Pharmacology Biochemistry & Behavior, Vol 28, pp 367–369 © Pergamon Journals Ltd , 1987 Printed in the U S A 0091-3057/87 $3 00 + 00

Increased Adult Behavioral 'Despair' in Rats Neonatally Exposed to Desipramine or Zimeldine: An Animal Model of Depression?

LEENA A HILAKIVI AND ILKKA HILAKIVI

Department of Physiology, University of Helsinki
Siltavuorenpenger 20, SF-00170 Helsinki, Finland

Received 23 January 1987

HILAKIVI, L A AND I HILAKIVI *Increased adult behavioral 'despair' in rats neonatally exposed to desipramine or zimeldine An animal model of depression?* PHARMACOL BIOCHEM BEHAV **28**(3) 367–369, 1987 —Occurrence of depressive behavior at mature age was studied in rats exposed neonatally to antidepressant drugs Early antidepressant treatments have been shown to increase voluntary alcohol consumption and the percentage of rapid-eye-movement (REM) sleep relative to total sleep time in adult rats as well as to cause long-lasting reduction in the concentrations of monoamines in the forebrain In the present study rats were daily given either 5 mg/kg desipramine or 25 mg/kg zimeldine from the 7th to the 18th postnatal days When they were 2 months and 5 months of age behavioral 'despair' was studied by using a modified version of Porsolt's swim-test At both ages the desipramine-treated and zimeldine-treated rats expressed lengthened immobility times in the water pail The findings indicate that neonatal exposure of rats to desipramine or zimeldine induces behavioral 'despair' at mature age Thus, early exposure of rats to antidepressants causes long-lasting behavioral disorders, and, moreover, may be used to devise an animal model of subsequent depression

Newborn rats Desipramine Zimeldine Behavioral 'despair'

VOLUNTARY alcohol consumption increases in rats which have been exposed to antidepressant drugs during the neonatal period [6,7]. In addition, these treatments reduce the neonatal amounts of rapid-eye-movement (REM) sleep [7,12], increase the percentage of adult REM sleep relative to total sleep time [12] and cause long-lasting alterations in the forebrain concentrations of monoamines [7] In the present study, we examined the possible association between neonatal antidepressant exposure and adult depressive behavior

In humans, depression is characterized by shortened REM sleep latency [2] and total sleep time [5] Moreover, altered monoaminergic function is related to depression [1,8]. Several clinical investigations suggest that human depression is associated with alcoholism [14,19] It is not known, however, whether excessive alcohol consumption causes the depressive symptoms [10] or whether a person who is depressed turns to alcohol as a form of self-medication [14] These two relatively frequent diseases may also occur in the same person by chance alone [11]

In this study neonatal rats were treated chronically with desipramine or zimeldine Desipramine is a monoamine uptake inhibitor with preferential affinity on norepinephrine [13] and zimeldine inhibits preferentially the uptake of serotonin [17]. Behavioral 'despair' was studied by using a modified version of Porsolt's swim-test [16,18].

METHOD

Subjects

Eighteen male, newborn rats of Wistar strain (supplied by University of Kuopio, Finland) served as subjects. The desipramine and zimeldine rats were housed in four cages containing 4–6 males, 5–6 females and a nursing mother. The cages were maintained under a 12-hr light-dark (lights on 6 00 a m.–6 00 p.m) illumination cycle, at a temperature of 22–24°C and a relative humidity of about 50%. Non-suckling animals had free access to standard food (powdered R3 rat diet, Astra Ewos, Sweden). After weaning at the age of 25 days, the rats were housed in group cages with six rats in each.

Neonatal Drug Exposure

Antidepressant drugs were administered to pups from the 7th to the 18th postnatal days. Seven male rat pups were injected IP with 5 mg/kg desipramine (0.2 w/v) (Ciba Geigy), eight male pups with 25 mg/kg zimeldine hydrochloride (1.0 w/v) (Astra Lakemedel), and seven male pups with the corresponding amount of 0.9% sodium chloride. Each of the cages contained pups from all three treatment groups; a color code was used to identify the animals. All injections were given between 10–11 a.m

TABLE 1

EFFECT OF NEONATAL DESIPRAMINE AND ZIMELDINE EXPOSURES ON THE TOTAL DURATION OF IMMOBILITY DURING A 10 MIN SWIM-TEST (57-DAY-OLD RATS) AND TWO 5 MIN SWIM-TESTS (58- AND 153-DAY-OLD RATS)

Neonatal Exposure	n	Immobility Time (sec) 57-Day-Old Rats	58-Day-Old Rats	153-Day-Old Rats
Sodium chloride	6	118 3 ± 61 3	47 8 ± 26 0	63 5 ± 34 1
Desipramine	6	184 2 ± 42 9†	93 0 ± 23 4‡	107 2 ± 21 3†
Zimeldine	6	203 5 ± 67 8†	95 8 ± 27 1†	89 3 ± 31 3*

Means ± S D are given Statistically significant differences (Mann-Whitney U-test) *$p<0$ 1, †$p<0$ 05, ‡$p<0$ 01

Porsolt's Swim-Test

Behavioral 'despair' of the desipramine-treated and zimeldine-treated rats was tested with the Porsolt's swim-test at the ages of two and five months [16] Six rats from the desipramine, zimeldine and control groups were used. A rat was placed in a plastic pail (height 51 cm, diameter 40 cm) containing 17 cm of water maintained at 29°C. After 10 min in the cylinder the rat was removed and allowed to dry for 15 min in a heated enclosure (30°C) before being returned to its cage The rat was replaced into the pail 24 hr later and the swimming behavior was measured for 5 min Three months later, the rats were again tested in the water pail for 5 min During the measurement periods, the length of time for which a rat had floated passively in the water, making only small movements to keep its head above water, was measured.

The original Porsolt's swim-test was modified by raising the water temperature by 4°C and by increasing the diameter of the pail by 22 cm This was done in order to make the test more sensitive in the detection of changes in immobility times, the control rats of our study were immobile for 1 0±0 5 min instead of the 4 min generally seen in this test during the 5 min observation period [16]

The Porsolt's swim-test was done in a noise-attenuated room (10 m^2), the degree of illumination of which was about 200 lux at floor level The test took place between 10 a m. and 3 p.m The test was done blindly, so that the investigator observing the behavior of the rats knew nothing about their neonatal treatments

RESULTS

During the first test day at the age of 57 days, the immobility time in the water pail of the desipramine and zimeldine rats was almost twice as long as that of the control rats (Kruskal-Wallis one-way analysis of variance, $df=2$, $H=6.44$, $p<0.05$) (Table 1) The same was true during the second day, when the rats were observed for 5 min. the desipramine and the zimeldine rats spent more time floating in the water than the controls ($H=6$ 84, $p<0$ 05) (Table 1) At the age of 153 days the desipramine-treated rats were still immobile for a longer time than the controls, and the zimeldine rats tended to do so ($H=4.60$, $p<0$ 1)

DISCUSSION

Our major finding, which was that rats treated neonatally with desipramine or zimeldine are immobile for a longer period in the water pail than the controls, suggests that early antidepressant exposure is related to a later increase in behavioral 'despair ' Previous findings of a change in the percentage of REM sleep [12], reduced monoamine concentrations in the forebrain [7] and increased voluntary alcohol consumption [6,7]—all of which may be linked to depression—after neonatal antidepressant exposure further support the relation between early antidepressant administration and later depressive behavior

In adult rats, chronic exposure to antidepressant drugs shortens the period of immobility in the water pail [15] The difference in the effect of neonatal or adult antidepressant exposure on adult behavioral 'despair' may be due to alterations in the function of cerebral monoaminergic systems In adult rats, chronic treatments with desipramine and zimeldine reduce the forebrain concentration of MHPG, a metabolite of norepinephrine, and HVA, a metabolite of dopamine, as well as increase the concentration of serotonin [9] Early postnatal exposure to these drugs causes a long-lasting elevation in the concentration of MHPG and a reduction in that of dopamine, serotonin and its metabolite 5-HIAA in the forebrain [7]

Both the present and several previous findings indicate that perinatal antidepressant administration leads to severe neurotoxicological consequences, the best known of which are changes of certain components of open field behavior [2,12] Open field behavior is a measure of emotionality in rats [3] We found here that neonatal exposure to desipramine and zimeldine increases behavioral 'despair' at adulthood, and earlier these exposures have been shown to later increase voluntary alcohol consumption [6,7] and cause long-lasting reductions in the concentrations of monoamines in the brain [7] Therefore, neonatal antidepressant treatment may specifically affect the subsequent emotionality of rats, and moreover, serve as a new animal model of depression

ACKNOWLEDGEMENTS

The work was supported by the Academy of Finland and by grants from the Finnish Foundation for Culture and the Finnish Foundation for Alcohol Studies

REFERENCES

1 Åsberg, M , P Thoren and L Traskman "Serotonin depression"—a biochemical subgroup within the affective disorders? *Science* **191:** 479–480, 1976
2 Coble, P A , D J Kupfer and D H Shaw Distribution of REM latency in depression *Biol Psychiatry* **16:** 453–464, 1981
3 Cuomo, V , I Cortese, R Cagiano, G Renna and G Racagni Behavioral changes in rats after prenatal administration of typical and atypical antidepressants In *Disease, Metabolism and Reproduction in the Toxic Response to Drugs and Other Chemicals*, edited by P L Chambers, P Preziosi and C M Chambers *Archives of Toxicology*, Suppl 7 Berlin Springer-Verlag, 1984, pp 504–507
4 Denenberg, V H Open-field behavior in the rat what does it mean? *Ann NY Acad Sci* **159:** 852–859, 1969
5 Galuszko, P , Z Nowicki, J Jakitowicz, J Landowski and Z Wontrobski Clinical state and sleep patterns in patients with depression In *Sleep '84*, edited by W P Koella, E Ruther and H Schulz Stuttgart Gustav Fischer Verlag, 1985, pp 449–450
6 Hilakivi, L , J D Sinclair and I Hilakivi Effect of neonatal treatment with clomipramine on adult alcohol related behavior in the rat *Dev Brain Res* **15:** 129–132, 1984
7 Hilakivi, L , D Stenberg, J D Sinclair and K Kiianmaa Neonatal desipramine or zimeldine treatment causes long-lasting changes in brain monoaminergic systems and alcohol related behavior in rats *Psychopharmacology (Berlin)* **91:** 403–409, 1987
8 Hornykiewicz, O Imbalance of brain monoamines and clinical disorders In *Chemical Transmission in the Brain*, edited by R M Buijs, P Pevet and D F Swaab *Progress in Brain Research*, vol 55 Amsterdam Elsevier Medical, 1982, pp 419–429
9 Karoum, F , E Korpi, M Linnoila, L -W Chuang and J Wyatt Reduced metabolism and turnover rates of rat brain dopamine, norepinephrine and serotonin by chronic desipramine and zimeldine treatments *Eur J Pharmacol* **100:** 137–144, 1984
10 Madden, J S Psychiatric advances in the understanding and treatment of alcohol dependence *Alcohol Alcohol* **19:** 339–353, 1984
11 Merikangas, K R , M M Weissman, B A Prusoff, D L Pauls and J F Leckman Depressiveness with secondary alcoholism psychiatric disorders in offspring *J Stud Alcohol* **46:** 199–204, 1985
12 Mirmiran, M , N van de Poll, M Corner, H van Oyen and H. Bour Suppression of active sleep by chronic treatment with chlorimipramine during early postnatal development effects upon adult sleep and behavior in the rat *Brain Res* **204:** 129–146, 1981
13 Nielsen, M and C Braestrup Chronic treatment with desipramine caused a significant decrease in 3,4-dihydroxyphenylglykol-sulphate and total 3-methyl-4-hydroxyphenylglykol in the rat brain *Naunyn Schmiedebergs Arch Pharmacol* **300:** 87–92, 1977
14 O'Sullivan, K Depression and its treatment in alcoholics a review *Can J Psychiatry* **29:** 379–384, 1984
15 Porsolt, R D , A Bertin, N Blavet, M Deniel and M Jalfre Immobility induced by forced swimming in rats effects of agents which modify central catecholamine and serotonin activity *Eur J Pharmacol* **57:** 201–210, 1979
16 Porsolt, R D , M Le Pichon and M Jalfre Depression a new animal model sensitive to antidepressant treatments *Nature* **266:** 730–732, 1977
17 Ross, S B , S O Ogren and A L Renyi (Z) Dimethylamino-1(4-bromophenyl)-1-(3-pyridyl) propene (H102/09), a new selective inhibitor of the neuronal 5-hydroxytryptamine uptake *Acta Pharmacol Toxicol* **39:** 152–166, 1975
18 Willner, P The validity of animal model of depression *Psychopharmacology (Berlin)* **83:** 1–16, 1984
19 Winokur, G Alcoholism and depression *Subst Alcohol Actions Misuse* **4:** 111–119, 1983