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ANTAGONISM OF ANALGESIA BY *p-CYCLO*HEXYLOXY-α-PHENYLETHYLALLYLAMINE AND SOME OBSERVATIONS ON HYPERALGESIA

BY

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WITH AN ADDENDUM BY D. M. ZAUSMER*

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Nalorphine (*N*-allylnormorphine) appears to have little analgesic activity in man (Wikler, 1951). The *N*-allyl derivatives of normorphine, norcodeine, and 3-hydroxy-morphinan, however, antagonize morphine-like activity (Pohl, 1915 ; Unna, 1943; Hart and McCawley, 1944; Fromherz and Pellmont, 1952). Nalorphine also exacerbates—and can precipitate—the morphine abstinence syndrome in addiction (Isbell and Fraser, 1950 ; Wikler, 1952; Irwin and Seevers, 1952), and antagonizes the morphine-like properties of methadone and pethidine (Huggins, Glass, and Bryan, 1950; Radoff and Huggins, 1951; Huggins, 1951; Benson, O'Gara, and van Winkle, 1952; Smith, Lehman, and Gilfillan, 1951). It seemed that the morphine-like properties of *p-cyclo*hexyloxy-α-phenylethylamine (McCoubrey, 1953) might be antagonized by its *N*-allyl derivative. This expectation was realized in the measures of antagonism used—reduction in analgesic activity and elevation of the LD50. The frequent occurrence of hyperalgesia† has prompted the assembling of records of similar responses with other phenylethylamines.

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† The term "hyperalgesia" is used for the sake of uniformity. Here it indicates hyperreflexia in assays which measure algesia by effects on certain reflexes.

METHODS

All drugs, except nalorphine hydrobromide, were given intraperitoneally as hydrochlorides. The structures of new amines and their LD50's in mice are given in Table I. Doses for albino rats were 20 mg./kg. unless stated otherwise. Analgesic assays in groups of six to eight albino rats were those of Thorp (1946), measuring changes in reaction threshold, or of D'Amour and Smith (1941), measuring changes in reaction time, of the blacked tip of a rat's tail to a radiant heat stimulus. The comparative analgesic assays in two similar groups of rats, one group pretreated with saline and one with antagonist, were completed on the same day. The average reaction times of the groups were determined before, and at intervals during one hour after, the dose of analgesic. To avoid burning the tail, reaction times of 30 sec. were taken as maximal. Comparative LD50's in two similar groups of 30 albino mice, one group pretreated with saline and one with antagonist, were completed on the same day using 10 mice per dose-level of "toxic" drug. LD50's were calculated by using probits.

RESULTS

Properties of p-Cyclo*hexyloxy-α-phenylethylallylamine*

Acute Toxicity.—Table II shows that pretreatment of mice with *p-cyclo*hexyloxy-α-phenyl-

TABLE I

STRUCTURE AND ACUTE TOXICITY IN MICE OF SUBSTITUTED α-PHENYLETHYLAMINES

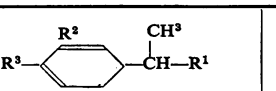
Drug				Intraperitoneal LD50 (mg./kg.) (Limits of Confidence, P = 0·05, in parentheses)
	R^1	R^2	R^3	
*p-Cyclo*hexyloxy-α-phenylethylallylamine	NHC_3H_5	H	OC_6H_{11}	164 (161–167)
α-(3-*Cyclo*hexyloxy-4-hydroxyphenyl)ethyldimethylamine	NMe_2	OC_6H_{11}	OH	146 (103–185)
α-(*p*-Phenoxyphenyl)ethyldimethylamine	NMe_2	H	OC_6H_5	91 (89–93)
α-(*p*-Phenoxyphenyl)ethyldiethylamine	NEt_2	H	OC_6H_5	92 (89–95)

TABLE II

THE ACUTE TOXICITY OF α-PHENYLETHYLAMINES IN MICE AFTER PRETREATMENT WITH RELATED DRUGS

Pretreatment			Test Drug	Intraperitoneal LD50 (mg./kg.) (Limits of Confidence, P=0·05, in parentheses)	
Drug	Dose mg./kg.	Interval before Test		With Antagonist	With Saline
Nalorphine HBr	45	10 min.	*p-Cyclo*hexyloxy-α-phenylethylamine	155 (151–158)	170 (166–174)
*p-Cyclo*hexyloxy-α-phenylethylallylamine HCl	50	24 hr.	*p-Cyclo*hexyloxy-α-phenylethylamine	190 (185–194)	169 (158–170)
*p-Cyclo*hexyloxy-α-phenylethylallylamine HCl	50	24 hr.	*p-Iso*propyloxy-α-phenylethylamine ..	208 (202–214)	206 (197–215)
Dibenamine HCl	20	48 hr.	*p-Cyclo*hexyloxy-α-phenylethylamine	210 (202–218)	205 (199–211)

ethylallylamine (the " *N*-allylamine ") (50 mg./kg.) elevated the LD50 of *p-cyclo*hexyloxy-α-phenylethylamine, but had no influence on that of the non-analgesic *p-iso*propyloxy-α-phenylethylamine. Conversely, nalorphine (45 mg./kg.) slightly reduced the LD50, whereas dibenamine had no effect. No significant difference was found in the slopes of the regression lines; nor was there any discernible difference, between any one pair of saline and drug pretreated groups, in the pattern of toxic symptoms. The survivors of the group pretreated with the *N*-allylamine, however, had not recovered in twelve hours from the toxic effects of *p-cyclo*hexyloxy-α-phenylethylamine as had the saline controls.

Analgesic Activity.—The analgesic effect of *p-cyclo*hexyloxy-α-phenylethylamine was antagonized by pretreatment with either dibenamine or the *N*-allylamine. Nalorphine had rather less effect under the conditions used (Table III). The action of the *N*-allylamine was prolonged, though slow in onset. If given 5 min. before the analgesic, slight antagonism was evident, but this became complete for the dose of analgesic used if the rats were pretreated the day before the test. Morphine (10 mg./kg.) was also completely antagonized, and the effect of a larger dose (20 mg./kg.) was reduced but not abolished. The antagonistic effect of one dose persisted for one to three weeks. Nalorphine given 10 min. beforehand completely antagonized morphine (10 mg./kg.), but the antagonism did not persist more than a few hours.

The *N*-allylamine itself was as effective as the parent amine in causing a brief prostration in rats, but it produced both analgesic and hyperalgesic responses. In a total of 35 rats, six showed slight

TABLE III

THE INFLUENCE OF ANALGESIC ANTAGONISTS ON THE ANALGESIC ACTIVITY OF MORPHINE AND *p-CYCLO*HEXYLOXY-α-PHENYLETHYLAMINE

Two similar groups of six rats received drugs intraperitoneally. Average preinjection reaction times and maximum change (time in min. in parentheses) are recorded.

Antagonist			Analgesic		Average Reaction Time (sec.)±S.D.			
					With Saline		With Antagonist	
	Dose mg./kg.	Time Interval Before Test Drug		Dose mg./kg.	At Time 0	Max. Change	At Time 0	Max. Change
Nalorphine	20	5 min.	*p-Cyclo*hexyloxy-α-phenylethylamine	20	10·0±2·3	21·0±1·2 (15)	10·7±1·8	15·3±9·0 (15)
„	20	10 min.	Morphine	10	11·0±2·0	23·2±8·2 (30)	9·3±1·3	12·7±3·2 (15)
		24 hr.	„	10			7·8±0·9	19·5±6·5 (30)
*p-Cyclo*hexyloxy-α-phenylethylallylamine	30	48 hr.	Morphine	20	8·7±1·0	24* (60)	8·8±1·3	17·2±5·3 (30)
		96 hr.	„	10			9·0±0·8	11·3±3·2 (60)
*p-Cyclo*hexyloxy-α-phenylethylallylamine	20	5 min.	*p-Cyclo*hexyloxy-α-phenylethylamine	20	12·0±3·8	22·3±8·7 (10)	9·7±1·2	15·7±5·5 (40)
		24 hr.	„	20			9·7±1·7	12·8±2·5 (30)
		3 days	„	20			10·5±0·8	11·0±1·0† (30)
		7 days	„	20			8·3±1·3	10·2±2·3 (30)
		12 days	„	20			12·5±2·0	20·8±14·8‡ (20)
		21 days	„	20			12·2±1·3	18·8±12·2§ (20)
Dibenamine	20	2 days	*p-Cyclo*hexyloxy-α-phenylethylamine	20	11·0±1·3	18·3±6·2 (10)	9·9±2·0	8·9±1·2‖ (20)
*p-Iso*propyloxy-α-phenylethylamine	20	10 min.	„	20	—	—	11·5±2·8	18·2±5·0 (10)

* 4 rats completely analgesic at 60 min. † One rat which showed complete analgesia omitted. ‡ 1 rat completely analgesic. § 3 rats analgesic. ‖ 2 rats analgesic.

analgesia (8–33% elevation of reaction time), seven a marked analgesia (47–120% elevation), and 19 showed hyperalgesia (16–56% reduction of reaction time), within 20 min. of injection. Three gave no response. The marked analgesic responses, equal to those of the parent amine, lasted about 30 min., as did the hyperalgesia. Marked degrees of analgesia and hyperalgesia were not seen as successive responses in the same animal. Three rats given the *N*-allylamine daily for sixteen days showed no marked change in pre-injection reaction threshold, but block of analgesic activity developed in 24 hours and persisted during the experiment. There was no obvious diminution in depressant activity, and the excitability that develops during prolonged dosage with *p-cyclo*hexyloxy-α-phenylethylamine did not appear. At autopsy the brains of these rats had an abnormal grey shrunken appearance, though the animals had developed no neurological signs.

Dibenamine given two days beforehand completely abolished the analgesic response to *p-cyclo*hexyloxy-α-phenylethylamine in four of six rats, three being hyperalgesic within 20 min. of injection (26–44% reduction in reaction time). Two rats, however, gave the normal analgesic response.

Pretreatment with *p-iso*propyloxy-α-phenylethylamine had no influence on analgesic activity.

Hyperalgesic Responses with Other Phenylethylamines.

Time-action curves of individual rats for various analgesic phenylethylamines showed sometimes, but not consistently, a secondary transient hyperalgesic phase. A strain of albino rat was found, however, which consistently gave hyperalgesic responses after *p-cyclo*hexyloxy-α-phenylethylamine at 20 mg./kg., and analgesic responses at 30–40 mg./kg. (Fig. 1). At the higher doses the analgesic phase was preceded by a transient hyperalgesia. The *N*-allylamine also induced marked degrees of hyperalgesia in this strain, but no analgesic responses were seen; this amine, given the day before, appeared to antagonize only the analgesic response to *p-cyclo*hexyloxy-α-phenylethylamine (Fig. 2). This strain of rat gave purely analgesic responses to morphine (10 mg./kg.), and showed no hyperalgesia when pretreated with nalorphine, but hyperalgesia was seen after *N*-allylamine pretreatment. In other strains of rat *p-cyclo*hexyloxy-α-phenylethylamine only occasionally gave hyperalgesic responses after pretreatment with the *N*-allylamine. Saline injections never gave marked degrees of hyperalgesia.

α-(*p*-Phenoxyphenyl)ethyldimethylamine normally gave moderate analgesic responses (30% elevation of reaction threshold) by the oral, subcu-

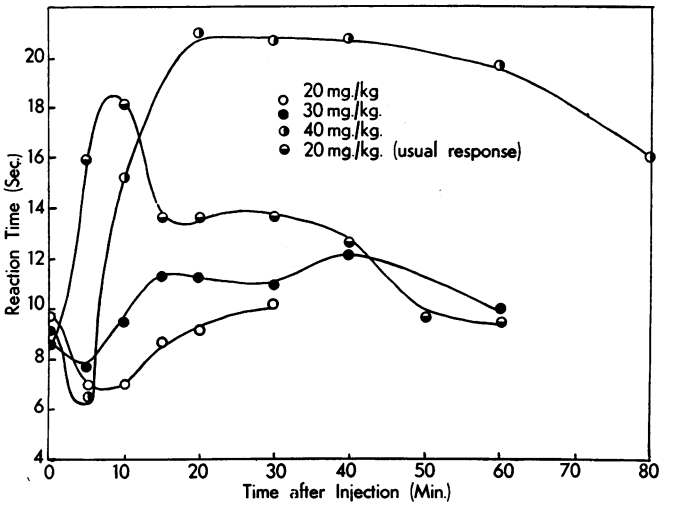


FIG. 1.—Hyperalgesic and analgesic responses of an atypical strain of rat to *p-cyclo*hexyloxy-α-phenylethylamine. A curve showing the usual response is included for comparison. Groups of six rats.

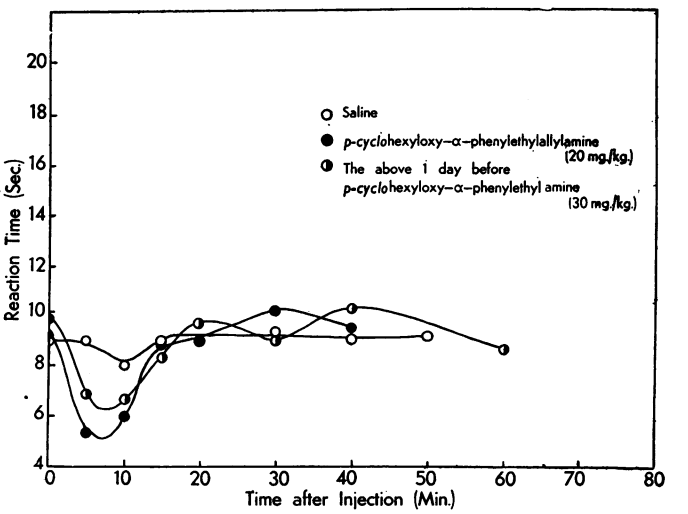


FIG. 2.—To show, in an atypical strain of rat, (a) the abolition of the analgesic but not the hyperalgesic response to *p-cyclo*hexyloxy-α-phenylethylamine by its *N*-allyl derivative, and (b) the hyperalgesic response to the *N*-allyl derivative. Groups of six rats.

taneous, and intraperitoneal routes at 60, 40, and 20 mg./kg. respectively. This amine had only slight respiratory depressant activity as measured by the method used previously (McCoubrey, 1953), and usually induced mild excitation. It had a spasmolytic activity equal to pethidine on the rat ileum contracted by acetylcholine. A limited trial in normal human subjects disclosed activity approximately equal to pethidine at 50–75 mg. intramuscularly, but little activity at 100 mg. (see Addendum). Similar behaviour was apparent in rats, since 30 mg./kg. intraperitoneally was followed by a decline in analgesic activity. In one batch of rats, however, in the dose range 20–40 mg./kg., this amine gave purely hyperalgesic responses amounting to an average reduction in reaction time of 41%. There was no apparent diminution in effect with increasing dose. α-(*p*-Phenoxyphenyl)ethyldiethylamine in the same batch gave a similar response (31% reduction in reaction time), although in another strain it had given both weak analgesic and hyperalgesic responses.

α-(3-*Cyclo*hexyloxy-4-hydroxyphenyl)ethyldimethylamine (12–25 mg./kg.) gave only weak hyperalgesic responses (average of 14% reduction in reaction threshold), but failed to give any response in the same strain at 50 mg./kg. At the lower doses the rats tended to be excitable and difficult to handle, whereas at the higher doses they showed mild depression. This amine (20 mg./kg.) failed to induce hyperalgesia in those rats which had hyperalgesia with *p-cyclo*hexyloxy-α-phenylethylamine ; but insufficient material was available for further assays.

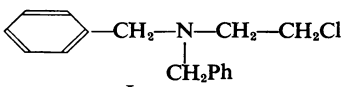
Discussion

Abolition of the analgesic activity of both morphine and *p-cyclo*hexyloxy-α-phenylethylamine by *p-cyclo*hexyloxy-α-phenylethylallylamine lends support to the hypothesis that these two analgesics have similar mechanisms of action (McCoubrey, 1953). Though nalorphine failed to antagonize *p-cyclo*hexyloxy-α-phenylethylamine completely, it is probable that suitable conditions were not used, since its short-lived antagonistic effect would make correct choice of dose and time more important than for the long-lived *N*-allylamine antagonism.

Hyperalgesic responses were frequently given by the phenylethylamines, but were infrequent after morphine. In the literature hyperalgesia is mentioned often as a sequel to morphine analgesia in studies using experimental pain in man (Isbell and Frank, 1950; Andrews, 1943; Seevers and Pfeiffer, 1936; Mullin and Luckhardt, 1934). Secondary hyperalgesia has been noted after methadone (Glazebrook, 1949), alcohol (Mullin and Luckhardt, 1935), and adrenaline (Gross, Holland, Carter, and Christensen 1948), and has been described as a primary response in man after 11-deoxycorticosterone (Lee and Pfeiffer 1951), in guinea-pigs after mescaline (De Nito, 1934), and in cats after barbiturates (Eddy, 1928). Reduced reaction thresholds have been described after aspirin (Hardy, Wolff, and Goodell, 1941). Winter and Flataker (1951) found secondary hyperalgesia after morphine in rats which had previously received ACTH. In general, the response appears sporadically, usually as a sequel to an analgesic phase.

The experiments described indicate that time-action curves to analgesic phenylethylamines may be the resultant of two opposed and independent responses, one—relatively weak—which lowers, and another which raises, the threshold to heat stimuli. Variation in the duration of the two effects in individual rats could explain the sporadic appearance of hyperalgesia. The best evidence for this view is afforded by the results from the strain of rats which consistently gave a purely hyperalgesic response to *p-cyclo*-hexyloxy-α-phenylethylamine, this being gradually superseded by an analgesic response as the dose increased. Only the analgesic response was antagonized by the *N*-allylamine. Further evidence is available from the purely hyperalgesic activity of α-(3-*cyclo*hexyloxy-4-hydroxyphenyl)-ethyldimethylamine which indicates that hyperalgesia can occur independently of analgesia.

Block of analgesic but not of hyperalgesic activity by the *N*-allylamine recalls block of the excitatory but not the inhibitory actions of adrenaline by adrenolytic agents. That this may be more significant than a mere parallel is indicated by the following observations: (*a*) that dibenamine can sometimes block the analgesic activity of *p-cyclo*hexyloxy-α-phenylethylamine [Gross *et al.* (1948) and Semler and David (1952) find that dibenamine given 30 min. before morphine or methadone potentiates the analgesic activity], (*b*) that dibenamine (I) and the *N*-allylamine (II) have related structures (β-chloroethyl can be regarded as equivalent to vinyl, the lower homologue of the allyl



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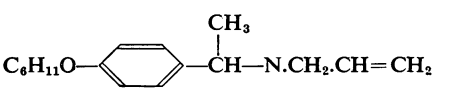

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group), and both have a prolonged action, (*c*) that all analgesics of "opiate" type incorporate the elements of sympathomimetic structure—an aromatic nucleus, an alkylamine side chain or its equivalent, and usually oxygen groups, (*d*) that adrenaline can exert marked analgesic effects (Ivy, Goetzl, Harris, and Burrill, 1944; Leimdorfer and Metzner, 1949).

Chemical Section

The following amines have not been described previously:

(±)-α-(p-Cyclo*hexyloxyphenyl*)*ethylallylamine.*—*p-Cyclo*hexyloxyacetophenone was reduced in alcohol by hydrogen in the presence of Raney nickel at room temperature and pressure to give (±)-α-(p-cyclo*hexyloxyphenyl*)*ethanol* (82%). It crystallized from light petroleum in prisms, m.p. 45°. (Found: C, 76.1; H, 9.0. $C_{14}H_{20}O_2$ requires C, 76.4; H, 9.1%.) Treatment at 5° with phosphorus tribromide in dry benzene gave a bromide, not isolated, which reacted with excess allylamine at room temperature to give the required base (74%), b.p. 145–150°/1 mm. (bath temperature). The *hydrochloride* crystallized from benzene-light petroleum in prisms, m.p. 165°. (Found: C, 69.1; H, 8.9; N, 4.9. $C_{17}H_{26}ONCl$ requires C, 69.0; H, 8.8; N, 4.7%.)

(±)-α-(3-Cyclo*hexyloxy*-4-*hydroxyphenyl*)*ethyldimethylamine.*—3-*Cyclo*hexyloxy-4-hydroxyacetophenone by similar methods to the above gave the required base, which was purified as the *hydrochloride* (19%), prisms from alcohol-ether, m.p. 140°. (Found: C, 63.3; H, 8.8; N, 4.3. $C_{16}H_{26}O_2NCl$ requires C, 64.0; H, 8.7; N, 4.7%.) The intermediate alcohol and bromide were unstable and were not purified.

(±)-α-(p-*Phenoxyphenyl*)*ethyl-dimethylamine and -diethylamine.*—*p*-Phenoxyacetophenone (10 g.) was reduced as above to α-(*p*-phenoxyphenyl)ethanol (9.1 g.), b.p. 160–162°/2 mm. The *phenylurethane* crystallized from light petroleum in feathery plates, m.p. 65°. (Found: C, 75.6; H, 5.6; N, 3.8. $C_{21}H_{19}O_3N$ requires C, 75.7; H, 5.7; N, 4.2%.) The alcohol, as above (5.3 g.), gave a bromide, not isolated, which reacted with excess dimethylamine to give the required base (4.3 g.), b.p. 145–150°/0.4 mm. The *hydrochloride* crystallized from benzene-alcohol in prisms, m.p. 156–157°. (Found: C, 69.2; H, 7.3; N, 4.7. $C_{16}H_{20}ONCl$ requires C, 69.2; H, 7.3; N, 5.0%.) Excess diethylamine similarly gave α-(p-*phenoxyphenyl*)*ethyldiethylamine*, prisms from light petroleum, m.p. 54°. (Found: C, 80.3; H, 8.7; N, 5.2. $C_{18}H_{23}ON$ requires C, 80.3; H, 8.6; N, 5.2%.) The hydrochloride did not crystallize.

Summary

1. The LD50 of *p-cyclo*hexyloxy-α-phenylethylamine in mice was elevated and analgesic activity in rats was abolished by prior treatment with its *N*-allyl derivative.

2. Analgesic antagonism due to the *N*-allylamine developed slowly, but was of long duration.

3. The *N*-allylamine induced either hyperalgesia or analgesia in rats.

4. In an atypical strain of rats which were rendered hyperalgesic or analgesic by *p-cyclo*hexyloxy-α-phenylethylamine, according to dose, the *N*-allylamine abolished only the analgesic activity.

5. Various other hyperalgesic responses to α-phenylethylamines are described.

ADDENDUM

By D. M. Zausmer

α-(*p*-Phenoxyphenyl)ethyldimethylamine had shown moderate analgesic activity in rats without marked respiratory depression. It tended to be excitatory rather than depressant. Since the value of an analgesic does not necessarily depend on potency but rather on freedom from side-effects, a short trial in human subjects was started after animal tests had shown no undue toxicity. Unfortunately, it was not possible to complete the experiment as planned; but the results are of interest, for they are parallel to those in rats, except that no hyperalgesic effects were detected.

The drug was given intramuscularly to medical or scientific people, who were aware of the experimental methods but had no knowledge of the drugs to be given. Activity was assessed by the method of Hardy, Wolff, and Goodell (1941). The results are summarized in Table IV. The experiment had to be terminated before saline controls could be done in the same subjects. The number of pethidine controls was limited by the incidence of side-effects (fainting, nausea, and vertigo). The drug gave no side-effects whatever beyond a slight

Table IV

ANALGESIC ACTIVITY OF α-(*p*-PHENOXYPHENYL)-ETHYLDIMETHYLAMINE IN MAN

Method of Hardy, Wolff, and Goodell (1941). Ranges in parentheses.

Dose (mg., i.m.)	No. of Subjects	No Response	% Elevation of Threshold	Duration (min.)	Time to Peak Activity (min.)
50	5	1	21 (20–35)	71 (40–115)	76
75	7	0	28 (9–64)	133 (70–180+)	80
100	5	2	23 (14–31)	120 (50–180+)	—
250 orally	1	—	62	180	110
50 (pethidine)	2	0	23	130	83
75 (pethidine)	1	—	25	140	55

drowsiness in three subjects. Most were able to read during the experiment. No hyperalgesic responses were observed. The failure to obtain increased responses at 100 mg. seems to be real and not due to sampling error. There was wavering of threshold above control level, but without definite peaks. Similar behaviour had been observed in the rat.

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