possibility of dopamine interacting with noradrenaline receptors in the brain (Carlsson, 1966) remains.

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On the mechanism of chlorpromazine-induced changes of cerebral homovanillic acid levels

SIR,—In various animal species, chlorpromazine and other neuroleptic drugs increase the concentration of the dopamine metabolite 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid) in the brain, especially in the extrapyramidal centres, without markedly interfering with the content of dopamine and 5-hydroxyindoleacetic acid (Andén, Roos & Werdinius, 1964; Gey & Pletscher, 1964; Juorio, Sharman & Trajkov 1966; Laverty & Sharman, 1965; Da Prada & Pletscher, 1966; Roos, 1965). Hydroxylation of tyrosine is thereby enhanced (Burkard, Gey & Pletscher, 1966). The question has been raised whether neuroleptics might enhance the formation of dopamine through a feedback mechanism due to blockade of dopaminergic receptors (Carlsson & Lindqvist, 1963; Gey & Pletscher, 1964; Da Prada & Pletscher, 1966). The results of the present experiments accord with this assumption and indicate that the storage sites of dopamine are possibly involved in the feedback mechanism.

Normal rats were injected i.p. with various psychotropic drugs (see Table 1). In addition, 10 mg/kg chlorpromazine was administered subcutaneously at various time intervals after intraperitoneal injection of 2·5 mg/kg reserpine. The animals were kept at an environmental temperature of 31–32° so that the rectal temperature remained normal within a range of ±1–2° during the course of the experiments. Homovanillic acid, 5-hydroxyindoleacetic acid (5-HIAA) and dopamine were measured in the brain stem (including basal ganglia, but without medulla oblongata and pons) with spectrophotofluorimetric methods (Andén, Roos & Werdinius, 1963; Carlsson & Waldeck, 1958; Pletscher, Burkard & Gey, 1964).

Neuroleptics of various chemical structures (chlorpromazine, chlorprothixene, haloperidol), in contrast to thymoleptics (imipramine, amitriptyline), tranquillisers (meprobamate, chlordiazepoxide, diazepam), and hypnotics (pheno-

barbitone, hexobarbitone), markedly increased the homovanillic acid content of the brain stem. Whereas none of the drugs produced more than a moderate elevation of the level of 5-HIAA, the thymoleptics even caused a slight but significant decrease of this substance (Table 1).

These findings suggest the possibility of a relationship between disturbed extrapyramidal function and increased formation of cerebral homovanillic acid. Thus, only those psychotropic drugs, i.e. the neuroleptics, which are known to interfere markedly with the function of the extrapyramidal centres in man and animals cause a major increase of the cerebral homovanillic acid levels. Since

TABLE 1.—THE EFFECTS OF PSYCHOTROPIC DRUGS ON THE CONTENT OF HOMOVANILLIC ACID (HVA) AND 5-HYDROXYINDOLEACETIC ACID (5-HIAA) IN THE BRAIN STEM OF RATS

Drug	Dose	HVA	Dose	5-HIAA
Chlorpromazine	10	314 ± 21	20	119 ± 3
Chlorprothixene	10	300 ± 17	20	125 ± 4
Haloperidol	5	340 ± 8	10	122 ± 5
Imipramine	10	91 ± 9	20	72 ± 3
Amitriptyline	10	125 ± 17	20	82 ± 5
Meprobamate	50	115 ± 8	50	130 ± 6
Chlordiazepoxide	50	83 ± 5	50	132 ± 7
Diazepam	10	83 ± 8	10	124 ± 5
Phenobarbitone	50	100 ± 17	50	111 ± 5
Hexobarbitone	50	100 ± 17	50	120 ± 14

The results are expressed in percent of untreated controls and represent averages of 4–10 experiments ± s.e. The drugs were administered i.p. 2–3 hr before death.

at least part of the extrapyramidal system seems to be dopaminergic (Sourkes, 1961; Andén, Carlsson, Dahlström & others, 1964; Carlsson, 1964; Hornykiewicz, 1964), a blockade of dopaminergic receptors by the neuroleptics and a secondary enhancement of dopamine synthesis, for example by a feedback mechanism, is conceivable.

Experiments with reserpine plus chlorpromazine indicate that the storage sites for dopamine may be involved in the feedback mechanism. Thus, after depletion of the dopamine stores by reserpine, chlorpromazine no longer causes a major rise in homovanillic acid, although reserpine does not seem markedly to decrease the activity of the enzymes involved in dopamine biosynthesis (Glowinski, Iverson & Axelrod, 1966). Both the decrease of the dopamine content and the inhibition of the chlorpromazine-induced rise in homovanillic acid follow a similar time course (Table 2).

TABLE 2. THE EFFECT OF RESERPINE ON THE CHLORPROMAZINE-INDUCED INCREASE OF HOMOVANILLIC ACID (HVA) AND ON THE DOPAMINE CONTENT IN THE BRAIN STEM OF RATS

Hr after reserpine	HVA*	Dopamine†
0 (controls)	100 ± 15	100 ± 3
2	—	20 ± 4
4	8 ± 3	—
7	—	19 ± 4
19	19 ± 6	20 ± 4
50	35 ± 17	36 ± 2

In the experiments with HVA, 10 mg/kg chlorpromazine were administered s.c. after 2·5 mg/kg reserpine i.p. at the time intervals indicated above; death was 3 hr after chlorpromazine. Reserpine alone did not markedly change the HVA content after 4–50 hr.
Each figure indicates an average of 3 experiments ± s.e.

* Chlorpromazine-induced increase of HVA as per cent of that in controls not pretreated with reserpine (absolute increase of HVA of controls: 0·33 ± 0·05 μg/g).
† In percent of untreated controls (absolute values of controls: 1·78 ± 0·05 μg/g).

The exact role of the dopamine stores in the above-mentioned feedback mechanism is not known. One may speculate that dopamine synthesis is regulated by the amount of the amine liberated from the stores. In consequence of blockade of dopaminergic receptors by chlorpromazine, a compensatory discharge of the amine might occur leading to an activation of its synthesis. Such an enhanced liberation of dopamine seems no longer possible if the stores have been emptied by reserpine. Consequently, the feedback mechanism may be impaired. An analogous regulatory mechanism possibly exists for the noradrenergic system, since neuroleptics are also known to block noradrenergic receptors.

In conclusion, experiments with various psychotropic drugs indicate that a relationship between disturbed extrapyramidal function and increased cerebral homovanillic acid levels seems to exist. The storage sites of dopamine may be involved in a feedback mechanism leading to an enhanced formation of homovanillic acid after blockage of dopaminergic receptors by neuroleptics.

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The importance of the nervous impulse flow for the depletion of the monoamines from central neurones by some drugs

SIR,—It is known from previous work that the neuronal impulse flow is of great importance for the catecholamine depleting effect of α-methyl-*p*-tyrosine methylester (H 44/68), a potent and selective inhibitor of the enzyme tyrosine hydroxylase, since this drug causes a much more pronounced depletion of noradrenaline from the spinal cord cranial than caudal to a transection (Andén, Corrodi, Dahlström, Fuxe & Hökfelt, 1966). That study was based on the fact that all the 5-hydroxytryptamine (5-HT) and noradrenaline nerve terminals of the spinal cord belong to axons which originate from 5-HT and noradrenaline nerve cell bodies of the lower brain stem (Carlsson, Falck, Fuxe & Hillarp, 1964; Dahlström & Fuxe, 1965). Thus, after total transection of the spinal cord the nerve impulses will reach the monoamine nerve terminals lying cranial but not caudal to the lesion.