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Effects of certain tranquillisers on the level of homovanillic acid in the corpus striatum

SIR,—Earlier investigations have shown that chlorpromazine or haloperidol increase the levels of dihydroxyphenylacetic acid and homovanillic acid but not of 5-hydroxyindoleacetic acid in the corpus striatum of the rabbit (Andén, Roos & Werdinius, 1964). This increase occurs without any concomitant change in tissue monoamine levels. The first biochemical evidence of an influence on the monoamine metabolism *in vivo* by chlorpromazine and haloperidol was the observation that the accumulation of methoxytyramine and normetanephrine in brain after treatment with a monoamine oxidase inhibitor was enhanced by chlorpromazine or haloperidol (Carlsson & Lindqvist 1963). There is some evidence for the view that the elimination of the dopamine acid metabolites is retarded by the two drugs but other data support the suggestion that the synthesis of the acid metabolites is increased. Against the former and in favour of the latter hypothesis are the facts that the dihydroxyphenylacetic acid and homovanillic acid levels increase simultaneously and that 5-hydroxyindoleacetic acid is unchanged after chlorpromazine or haloperidol.

It is known that these drugs may block both peripheral and central effects of catecholamines. The blockade of the catecholamine receptors of the effector cells may have the effect of increasing the release of transmitter from the neurones with a compensatory stimulation of the catecholamine synthesis. In this instance it might be possible to assume that a stronger inhibition of the receptor may result in a greater increase of the levels of the phenolic acids in the brain. Homovanillic acid is formed from dihydroxyphenylacetic acid after the attack by the enzyme catechol-*O*-methyl transferase. This reaction is so far not known to be influenced by chlorpromazine or haloperidol.

The effect of 15 tranquillising substances has been investigated by giving them intravenously to rabbits. The homovanillic acid was measured 3 hr after the injection by the method developed in this laboratory (Andén & others, 1963) (Table 1). The animals were kept in a warm environment. Hypothermia can thus be excluded as a causative factor in the changes of the acid metabolites after these drugs.

It is interesting to note that major tranquillisers with a well-known antipsychotic effect, such as perphenazine, triflumethazine and clopenthixol, also strongly increase the homovanillic acid level. On the other hand, phenothiazines used as minor tranquillisers, for instance, prothipendyl or promazine hydrochloride, have only a slight effect, or none at all, on the level of the acid. The substances R6109 and R5147 are derivatives of the butyrophenone made by Janssen Ltd. in Belgium. Like haloperidol they seem to have a rather strong effect on homovanillic acid levels. Further work on the possible connection between the antipsychotic action and the homovanillic acid-increasing effects of tranquillising drugs is in progress.

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TABLE 1. LEVEL OF HOMOVANILLIC ACID IN RABBIT CORPUS STRIATUM 3 HR AFTER THE I.V. INJECTION OF TRANQUILLISER DRUGS

Drug	Dose mg/kg	Homovanillic acid µg/g	Drug	Dose mg/kg	Homovanillic acid µg/g
Controls	—	3·9 ± 0·9*	Prothipendyl HCl ..	10	5·0
Clopenthixol ..	10	10·6	Prothipendyl HCl ..	20	6·8
Triflumethazine ..	10	10·2	Prothipendyl HCl ..	30	6·4
Perphenazine	5	10·0	Azacyclonol ..	10	4·3
Dixyrazine	5	10·0	Azacyclonol ..	20	4·6
Prochlorperazine ..	0·5	4·6	Hydroxyzine ..	10	3·7
Prochlorperazine ..	2	9·5	Hydroxyzine ..	20	5·8
Methopromazine ..	10	8·4	Hydroxyzine ..	35	6·9
Thiroidazine ..	5	8·2	Earlier investigations (Anden & others, 1964)		
Levomepromazine ..	0·2	4·4			
Levomepromazine ..	5	8·4			
R6109 Isospirilene ..	0·5	8·0	Controls		2·2 ± 0·6*
R5147 Spiroperidol ..	0·5	8·3	Chlorpromazine ..	5	4·9
Chlorprothixene ..	10	8·0	Haloperidol	0·5	5·1
Trimeprazine	5	3·5	Promethazine ..	20	2·2
Trimeprazine	10	7·2	Phenoxybenzamine ..	10	2·4

*Mean ± s.d.

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