subcortical structures were affected significantly. Thus, the gross behavioral alterations were preceded by changes in regional perfusion, which became less variable and more pronounced with time. Blood gases were unaffected at 10 min after injection of LSD although a slight hypoxia was observed by 20 min.

LSD derivatives – Table II. The 2-methyl-LSD, 6-nor-LSD and $\Delta^{8,9}$-LSD derivatives failed to alter rat behavior in any observable way at a dose level which was markedly effective in the case of LSD; in additional subgroups of animals behavioral effects were not detected beyond 40 min after i.v. injection. Furthermore, the 2-methyl and $\Delta^{8,9}$ derivatives also failed to alter blood pressure or cardiac outputs. The 6-nor-LSD, however, appeared more potent in mimicking the peripheral effects of LSD by elevating arterial pressures by about 40 mm Hg above mean pressures and significantly reducing cardiac outputs by 25%. None of these compounds affected regional perfusion of the brain, with the possible exception of 2-methyl LSD which caused a fall in olfactory bulb flow.

Discussion. The flow changes to the parietal and frontal cortex, cerebellar and, perhaps, the dorsal hippocampal regions appear to be related to the behavioral effects. The findings with 2-methyl LSD, 6-nor LSD, and $\Delta^{8,9}$ LSD to which rats are not visibly responsive, reveal no changes in regional perfusion of the brain, although some of these compounds have considerable peripheral cardiovascular effects (Table II). Assuming as other do[3–8] then, that regional blood flow in the brain is secondary to function, the most parsimonious explanation for these findings is that the flow changes signal net increases in the activities of the parietal, frontal, and cerebellar cortices of the rat at the same time that some functions of the dorsal hippocampus perhaps decrease. In past studies in conscious men[10] and anesthetized cats[11] gross cerebral perfusion appeared unchanged by LSD administration. That LSD, indeed, increased the flow of blood to certain areas of the brains of conscious rats emphasizes our contention that these relatively restricted responses were the result of tissue activity responses likely to be obscured by whole brain measurements or the use of anesthetics[9].

Although the changes in regional perfusion of the brain may signal changes in function, the primary sites of action of LSD remain obscure. Some regions which retain radiolabelled LSD have been interpreted as possible sites of action[1]. Thus, accumulations of LSD in those mesencephalic and diencephalic structures associated with autonomic centers in the brain correlate well with the centrally mediated autonomic effects of the drug[12]. Although LSD also binds selectively to a minority of cells in frontal cortex and cerebellum[1,2], regions to which the flow of blood also is increased, the widespread uptakes of LSD in many subcortical areas are not paralleled by flow changes. Along with the acknowledged effects in subcortical regions then, the flow data suggest that some cortical regions and cerebellum also are responsive to LSD. At this time, however, it is impossible to distinguish between secondary functional aspects and primary sites of drug action[13].

Zusammenfassung. Die i.v. Verabreichung von LSD an Ratten steigert den Blutkreislauf im Hirnstamm sowie im frontalen und parietalen Cortex selektiv. Es wurden durch 6-Nor-LSD, 2-Methyl-LSD und $\Delta^{8,9}$-LSD weder wahrnehmbare Verhaltensänderungen noch Änderungen des regionalen Blutkreislaufs verursacht.

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[10] L. SOKOLOFF, S. PERLIN, C. KORNETSKY and S. S. KETY, Ann. N. Y. Acad. Sci. *66*, 468 (1957).
[11] D. H. INGVAR and U. SODERBERG, Experientia *12*, 427 (1957).
[12] N. J. GIARMAN, *LSD, Man and Society* (Weslyan, Middletown, Conn. 1967), p. 143.
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Inhibition of Prostaglandin Synthetase by Psychotropic Drugs

According to the hypothesis advanced by VANE, the pharmacodynamic activity of non-steroidal anti-inflammatory agents (NSAA's) is attributable to the inhibition of prostaglandin (PG) synthetase[1–3]. It therefore seemed of interest to determine whether this effect is peculiar to this class of compounds. With this end in view, and in the light of recently published observations indicating that certain psychotropic agents may interfere with PG synthesis[4,5], we undertook experiments to find out whether compounds possessing neuroleptic, antidepressant and/or tranquillizing properties, inhibit PG synthetase in vitro.

Material and methods. The enzymatic assay was carried out according to a modification of the technique described by TAKEGUCHI et al.[6]. The incubation medium contained 3 mg of the lyophilized microsomal fraction of bovine seminal vesicle as enzyme, 0.33 μM ^{14}C-labelled arachidonic acid (spec. activity: 58 mCi/mM) and 9.85 μM unlabelled arachidonic acid as substrate, and 2.95 mM l-adrenaline and 2.93 mM reduced l-glutathione as cofactors in 5 ml *Tris* buffer at pH 8.3. Each of the compounds tested was added to the reaction mixture in three different concentrations. After incubation for 30 min, the reaction was stopped by the addition of one drop of concentrated hydrochloric acid, and the lipid fraction extracted twice with ethyl acetate and separated by thin-

[1] J. R. VANE, Nature, New Biol. *231*, 232 (1971).
[2] J. R. VANE, in *Inflammation, Mechanisms and Control* (Ed. I. H. LEPOW and P. A. WARD; Academic Press, New York and London 1972), p. 261.
[3] S. H. FERREIRA and J. R. VANE, A. Rev. Pharmac. *14*, 57 (1974).
[4] R. E. LEE, Prostaglandins *5*, 63 (1974).
[5] E. C. KU, J. M. WASVARY and W. D. CASH, personal communication.
[6] C. TAKEGUCHI, E. KOHNO and C. J. SIH, Biochemistry *10*, 2372 (1971).

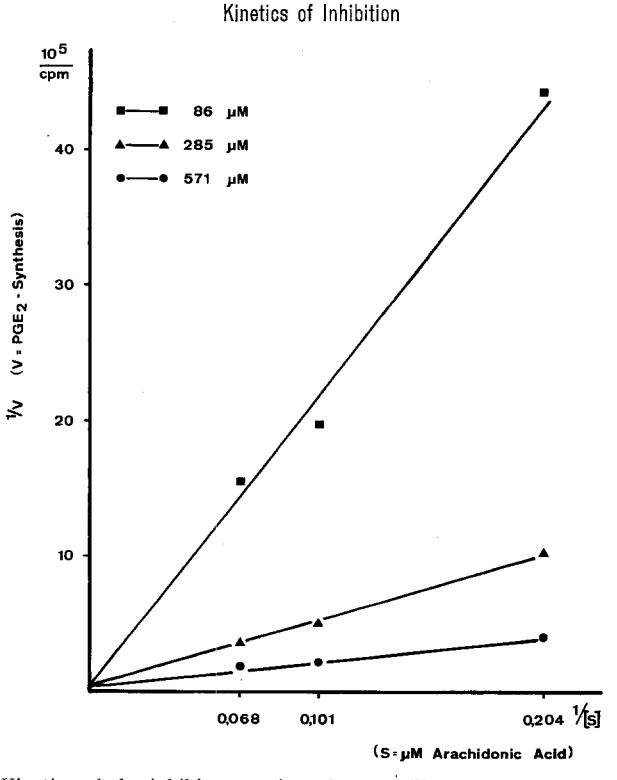
Inhibition of PG-synthetase by psychotropic drugs (Interpolated values; (ID_{50} and Ki; $n \geqq 9$ per drug)

Preparation	ID_{50} (μg/ml)	Ki (mM)
Chlorpromazine	46	1.3×10^{-1}
Clomipramine (1)	52	1.5×10^{-1}
Maprotiline (2)	95	2.7×10^{-1}
Benzoctamine (3)	110	3.4×10^{-1}
Amitriptyline	155	4.9×10^{-1}
Desipramine (4)	165	5.5×10^{-1}
Imipramine (5)	280	8.8×10^{-1}
Haloperidol	>300	$>7.3 \times 10^{-1}$

Registered names: (1) Anafranil®; (2) Ludiomil®; (3) Tacitin®; (4) Pertofran®; (5) Tofranil®.

layer chromatography[7]. The zone on the chromatogram corresponding to PGE was scraped off, the substance extracted once again and the radioactivity present determined in a liquid scintillation counter. In preliminary experiments, it had been shown that the radioactivity detected was attributable to the PGE_2 formed, and that the kinetics of the enzyme assay conform to the Michaelis-Menten equation with K_m of 2.2×10^{-5} M.

Results. As is evident from the Table, all the psychotropic agents tested inhibited the conversion of arachidonic acid to PGE_2, and the degree of inhibition was related to the concentrations used. The most potent were the tricyclic compounds chlorpromazine and clomipramine, followed by the ethaneanthracene derivatives maprotiline and benzoctamine. The tricyclic antidepressants amitriptyline, desipramine and imipramine were less active, and haloperidol, which is a butyrophenone derivative and hence structurally quite different from the other drugs studied, had only a very slight effect. Generally speaking, the order of activity displayed by these compounds was comparable with that of the NSAA phenylbutazone, which in a concentration of approximately 0.5 mM inhibits the synthesis of PGE_2 in this test system to the extent of about 50%[8].



Kinetics of the inhibitory action of maprotiline on prostaglandin synthesis (double reciprocal plot).

The kinetics of the inhibitory action of maprotiline were examined more closely; the effects of this preparation at various concentrations on the rate of synthesis were determined at different substrate concentrations. From the results shown in the Figure, it is clear that the inhibition was competitive to the substrate.

Discussion. The results obtained clearly indicate that inhibition of PG synthetase is not a pharmacodynamic action peculiar to compounds belonging to the class of NSAA's. As has already been reported by other authors[4,5], psychotropic agents also have this effect. The fact that Flower[9] did not observe any inhibitory action of chlorpromazine on this enzyme may be due to differences in the isolation procedure and incubation conditions.

The findings described are interesting in various respects. In the first place, the results at least partly explain the anti-inflammatory activity shown by certain of these preparations, i.e. by benzoctamine[10] and chlorpromazine[10,11] in animals, and by imipramine[12] in man also. Secondly, there is a possibility that the observed inhibitory effect might also have a significant bearing above all on the antidepressant activity of these compounds: on the one hand, the PGs released at adrenergic synapses reduce the liberation of the transmitter substances[13,14]; on the other hand, since the action of antidepressants is ascribed to an increase in the concentration of transmitter substances at the postsynaptic membrane[15], inhibition of PG synthetase could contribute towards this effect. Finally, the fact that a substance such as haloperidol with a distinctly neuroleptic action has scarcely any influence on PG synthesis suggests that interference with PGs is not a crucially important factor in this psychotropic activity.

Zusammenfassung. Psychopharmaka mit neuroleptischer, antidepressiver und/oder tranquillisierender Wirkung, die eine trizyklische Struktur besitzen, hemmen in vitro dosisabhängig die Prostaglandin-Synthetase, welche aus Ochsensamenblase isoliert wurde. Hingegen weist das Neuroleptikum Haloperidol, das sich strukturell von den anderen untersuchten Präparaten wesentlich unterscheidet, kaum einen solchen Effekt auf. Die pharmakologische Bedeutung dieser Befunde wird diskutiert.

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[7] K. Green and B. Samuelsson, J. Lipid Res. *5*, 117 (1964).
[8] P. Krupp, B. Exer, R. Menassé and R. Ziel, in preparation.
[9] R. J. Flower, Pharmac. Rev. *26*, 33 (1974).
[10] R. Jaques and L. Riesterer, Pharmacol. *6*, 29 (1971).
[11] M. Rocha e Silva and J. Garcia Leme, in *Chemical Mediators of the Acute Inflammatory Reaction* (Pergamon Press, London 1973), p. 76.
[12] M. D. Scott, Practitioner *202*, 802 (1969).
[13] L. Stjärne, Acta physiol. scand. *86*, 388 (1972).
[14] P. Hedqvist, in *Advances in the Biosciences*, Suppl. (Eds. S. Bergström and S. Bernard; Pergamon Press, London 1973), Vol. 9, p. 75.
[15] F. Sulser and E. Sanders-Bush, A. Rev. Pharmac. *11*, 209 (1971).