The mechanism of action of antidepressants revised

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Summary. The discovery of the clinical efficacy of imipramine and of the MAO-inhibitor iproniazid intensively stimulated biochemical-pharmacological research on the mechanism of action of antidepressants. Due to these investigations, until recently an enhanced activity of the central noradrenergic and/or serotonergic transmitter system was considered essential for the clinical antidepressive action. Such enhancement could be achieved either presynaptically by blocking \( \alpha_2 \)-adrenergic receptors, or in the synaptic cleft by inhibiting the transmitter reuptake or the main metabolic enzyme, MAO. The common final result, especially of chronic treatment, was the down-regulation of postsynaptic \( \beta \)-receptors, modulated by interaction with the serotonergic system, neuropeptides, and hormones. The delay of clinical response corresponded better with such receptor alterations. However, the introduction of new, more selective antidepressants led to new reflections upon the mechanism of action. On the level of transmitters, \( \alpha_1 \)-up-regulation, increased activity of the dopaminergic system, an alteration in the balance between the different transmitter systems, are reported and seem to be important. Most promising are recent investigations of the second messenger systems, the adenylate cyclase system and the phosphatidylinositol system. Both systems are modulated by antidepressant drugs including lithium and carbamazepine. These second messengers, in turn, modulate the phosphorylation status of neuronal proteins via protein kinase, which may lead to elevations of the above mentioned receptors and again their transduction systems.

Introduction

The discovery of the antidepressant activity of imipramine (Kuhn, 1957) and of the monoamine oxidase (MAO) inhibitor iproniazide (Crane, 1957) enormously stimulated biological investigations on the pathophysiology of
depressive illnesses and the mechanism of action of antidepressants. The observation of the frequent occurrence of depressive symptoms after treating hypertension with reserpine, which depletes the vesicles in nerve endings from catecholamine and serotonin (5-HT), lead to the development of the catecholamine (Schildkraut, 1965; Matussek, 1969) and serotonin (Coppen, 1967) hypotheses of depression. It should be mentioned that some other hypotheses, such as the GABA and acetylcholine-hypotheses, are postulated, too. In relation to the mechanism of action of antidepressants this article mainly focuses on the 5-HT, DA and second messenger systems without, however, claiming to be complete. Tricyclic antidepressants reverse the behavioural symptoms such as catalepsy of reserpine in animals and this effect is related to the reuptake inhibition of norepinephrine (NE) and 5-HT into the nerve endings. This reuptake inhibition, which is an important inactivating step, results in an enrichment of the two transmitters NE and 5-HT in the synaptic cleft and thereafter the stimulation of postsynaptic α- and β-adrenergic and 5-HT receptors. A similar effect could be achieved with MAO inhibitors by affecting the catabolism of both NE and 5-HT. For many years this effect was considered to be the precondition for antidepressant activity. Controversial discussions arose only with regard to the relative potency of inhibiting NE or 5-HT reuptake. These controversial discussions were complicated by the fact that tricyclic antidepressants were metabolized, e.g. demethylated in the body and, frequently, the active metabolite had a different potency on these inhibitory effects. However, neither the catecholamine nor the serotonin hypothesis could be confirmed in depressive patients. As reasons for this failure were discussed the heterogeneity of the illness, e.g. neurotic vs. endogenous depressives, and adaptions of the transmitter systems. MHPG and 5-HIAA, the metabolites of the two amines NE and 5-HT, were influenced similarly (Potter et al., 1985) and could neither clarify the discussion. Clinically, the onset of the antidepressant action differs from the biochemical effects. The uptake inhibition occurs suddenly, whereas the therapeutic effect needs two to three weeks.

The development of new antidepressants, e.g. mianserine, having no reuptake inhibition lead to further doubts concerning the validity of this concept. In the meantime Vetulani and Sulser (1975) demonstrated that treatment of animals with tricyclic antidepressants resulted in a decrease of the stimulation of cAMP by isoproterenol, which they termed β-down-regulation. This β-down-regulation was characteristic for all antidepressants known and occurred with a time delay, thus corresponding better with the clinical antidepressant activity. Even the controversy concerning the catecholamine and 5-HT hypotheses could be explained, because β-down-regulation requires an intact 5-HT system (Racagni and Brunello, 1984). The discovery of β-down-regulation together with neuroendocrine findings showing a decreased sensitivity of α2-receptors (Matussek et al., 1980) and, probably, an increased sensitivity of β-receptors in depressive patients