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Effects of Neonatally Administered Iprindole on Adult Behaviors of Rats

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VOGEL, G. AND M. HAGLER. *Effects of neonatally administered iprindole on adult behaviors of rats.* PHARMACOL BIOCHEM BEHAV **55**(1) 157–161, 1996.—In past studies, administration of the antidepressant drugs clorimipramine, zimeldine, or desipramine to neonatal rats produced abnormalities in adult rats that modeled some behavioral and/or REM sleep features of human endogenous depression. Although these three drugs affected different neurotransmitter systems, all caused REM sleep deprivation (RSD). This suggested the hypothesis that RSD of neonatal rats caused their adult depression. One prediction of this hypothesis is that neonatally administered iprindole, an antidepressant drug that does not produce RSD, will not produce adult rats that model depression. The present study tested this hypothesis. Iprindole was administered to neonatal experimental rats and saline was administered to neonatal control rats. When the rats matured, compared with control rats, experimental rats were not significantly different in aggressive behavior (shock induced fighting), sexual behaviors, open field locomotion, and REM sleep. In our previous studies on rats, all these adult behaviors were affected in a depressive-like way by neonatally administered clorimipramine. Because iprindole does not decrease REM sleep, the present results support the hypothesis that in rats neonatal RSD causes adult depression.

Rat depression model Iprindole Neonatally administered iprindole REM sleep Deprivation

CLORIMIPRAMINE, administered daily for 2 weeks to neonatal rats (CLI rats), produced behavioral and REM sleep abnormalities in adult animals. The abnormalities were similar to features of human endogenous depression (29,34). Behaviorally, compared with control rats that were treated neonatally with saline (SAL rats), adult CLI rats showed—like patients with endogenous depression (29)—decreased aggressive (28), sexual (15,21,26), and pleasure-seeking (intracranial self-stimulating) activities (30). Like other animal models of depression, CLI rats showed increased immobility in the forced swim test (22). In their sleep characteristics, compared with SAL rats, adult CLI rats showed—like patients with endogenous depression (2,4,10,32,35), increased long periods of wakefulness, increased REM sleep percent, decreased REM latency, and after REM sleep deprivation, an abnormal temporal course of REM rebound in the presence of a normal total REM rebound (31). The response of the sexual and aggressive deficiencies of CLI rats to antidepressant treatments was tested (27,29). Each improved with imipramine and in preliminary studies each improved with REM sleep deprivation (RSD) by arousals. Finally, the course of the CLI rat disorder resembled the course of human endogenous depression (29). After a grossly normal development, when CLI rats matured, the disorder began spontaneously without an external or stressful precipitant, persisted for months, and then, according to preliminary observations, began to remit spontaneously. These features—particularly the autonomous course that was independent of life events (9,11,17) and the REM sleep abnormalities that are more characteristic of endogenous depression than reactive depression (4)—suggest that the adult CLI rat depression resembles human endogenous depression rather than reactive depression, which is resembled by stress induced animal models of depression (19,36).

At present, the processes that mediate the adult depressive features caused by neonatally administered CLI are unknown.

One hypothesis is that neonatally administered CLI caused long-term changes in 5-HT neurotransmission, which led to the depressive features (29). This hypothesis is supported by pharmacological evidence that CLI is a potent blocker of 5-HT reuptake (16). Also, in adult CLI rats, the firing rate of 5-HT neurons in the dorsal raphe nucleus was significantly less than in control adult SAL rats (37). However, the 5-HT

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hypothesis does not easily explain two other findings. First, clorimipramine and its desmethyl metabolite also block presynaptic reuptake of noradrenaline with a potency near the effect of clorimipramine on 5-HT reuptake (16). Second, neonatal administration of desipramine, which preferentially blocks reuptake of noradrenaline (16), can cause some depression like symptoms in adult rats (8). These findings indicate that a change in 5-HT neurotransmission—or in any one neurotransmitter—is unlikely to be a necessary mediator of the adult depressive disorder.

Another hypothesis is that neonatal REM sleep deprivation (RSD) by CLI caused the delayed depressant effect. CLI is a potent REM sleep suppressant (13,14,25). Two other antidepressant drugs (desipramine and zimeldine) administered to neonatal rats have also produced some features of depression in adult rats (8)—although all effects of neonatal CLI (behavioral, REM sleep, and treatment responses) have not been tested. To the best of our knowledge, nonantidepressant drugs, administered to neonates, have not produced depressive features in adult animals (21). Like clorimipramine, desipramine and zimeldine are antidepressants that produce large RSD (25). Thus, neonatal RSD is a common effect of the three antidepressant drugs. This has suggested to several investigators the hypothesis that neonatal RSD is the common mediator of the delayed depressive effects of antidepressant drugs (13,14,29).

Iprindole is a drug with two pharmacological properties that are relevant to the neonatal RSD hypothesis. First, although an early review questioned the antidepressant efficacy of iprindole in the treatment of endogenous depression (38), a later, more comprehensive review concluded that iprindole was as efficacious as imipramine and amitriptyline, the standard antidepressant drugs, in the treatment of major depressions, including endogenous depression (5). Second, iprindole does not suppress REM sleep (1,25). Iprindole, then, is an antidepressant drug that does not suppress REM sleep. Hence, the hypothesis that neonatal RSD mediates the later depressive effect of neonatally administered antidepressant drugs predicts that neonatally administered iprindole will have no delayed depressive effects. The present study tested this prediction in rats by determining the effects of neonatally administered iprindole on their adult sexual behavior, open field activity, aggression, and REM sleep.

METHOD

Details of the rearing and crossfostering of Sprague–Dawley have been previously described (28). Male rats were treated from age 8 days through age 21 days. Forty-four experimental rats received iprindole 15 mg/kg SC twice daily (IPRIN rats) and 39 control rats received equivolume saline in the same schedule (SAL rats). Rats were weaned at age 1 month, raised with individual housing on a reverse 12 L:12 D schedule. This treatment protocol was the same as that used in previous studies of the effect of neonatally administered clorimipramine on adult behaviors. In those studies the dose of neonatal clorimipramine was 15 mg/kg twice daily, the same as the dose of neonatal iprindole used in the present study. Because the human antidepressant dose range of clorimipramine (100–250 mg/day) is greater than that of iprindole (30–120 mg/day) (25), administration of the same doses (15 mg/kg) of iprindole and CLI to neonatal rats meant that iprindole-treated rats received a greater antidepressant dose of their drug than did the CLI-treated rats.

At age 3 months aggression was tested by the shock-induced fighting procedure. Details of the method have been published elsewhere (28). Briefly, 10 pairs of rats, each pair consisting of one IPRIN rat and one SAL rat, fought in response to randomly delivered intermittent foot shock. Observers blind to neonatal treatment recorded number of offensive and defensive behaviors of each rat (28).

TABLE 1

EFFECT OF NEONATAL IPRINDOLE ON SHOCK INDUCED FIGHTING

	IPR $n = 10$	SAL $n = 10$	p
Offensive behaviors	6.5 ± 1.6	5.1 ± 1.6	NS
Defensive behaviors	5.4 ± 1.6	6.5 ± 1.6	NS
Difference (off-def)	1.1 ± 2.3	−1.4 ± 2.3	NS

Each entry is a mean ± standard error of mean. Probability was determined by a two-factor (treatment and day) ANOVA with day as a repeated measure. NS = $p > 0.10$.

At age 4 months 40 other rats (20 IPRIN and 20 SAL) were tested for motoric activity in a circular open field chamber with its floor marked into grid-like sectors. Details of the procedure have been published elsewhere (7). The open field tests were conducted on 5 consecutive days, each test lasting 2 min. Observers, blind to neonatal treatment, counted the number and location of sectors entered by a rat during its 2-min test sessions.

At age 4 months 23 other rats (14 IPRIN and 9 SAL) were tested for sexual behavior on three occasions. The tests were conducted every other day and consisted of 30-min test sessions with a receptive female. Details of the procedure have been published elsewhere (15). Observers blind to neonatal treatment counted number of mounts, intromissions, and ejaculations; and measured latency to first mount, latency to first ejaculation, and latency to mount after first ejaculation (post ejaculatory interval).

At age 5–6 months seven IPRIN rats and seven SAL rats that had been tested for open-field locomotion, had polysomnographic (PSG) recordings to measure sleep–wake state. Details of the procedure have been published elsewhere (31). Briefly, at least 1 week after standard implants for recording (3), PSG recordings were made 24 h/day for 4 consecutive baseline days. Then rats were REM sleep deprived by the small pedestal method for 4 days. No PSG recordings were made during pedestal time. PSG recordings were then made during the first recovery day off the pedestal—a day to measure REM rebound. Coded PSG records were scored according to standard criteria by technicians blind to neonatal treatment (3).

In this study, procedures for rearing and crossfostering rats, and for testing aggression, locomotor activity, sexual behavior, and PSG sleep were the same as those used in our previous studies of the effects of neonatally administered CLI on adult behaviors (7,15,28,31).

In the statistical analysis of results, central tendency and variability were calculated as mean ± standard error of the mean. Experimental–control differences in behaviors were evaluated statistically by a repeat measure ANOVA with day as repeat measure.

RESULTS

Aggression

Ten pairs of rats, each consisting of one iprindole (IPRIN) rat and one SAL rat, were observed during shock induced fighting. Results are shown in Table 1. IPRIN and SAL rats

TABLE 2

EFFECT OF NEONATAL IPRINDOLE ON OPEN FIELD LOCOMOTION

	IPR $n = 20$	SAL $n = 20$	p
Total sectors	26 ± 3.1	28 ± 3.6	NS
Outer sectors	23 ± 2.9	25 ± 3.3	NS
Middle sectors	3 ± 0.6	3 ± 0.6	NS
Inner sectors	0.3 ± 0.1	0.3 ± 0.2	NS
Rearing	6 ± 1.0	7 ± 0.9	NS
Boli	0.02 ± 0.03	0.2 ± 0.16	0.03

Each entry is a mean ± standard error of mean. Probability was determined by a two-factor (treatment and day) ANOVA with day as a repeated measure. NS = $p > 0.10$.

were not significantly different in any measure of aggression. The measures included offensive behaviors, defensive behaviors, and the difference between number of offensive and number of defensive movements.

Locomotion

Nineteen IPRIN rats and 20 SAL rats (that had not been tested for aggression) were observed in the circular open-field apparatus. Results are shown in Table 2. IPRIN and SAL rats were not significantly different in any measure of open-field locomotion. The measures included total sectors entered, number of outer sectors entered, number of middle sectors entered, and number of inner sectors entered. Grooming time was not significantly different in IPRIN and SAL rats. However, SAL rats had significantly more fecal boli than IPRIN rats.

Sexual Behavior

Fourteen male IPRIN rats and nine male SAL rats (all sexually naive and not tested for other behaviors) were observed during sexual activity. Results are shown in Table 3. IPRIN and SAL rats were not significantly different in any measure of male sexual behavior, including numbers of mounts, intromissions, and ejaculations; and latencies to first mount, first ejaculation, and next mount.

Sleep

Seven IPRIN and seven SAL rats that had been observed in the open-field study were implanted with electrodes for standard polygraphic recordings of sleep–wake states during baseline before REM sleep deprivation and during one recovery day after 4 days of small pedestal REM sleep deprivation. Results are shown in Table 4. IPRIN and SAL rats were not significantly different in any sleep variable before or after REM sleep deprivation. The sleep variables included total sleep time, REM sleep time, REM sleep percent and REM latency.

TABLE 3

EFFECT OF NEONATAL IPRINDOLE ON SEXUAL BEHAVIOR

	IPR $n = 14$	SAL $n = 9$	p
Mounts	20 ± 3.7	24 ± 4.4	NS
Intromissions	10 ± 1.7	9 ± 1.5	NS
Ejaculations	2 ± 0.3	2 ± 0.3	NS
Mount latency (s)	392 ± 170	195 ± 117	NS
Ejac latency (s)	757 ± 165	736 ± 175	NS
Postejac latency (s)	714 ± 194	563 ± 201	NS

Each entry is a mean ± standard error of mean. Probability was determined a two-factor (treatment and day) ANOVA with day as a repeated measure. NS = $p > 0.10$.

TABLE 4

EFFECT OF NEONATAL IPRINDOLE ON SLEEP (24 h)

	IPR $n = 7$	SAL $n = 7$	p
Baseline			
Sleep time (min)	840 ± 28	834 ± 19	NS
REM (min)	84 ± 5	85 ± 3	NS
REM %	10 ± 0.6	10 ± 0.3	NS
REM latency (min)	7.0 ± 0.3	6.3 ± 0.4	NS
Post REM deprivation			
Sleep time (min)	911 ± 21	888 ± 28	NS
REM (min)	219 ± 16	200 ± 31	NS
REM %	24 ± 1.6	22 ± 2.9	NS
REM latency (min)	5.7 ± 0.2	5.6 ± 0.2	NS

Each entry is a mean ± standard error of mean. Probability was determined by a two-factor (treatment and day) ANOVA with day as a repeated measure. NS = $p > 0.10$.

DISCUSSION

We found no significant differences between IPRIN and SAL rats in measures of aggression, open-field locomotion, male sexual behavior, and sleep states. By contrast, in previous studies, compared with SAL rats, CLI rats had decreased aggressive (28) and sexual (15) activities, increased open-field locomotion in some (7,12,13) but not all studies (6,14,24), and increased REM sleep, decreased REM latency, and increased long periods of wakefulness (31). Because the present study used the same procedures as our earlier studies of effects of neonatal CLI, methodological changes cannot explain the absence of effects by iprindole compared with the presence of effects by clorimipramine. Also, two considerations make it unlikely that the neonatal dose of iprindole was too low to change the tested adult behaviors. First, although the maximum antidepressant dose of iprindole (120 mg) is less than the maximum antidepressant dose of CLI (250 mg), the present study found that neonatally administered iprindole (15 mg/kg twice daily) produced none of the adult behavioral abnormalities produced by the same dose of neonatally administered CLI (15 mg/kg twice daily) (7,14,28,31). Second, effects of neonatally administered CLI on adult behavior appear to be dose related (26). This suggests that if a neonatally administered drug like iprindole were effective in producing adult depression-like symptoms, a low dose should produce small, though possibly statistically insignificant effects. We found no hint of behavior differences between IPRIN and SAL rats.

We conclude that neonatally administered IPRIN did not produce depressive features in adult rats. IPRIN is a drug that does not suppress REM sleep (1,25). In contrast, the three antidepressant drugs whose neonatal administration produced depressive-like behavior in adult rats (CLI, desipramine, and zimeldine) have the common effect of suppressing REM sleep (25) but affect different neurotransmitter systems (16). These

findings are consistent with the hypothesis that neonatal REM sleep deprivation is the common mediator of the delayed depressive effect produced by the different neonatally administered antidepressant drugs.

Recently, this hypothesis has been challenged by the finding that scopolamine, administered daily for 2 weeks to neonatal rats, did not produce depressive-like behaviors when the rats matured (21). The challenge arose because it was hypothesized that the neonatally administered scopolamine produced RSD for 2 weeks. Unfortunately, REM sleep was not monitored and measured in this study. However, the scolpolamine-RSD hypothesis is not consistent with evidence that tolerance to the REM suppressant effects of daily scopolamine develops in less than a week (18,20); and the scopolamine dose used in the neonatal study was about one-third of a dose that did not produce sustained RSD in rats (20). Thus, rather than refuting the hypothesis that neonatal RSD mediates the adult depressive features, the failure of neonatally administered scopolamine to produce adult depressive features, was consistent with that hypothesis.

The present findings also bear on the paradox that some drugs have both depressant and antidepressant effects. A parsimonious hypothesis about the paradox is that a single effect of the drug, viz RSD, has depressant or antidepressant properties. The difference in outcomes depends, not on the drug, but on an unknown response characteristic that changes during brain development from immaturity to maturity. Evidence that RSD mediates the depressant effect of neonatally administered antidepressant drugs has been found in the present study and briefly reviewed above. Evidence that RSD mediates the adult antidepressant effects of most antidepressant drugs has been reviewed elsewhere (23,25) and is briefly summarized here. Because RSD by arousals improved endogenous depression (33), a similar RSD by drugs may improve endogenous depression. The salient characteristics of RSD by arousals are that it is a large and persistent (over weeks) RSD that is followed by REM rebound (33). Drug RSD with these three characteristics is called arousal type RSD. In a recent review, 22 of 25 antidepressant drugs produced arousal type RSD, and all 45 psychotropic drugs without antidepressant activity did not produce arousal type RSD (25). The latter included, among other drugs, barbiturates, benzodiazepines, cholinergic agonists and antagonists, ethanol, and narcotics. Some of these drugs did decrease REM sleep but their RSD was not large (e.g., benzodiazepines) or not persistent (e.g., barbiturates, cholinergic agonists, narcotics) or without REM rebound (e.g., benzodiazepines, barbiturates) (25). The improvement of endogenous depression by antidepressant drugs had the same efficacy (33), time course (33), and REM sleep correlates (23) as improvement by RSD via arousals. Patients unimproved by RSD via arousals were not improved by imipramine (33). In animals, RSD via arousals produced behavioral changes (increased aggressive, sexual, eating, pleasure-seeking activities) that were opposite to the behavioral changes of human endogenous depression (23). Although the hypothesis that antidepressant drugs improve depression by RSD is not disproved by finding a few antidepressant drugs that do not produce RSD (because these exceptions may work by a process other than RSD), the RSD hypothesis is falsifiable. The hypothesis would be disproved by finding a drug that produced arousal type RSD and did not improve endogenous depression. No such drug has been found (25). Thus, several lines of evidence support the view that both the depressant and antidepressant activities of most antidepressant drugs are mediated by RSD.

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