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Johann-vor-der-Brüggen, Verena (2005):

Pharmacological characterisation of subtype-selective adenosine receptor antagonists in animal models of Parkinson´s disease and depression

Adenosine is a neuromodulator which is involved in a multitude of both physiological and pathological mechanisms in the body. Within the CNS, adenosine plays an important role in the regulation of motor processes and behaviour. Its biological effects are mediated through interaction with one of four G protein-coupled, membrane-bound receptor subtypes currently known as A_1, A_{2A}, A_{2B} and A_3. The adenosine A_1 and A_{2A} receptors predominate in the brain whereas the adenosine A_{2A} receptors are mainly located in the striatum. In the striatum, the adenosine A_{2A} receptors antagonistically interact with colocalized dopamine D_2 receptors. A degeneration of the striatum with a progressive depletion of dopamine leads to the clinical situation of Parkinson´s Disease. This disease belongs to the most common neurodegenerative disorders in Germany. The motor impairment which comes along with this disease can be improved with adenosine A_{2A} receptor antagonists. In addition to this antiparkinsonian effect, animal models of depression also indicate an antidepressant effect of these compounds. Depression is a psychiatric disease with a high prevalence within the population. In European countries, 5-10 % of the population is affected. The exact pathophysiological mechanisms that underlie human depression are not yet completely understood. Besides the involvement of serotonine and noradrenaline, dopamine also seems to play an important role.

The goal of this project was to investigate the effect of three adenosine receptor antagonists of different subtypselectivity to the adenosine A_{2A} receptors in the Haloperidol-induced catalepsy, an animal model for Parkinson´s disease, and in two animal models of depression, namely the Forced Swim Test and the Olfactory Bulbectomy. The substances used in this project were the unselective adenosine receptor antagonist Theophylline, the moderately selective elbion substance A and the highly selective KW-6002.

In the Haloperidol-induced catalepsy, a possible correlation of the anticataleptic effect and the level of subtypselectivity of the investigated adenosine receptor antagonists was examined in addition to the time-effect curve. All three substances led to a clear reduction of the Haloperidol-induced catalepsy in the mouse and the rat. Differences in the level of effect and its duration were produced by pharmacokinetic parameters rather than the level of subtypselectivity.

The anticataleptic effective compounds were then examined for an antidepressant

effect in the Forced Swim Test in mice. The examined dosages of all three adenosine receptor antagonists revealed an antidepressant effect by significantly reducing the immobility time. This antidepressant effect was further investigated in the Olfactory Bulbectomy in rats, a valid animal model of depression. The removal of the olfactory bulbs induces numerous neurochemical, neuroendocrine and neuroimmune changes and also changes in the rats' behaviour. So bulbectomized rats show hyperactivity in a new, aversive environment. Paralleling the clinical situation in humans, this behavioural feature is reversed only by chronic treatment with antidepressants and not after acute treatment like in the Forced Swim Test. The adenosine receptor antagonists were applied to the animals for fifteen days. The antidepressant effect of the adenosine receptor antagonists that could be observed in the Forced Swim Test could not be seen in the Olfactory Bulbectomy. Unlike Imipramine and Amitriptyline, the two reference compounds, the treatment with adenosine receptor antagonists did not attenuate the hyperactivity of the bulbectomized rats. Theophylline (30 mg/kg b.w. p.o. sid), elbion substance A (30 mg/kg b.w. p.o. bid) and KW-6002 (10 mg/kg p.o. sid) further increased the locomotor activity of the bulbectomized rats. A statistically significant effect however was only achieved after treatment with elbion substance A. In the sham-operated animals, treatment with Theophylline and KW-6002 also led to an increase in locomotor activity in the *Open Field*. Due to this stimulative effect of adenosine A_{2A} receptor antagonists an antidepressant efficacy of the adenosine receptor antagonists in the Forced Swim Test should be evaluated cautiously. It is possible that the antidepressant effect in the Forced Swim Test reveals a false positive result. The Olfactory Bulbectomy is mainly used as an animal model for agitated depression. The likelihood is that it is not the adequate model for detecting an antidepressant efficacy of motor stimulating compounds. A false negative antidepressant effect of the investigated adenosine receptor antagonists in this model seems to be likely. Clinical studies in patients with different forms of depression should show whether adenosine A_{2A} receptor antagonists are suitable for an antidepressant treatment especially of the inhibited depression.