lasted for only a few hours. Histopathological examination of PGA-treated animals showed that a large number of these animals had acute renal tubular necrosis (fig.). In only one DBA/2 mouse, there was shrinkage of a few Purkinje cells in the cerebellum.

Discussion. PGA, as a water-soluble vitamin supplement, is expected to have a very high LD_{50} value, unlike drugs. It was surprising, therefore, to note a fairly low LD_{50} value in some of the murine strains. Histopathological examination has revealed acute renal tubular necrosis (fig.) as one of the causes of death. PGA has a low solubility in cold water but it dissolves in dilute solutions of alkali hydroxides and carbonates[11]. Vitamin B_{12} and folic acid appear to require binding to polypeptides as a precondition for storage. Levels above the serum and tissue-binding capacity tend to be excreted rather than retained[14]. Ther renal tubular necrosis observed by us might have been due to precipitation in the acidic urine within the tubules. This could result in renal shut-down and death after several hours or days. However, since the drug was given on a mg/kg basis, the large differences between various strains were surprising, especially because they were housed under identical experimental conditions and were given the same diet. Preterminal convulsions in only 2 strains and ataxia in the others suggest a specific susceptibility of certain strains possibly due to a difference in the metabolic conversion of the drug by the animal.

It was interesting to note that C57BL/6 mice which are used for transplantation of Lewis lung carcinoma (LL) and B16 melanoma (B16) have a relatively low LD_{50} value. LL responds well to methotrexate[15]. This suggests a possible biochemical uniqueness in the metabolic transformation of PGA by this specific strain.

The behavioral changes such as hyperkinesis and ataxia, convulsions and also coma suggested neural involvement. It is known that folic acid at a dose of 15 mg per day for 1–4 weeks to patients exacerbates epilepsy[6] and 5-methyltetrahydrofolate has been reported to be neurotoxic[16,17]. We did not detect any structural changes in the CNS of the mice treated with folic acid. It is possible that definite histological alterations may become manifest only after chronic repeated administration of folic acid. The acute changes in CNS function which were detected by us may have resulted from acute uremia resulting from renal tubular necrosis. No firm opinion regarding the CNS can be given on the basis of the present study.

In conclusion, it may be said that the administration of folic acid to different strains of mice by the i.p. route has shown a unique pattern of toxicity. The most common observation in the PGA-treated mice is renal tubular necrosis.

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0014-4754/85/010072-02$1.50 + 0.20/0

Circling behavior induced by phencyclidine in mice and its inhibition by naloxone

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Summary. Phencyclidine (PCP), when given to mice, induces general hyperactivity and rapid circling, similar to that caused by morphine. These effects are partially antagonized by naloxone.
Key words. Mice; circling behavior; phencyclidine; naloxone; hyperactivity.

Mice and rats manifest their activity by circling around the walls of a container in which they are placed. Animals have an innate preferred direction of circling, either clockwise or counter-clockwise. This tendency has been attributed to asymmetry between the two nigrostriatal systems[1].

Dopaminergic drugs increase the rate of circling and the degree of asymmetry[2]. Morphine, although not a direct dopaminergic agent, also increases, in mice, the rate of circling in the preferred direction[3,4].

Phencyclidine has previously been reported to induce rotatory behavior in rats with unilateral nigrostriatal lesions[5–7] as well as in intact rats[8]. This effect was attributed to interaction with the dopaminergic nigrostriatal system[5–8]. However, PCP shares some similarities with opiates[9] and in the present study we examined the possibility that the rotatory behavior induced by PCP is also mediated through opiate mechanisms.

Materials and methods. Male ICR albino mice weighing 20–35 g were studied. Rotation was measured as previously described[4]. Morphine sulfate (Assia), 40 mg/kg, phencyclidine hydrochloride (prepared by A. Kalir), 5 mg/kg and naxolone (Du Pont), 10 mg/kg, were injected i.p. Each dose was given to eight mice. Before drug administration each animal was harnessed to the rotometer for 1 h to verify its basic circling rate and preferred direction. Control groups were injected with saline prior to na-

Experientia 41 (1985), Birkhäuser Verlag, CH-4010 Basel/Switzerland

loxone. The timing of naloxone injection was chosen so that its maximal effect will coincide with the peak effect of morphine or PCP.

Results. Basic circling rates were low and did not exceed 10 turns per hour. Naloxone did not affect the circling rate significantly, as was found previously[10]. Morphine, 40 mg/kg, markedly increased the preferred turns up to 215/h. The peak effect occurred 40 min after drug administration. Naloxone decreased the morphine score to 45 preferred turns per hour (see fig. 1 and the table for further details).

Performance of mice injected with morphine (40 mg/kg), PCP (5 mg/kg) alone or in combination with naloxone (10 mg/kg). Each group contained 8 mice. Volumes indicate mean ± SEM

	Morphine	Morphine and naxolone	PCP	PCP and naxolone
Total turns/h	230 ± 21	52 ± 7*	170 ± 20	80 ± 7*
Preferred turns/h	215 ± 23	45 ± 8* (21%)	160 ± 19	70 ± 7* (44%)**
Total nonturn movements/h	1040 ± 156	74 ± 17* (7%)	960 ± 75	460 ± 52* (48%)**
Preferred nonturn movements/h	720 ± 75	30 ± 3* (4%)	510 ± 47	260 ± 26* (51%)**

* Statistically significant (Student's paired t-test) from the nonnaloxone score ($p < 0.01$). ** Statistically significant (Student's t-test) from the naxolone effect after morphine ($p < 0.001$).

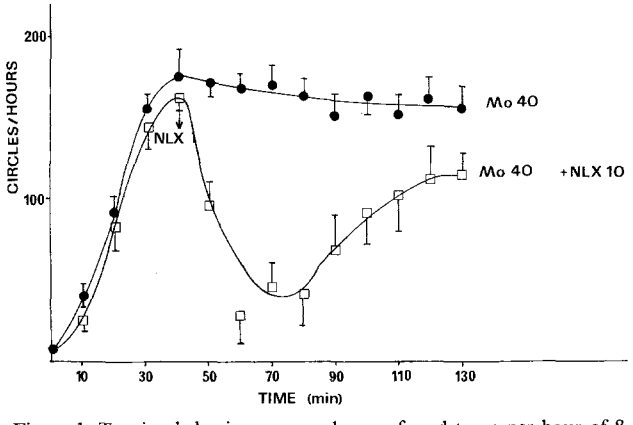

Figure 1. Turning behavior measured as preferred turns per hour of 8 mice injected with morphine, 40 mg/kg, and morphine and naloxone, 10 mg/kg, bars indicate SEM.

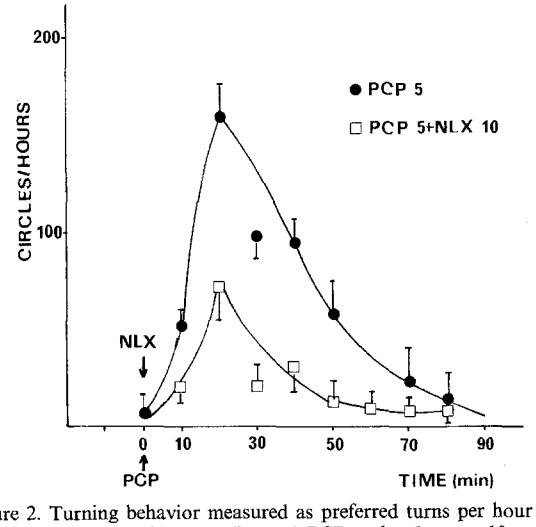

Figure 2. Turning behavior measured as preferred turns per hour of 8 mice injected with PCP, 5 mg/kg and PCP and naloxone, 10 mg/kg, bars indicate SEM.

PCP, 5 mg/kg, increased the preferred turns up to 160/h (peak effect, 20 min following drug administration). The effect of PCP lasted for 1 h. Naloxone antagonized this PCP effect, reducing it to 70 turns per hour (fig. 2 and the table). General motor activity, measured as nonturn movements per hour, was also antagonized by naloxone. However, the effect of naloxone was much lower against PCP-induced circling (and hyperactivity) than against the respective morphine effects (table).

Discussion. In the present work we have demonstrated that mice respond to PCP with hyperactivity and rotatory behavior. The circling is similar to that described in rats by Glick et al.[8]. Murray and Horita[11] found that PCP administered to rats induced turning behavior, in which the animals pivot around their hind limbs. These workers suggested that this tpye of turning is an expression of stereotyped behavior[11]. Phenomenologically it is different from the running observed by us in mice, or by Glick et al. in rats, although what we observed can probably be called stereotyped turning.

Previous workers[5–8] concluded that PCP interacts with dopaminergic mechanisms to produce circling in rats. This conclusion was based on the similarity between the effects of PCP and amphetamine and the antagonism of PCP-induced circling by neuroleptic drugs[7,11]. The use of neuroleptics, however, is not specific since any drug interfering with motility will antagonize both hyperactivity and circling.

The present results demonstrate that, as suggested by Glick et al.[8], circling induced by PCP is a complex action. Part of this effect is naloxone sensitive, i.e. mediated through opiate receptors. This could imply a direct interaction between PCP and opiate receptors[12] or release of endogenous endopioids by PCP, as suggested by us for somatostatin[13].

In contrast to opiate-induced rotation, the phenomenon caused by PCP was only incompletely blocked by naloxone (in spite of the high dose of the antagonist used by us).

A similar phenomenon exists for other systems, e.g. PCP-induced antagonism of guinea-pig ileum contraction, which is only partially naloxone-sensitive[14]. The reason is unclear, and may possibly indicate that the PCP effect occurs through different mechanisms[14].

* Acknowledgment. We are grateful to Professor A. Kalir for the donation of PCP. Correspondence and reprint requests should be addressed to A.M. Korczyn.

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