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Effect of probenecid on the level of homovanillic acid in the corpus striatum

SIR,—Active transport mechanisms seem to be involved in the removal of organic acids from the cerebrospinal fluid to the blood, as evidenced by perfusion and clearance experiments with the ventriculocisternal system *in vivo* (Pappenheimer, Heisey & Jordan, 1961; Prockop, Schanker & Brodie, 1962). The different substances tested, for example, *p*-aminohippuric acid and diodrast, compete for the same saturable transfer processes, which seem to be similar to those found in the renal tubules.

Probenecid reduces the renal excretion of a variety of organic acids, which includes acid monoamine metabolites such as 5-hydroxyindoleacetic acid (Despopoulos & Weissbach, 1957) and homovanillic acid, derived from the amines 5-hydroxytryptamine and dopamine, respectively. These amine metabolites also occur in the brain, with about the same distribution as the corresponding amines (Roos, 1962; Andén, Roos & Werdinius, 1963; Bernheimer, 1964). The present experiments investigated whether probenecid, given alone and in combination with reserpine or haloperidol, would interfere with the levels of homovanillic acid in the brain.

Adult hooded rats of either sex, five animals in each experiment, were treated with probenecid (50, 100 or 200 mg/kg i.p.), followed after 30 min by reserpine (10 mg/kg i.p.) or haloperidol (2 mg/kg i.p.). After another 3 hr the homovanillic acid was measured fluorimetrically in the pooled corpora striata (Andén & others, 1963). Control groups were run with none, or only one, of the drugs for the corresponding time intervals. The results are given in Table 1. In a few experiments (data not shown) dopamine was assayed fluorimetrically (Carlsson & Waldeck, 1958; Carlsson & Lindqvist, 1962).

TABLE 1. LEVELS OF HOMOVANILLIC ACID IN THE CORPUS STRIATUM OF RATS, 3·5 HR AFTER VARIOUS DOSES OF PROBENECID

Probenecid mg/kg i.p.	Homovanillic acid μg/g		
	Controls	Reserpine treated	Haloperidol treated
0	0·2 ± 0·06 (3)	0·6 ± 0·15 (3)	1·5; 1·4 (2)
50		0·6; 0·9 (2)	
100		1·2; 1·1 (2)	
200	0·5 ± 0·07 (3)	1·9 ± 0·15 (3)	2·7 ± 0·35 (3)

Reserpine (10 mg/kg i.p.) or haloperidol (2 mg/kg i.p.) was given 30 min after probenecid. The values are means ± s.e. of the means. Figures in brackets indicate number of experiments. Each experiment was performed on five pooled organs.

Normally, the concentration of homovanillic acid in the corpus striatum is rather low in rats, about 0·2 μg/g tissue (Juorio & Vogt, 1965; Juorio, Sharman & Trajkov, 1966), compared to that of dopamine (3–4 μg/g). Reserpine

produced a threefold increase in homovanillic acid in 3 hr, probably due mainly to release and breakdown of the stored dopamine, which had disappeared almost completely. The increase in homovanillic acid corresponded to only about 10% of the released dopamine, indicating a rapid removal of homovanillic acid, or the existence of alternative metabolic pathways for dopamine (see Juorio & others, 1966).

Pretreatment with probenecid, 200 mg/kg, given 30 min before reserpine increased the homovanillic acid level to about 1·9 μg/g in 3 hr, i.e. tenfold. Smaller doses of probenecid in combination with reserpine caused less pronounced increases. With probenecid alone, 200 mg/kg, 3·5 hr, there was a more moderate, two- to threefold increase in homovanillic acid, comparable with that produced by reserpine alone, while the dopamine level was not significantly changed. Reserpine and probenecid thus seem to increase the homovanillic acid concentration in the corpus striatum by different and independent mechanisms.

Haloperidol also produced a clear increase in homovanillic acid in 3 hr, without affecting the dopamine level. The increase has been attributed to an impaired elimination of the metabolite or, probably more important, to an increased amine turnover secondary to receptor blockage (Andén, Roos & Werdinius, 1964; Roos, 1965). However, since probenecid pretreatment nearly doubled the homovanillic acid level, the mechanisms which increase the acid are probably not identical for haloperidol and probenecid.

The results could be explained by an active transfer mechanism, which removed homovanillic acid from the brain tissue and which was inhibited by probenecid.

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