5	Weeks 7–8	Weeks 10–11	Weeks 13–14
CON	−0.29 ± 0.31	−0.16 ± 0.28	0.06 ± 0.49	−0.02 ± 0.18
SCOP	−0.51 ± 0.50	0.01 ± 0.18	−0.21 ± 0.75	0.10 ± 0.12
CMI	−0.26 ± 0.32	−0.14 ± 0.37	−0.13 ± 0.22	−0.05 ± 0.32
IMI	−0.18 ± 0.30	−0.13 ± 0.33	−0.19 ± 0.29	−0.52 ± 1.1

Mean activity onset time in hours after lights out ± SD.

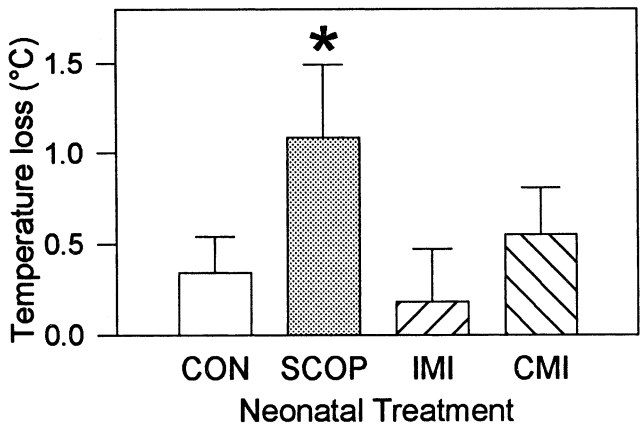

FIG. 2. Acute effect of oxotremorine on body temperature of hamsters treated as neonates with SCOP (scopolamine 3 mg/kg/day), IMI (imipramine 15 mg/kg/day), CMI (clomipramine 15 mg/kg/day), or CON (vehicle control). $*p < 0.05$ vs. vehicle control; n = 8–9/group.

function in SCOP-treated hamsters is presumably central, because the acute hypothermic effect of oxotremorine was observed following peripheral muscarinic blockade. The present results support previous reports that brief exposure of the developing brain to cholinergic agents can produce lasting functional alterations. For example, brief exposure of neonatal mice to cholinersterase inhibitors permanently decreases muscarinic cholinergic receptor density and increases spontaneous activity (1), and repeated injection of neonatal rats with SCOP significantly increased sexual behavior in adults (31).

Neonatal treatment with IMI did not affect any adult behavior in the present study, and the effects of CMI were weaker than SCOP. The small effect of CMI and IMI on hamster rhythms may be attributable to species differences or inadequate dosage. Unfortunately, development of skin lesions precluded higher antidepressant dose levels. Although previous studies with CMI in rats used a similar dose (15 mg/kg, once or twice/day) (16,19,32,37), recently Vogel et al. (35) reported that higher doses of CMI produce more consistent behavioral effects in rats, at the cost of increased mortality. Therefore, we cannot conclude from the present data that neonatal tricyclic treatment would not alter biological rhythms in hamsters.

Neonatal SCOP treatment may provide a model for human psychiatric disorders associated with increased cholinergic receptor sensitivity, comparable to the Flinders rat model and complementary to the monoamine receptor subsensitivity models utilizing neonatal treatment with tricyclic antidepressants. An increase in circadian amplitude and goodness-of-fit is problematic for an animal model of depression, however, because circadian rhythm amplitude is more often diminished in depression (21,24,28). However, increased amplitude may be a consistent finding in neonatal drug treatment models. Neonatal desmethylimipramine treatment reportedly increased cosinor amplitude of the circadian rhythm of drinking in rats (23). There is also evidence for an increased amplitude in the rhythm of REM sleep in neonatal CMI-treated rats in a 22°C environment, in which rats showed a significant decrease in REM sleep during the night, when REM pressure is usually lower, and an increase during the day (22). These data indicate that neonatal treatment of rodents with either SCOP or tricyclic antidepressants may not model the decreased rhythm amplitude reported in human affective disorders.

Cholinergic mechanisms have been implicated in the control of circadian rhythm entrainment by light and nonphotic stimuli. The suprachiasmatic nucleus, which is responsible for generation of mammalian circadian rhythms and their synchronization by environmental cues, receives cholinergic afferents from both brainstem and basal forebrain (4). Cholinergic agonists, including nicotine and the selective M1 muscarinic receptor agonist, McN-A-343, have been reported to shift the phase of neuronal activity in explanted SCN slices (15,30). Cholinergic antagonists can prevent effects of light on the SCN system, blocking light-induced phase shifts and c-*fos* expression in the SCN (41). Therefore, it might be predicted that upregulation of cholinergic receptors would be associated with increased sensitivity of the SCN system to effects of light. This interpretation would be consistent with an increased day–night difference in behavior, as reflected in an increased amplitude of entrained rhythms. However, this reasoning would predict that SCOP-treated would be more sensitive than controls to the behavior-suppressing effects of constant light. If anything, our data show that SCOP-treated hamsters are less sensitive to the amplitude-suppressing effects of light, because SCOP-treated hamsters show larger rhythm amplitudes than controls in constant light. Furthermore, the phase of light-synchronized rhythms was not significantly affected by neonatal SCOP treatment. Therefore, these data suggest that cholinergic afferents sensitive to neonatal SCOP treatment may influence the amplitude of circadian oscillators by a mechanism independent of entrainment by light.

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