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CC/NUMBER 48
DECEMBER 2, 1985

Carlsson A & Lindqvist M. Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain.
Acta Pharmacol Toxicol. **20**:140-4, 1963.
[Department of Pharmacology, University of Göteborg, Sweden]

Following inhibition of monoamine oxidase, the catecholamine metabolites 3-methoxytyramine and normetanephrine accumulated in mouse brain. This accumulation was specifically enhanced by small doses of neuroleptics. It is suggested that neuroleptics stimulate dopamine and noradrenaline turnover by a compensatory activation of monoaminergic neurons following blockade of their respective receptors. [This paper has been cited in over 1,010 publications, making it the most-cited paper for this journal.]

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September 27, 1985

This paper described for the first time a specific action of major neuroleptic (antipsychotic) drugs upon metabolic processes in the brain, and a mode of action was proposed. The study was undertaken in the hope that our recently improved fluorometric methods for the determination of basic catecholamine metabolites would enable us to solve the riddle of why the major antipsychotic agents, such as chlorpromazine and haloperidol, had a reserpine-like pharmacological and clinical profile and yet lacked the monoamine-depleting properties of the latter drug. Earlier, an inhibitory action of chlorpromazine on the turnover of monoamines in the brains of small rodents had been reported. However, when the chlorpromazine-induced hypothermia was prevented, the effect was no longer detectable.

As shown in this paper, chlorpromazine and haloperidol actually *enhanced* the turnover of dopamine and noradrenaline in brain; they accelerated the metabolite formation, while leaving the neurotransmitter levels unchanged. In support of the specificity we showed that promethazine (a sedative phenothiazine lacking antipsychotic and neuroleptic properties) did not change the turnover of the catecholamines. It did not seem farfetched, then, to propose that rather than reducing the availability of monoamines, as does reserpine, the major antipsychotic drugs block the receptors mediating dopamine and noradrenaline neurotransmission. This would explain their reserpine-like pharmacological profile. To account for the enhanced catecholamine turnover, we proposed that neurons can increase their physiological activity in response to receptor blockade. This, I believe, was the first time that a receptor-mediated feedback control of neuronal activity was proposed.

These findings and interpretations have been amply confirmed and extended by numerous workers, using a variety of techniques. In the following year three of my students discovered the neuroleptic-induced increase in the concentrations of deaminated dopamine metabolites.[1] Despite confirmatory work by others, our findings did not receive much attention until several years later. A possible explanation for this was that in the 1960s most workers in this field were focusing on other aspects of neurotransmission. However, a fairly dramatic change occurred in the early 1970s. Since then receptors have attracted an ever-increasing interest. Moreover, the ability of catecholaminergic, especially dopaminergic, agonists and antagonists to induce and alleviate, respectively, psychotic symptoms, led to the much-debated "dopamine hypothesis" of schizophrenia. The historical background and recent developments in this field have recently been reviewed.[2]

This research took place in the Department of Pharmacology, University of Göteborg, where I was (and still am) professor of pharmacology. Margit Lindqvist died in 1978 at the age of 54; she was a highly skillful research engineer who had been my close collaborator since the 1940s.

1 **Andén N-E, Roos B-E & Werdinius B.** Effects of chlorpromazine, haloperidol and reserpine on the levels of phenolic acids in rabbit corpus striatum *Life Sci* 3 149-58, 1964 (Cited 425 times)

2 **Carlsson A.** Antipsychotic agents elucidation of their mode of action (Parnham M J & Bruinvels J, eds) *Discoveries in pharmacology Volume 1 psycho- and neuro-pharmacology* Amsterdam Elsevier, 1983 p 197-206

