Central origin of the lenticular opacities induced in mice by opiates

SIR,—Weinstock (1961) showed that opiates injected subcutaneously or intraperitoneally induced a transient clouding of the lens of the mouse. This activity of the opiate was shown to parallel its analgetic activity and suggested a similarity of the receptors for each response. The lenticular response was thought to originate within the eye particularly because the uptake of tritiated levorphanol in the lens and in the brain was found to be virtually equal after intraperitoneal injection of labelled levorphanol (Smith, Karmin & Gavitt, 1966a). Furthermore, the lenticular effect of parenteral levorphanol was potentiated when concentrated adrenaline solutions were instilled into the eye. However, the fact that tolerance to the lenticular effect of opiates could be blocked by actinomycin or puromycin (Smith, Karmin & Gavitt, 1966b) suggested a more complex etiology for the opacity phenomenon.

We have now given levorphanol intracerebrally in a dose (22 μmol/kg) too low to produce a significant incidence of opacities when given intraperitoneally, and one third of the mice developed opacities (Table 1).

TABLE 1. THE INCIDENCE OF LENTICULAR OPACITIES PRODUCED BY INTRACEREBRAL INJECTION OF LEVORPHANOL COMPARED WITH INTRAPERITONEAL INJECTION IN FEMALE SWISS-WEBSTER MICE (20–25 G)

Treatment	No. Mice	No. Opacities	% Opacities	Deaths
Levorphanol, 22 μmol/kg (i.c.) (given in 30 μl at pH 7)	45	15	33	11
Levorphanol, 22 μmol/kg (i.p.)	25	1	4	0
0·9% Saline, 30 μl (i.c.)	29	0	0	0

The ED50 for intraperitoneal levorphanol was 118 μmol/kg.

As further evidence for a central origin of the lenticular effect, levorphanol-^{3}H, with a specific activity of 5 μc/μmol and diluted with carrier to provide a dose of 22 μmol/kg in a volume of 30 μl, was injected intracerebrally into the right cerebral hemispheres of mice. Thirty min after injection the mice were killed by decapitation and the brains, lenses, hearts and plasma separated. The tissues except for the lenses were washed in saline, homogenised in 0·1N hydrochloric acid and the clear supernatant counted in a liquid scintillation spectrometer (Smith & others, 1966a). The results were as follows: [tissue (no. of animals) μc/g or ml ± s.e.]: cerebrum (right) (5) 256 ± 46; cerebrum (left) (5) 186 ± 76; brain stem (4) 183 ± 81; plasma (5) 23·2 ± 6·5; heart (5) 23·4 ± 5·1; lens (4) 13·3 ± 5·0. Tissues of 2 mice were pooled for each independent value. Scans of the radiochromatographs prepared from brain stem or cortical extracts revealed only single radioactive areas. These areas corresponded to the carrier levorphanol. It appears that the labelled substance is concentrated in the region of the injection site but it is also present in high concentrations in stem and left cerebrum. The levorphanol-^{3}H seems to be transported from the injection site to other brain areas by cerebral fluid rather than by the blood because the blood has a relatively low concentration of radioactivity. The fact that the lens shows even less tritium than blood is further evidence in favour of a central origin.

It is therefore concluded that levorphanol induces lenticular opacities by a process initiated in the brain. Because of the previously demonstrated interaction between opiates and catecholamines to produce opacities, adrenergic nerves may be involved in this process.

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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