Pharmacological evaluation of some alpha-adrenoceptor and dopamine receptor agonists

Oene, Johannes Cornelis van

SUMMARY

This thesis describes the investigations that have been performed in order to assess the pharmacological properties of some putative dopamine receptor agonists.

Chapter I is an introduction to the subject of this thesis and deals with the neurotransmitters dopamine and noradrenaline and their physiological significance. The various postulated receptor (sub)types for these transmitters are mentioned and the potential significance of directly-acting agonists at these receptors for the therapy of various disease states is briefly discussed.

Chapter II contains a comprehensive treatise of the pharmacological methods that have been used to assess the stimulating properties of the investigated compounds at dopamine receptors and α_2-adrenoceptors.

Chapter III is an introduction to the first part of the original work, which deals with the pharmacological properties of the imidazolidine derivative DPI. This compound had been proposed as a selective agonist at a postulated subtype of dopamine receptor i.e. the so-called dopamine-inhibitory (DAi) receptor. The chapter describes the chemical synthesis of DPI and a number of its physico-chemical properties. Structure-activity relationships of imidazol(id)ine derivatives at α-adrenoceptors and histamine receptors are briefly discussed.

Chapters IV, V and VI are original publications that consider the effects of DPI in test models for the assessment of dopamine receptor and/or α-adrenoceptor stimulating potency. The results demonstrate that DPI was ineffective in stimulating dopamine receptors but that on the contrary all its effects could be satisfactorily explained by a stimulation of α_1- and/or α_2-adrenoceptors. These effects and the involved receptor types (between brackets) are : a reduction of the rate of dopamine synthesis, utilization and metabolism in the rat striatum (α_2), a reduction of the depolarization-induced release of noradrenaline from rat neocortical slices (α_2), a reduction of the motility of rats ($\alpha_1 + \alpha_2$), the induction of prostration in rats (α_1), an increase in the diastolic blood pressure of pithed rats ($\alpha_1 + \alpha_2$), and the reduction of the rectal temperature of rats ($\alpha_1 + \alpha_2$).

Chapter VIII summarizes these results as well as the available literature data concerning the pharmacological properties of DPI. It also contains a critical commentary upon those publications that report in any way a stimulation of dopamine receptors by DPI. The final conclusion is that DPI is not a dopamine agonist, but that it has to be pharmacologically classified as a mixed α_1/α_2-adrenoceptor agonist.

Chapter IX mentions the effects of a pair of octahydrobenzo(f)quinoline derivatives as rigid analogues of the selective dopamine autoreceptor agonist 3-PPP. The results obtained show that the *cis* compound c7-OBQ was inactive, whereas its *trans* isomer t7-OBQ had a much higher potency than 3-PPP in stimulating dopamine autoreceptors. In contrast to 3-PPP, however, t7-OBQ was clearly effective in stimulating postsynaptic dopamine receptors and thus

lacked the dopamine autoreceptor selectivity of 3-PPP.
Chapter X compares the effectiveness of a number of structurally related 2-aminotetralin derivatives in stimulating dopamine autoreceptors and postsynaptic dopamine receptors, respectively. Considering structure-activity relationships of these compounds in stimulating dopamine autoreceptors it appears that N,N-di-n-propyl substitution is optimal but that introduction of one N-substituent larger than n-propyl is tolerable without considerable loss of potency. Most prominent, however, is the importance of the position of the aromatic hydroxyl function. 5-Hydroxylated derivatives are somewhat more potent in stimulating dopamine autoreceptors than their 7-hydroxylated analogues, but the 5-hydroxyl substitution pattern appears to be essential in order to achieve a more than moderate potency in stimulating postsynaptic dopamine receptors. Compounds that lack the 5-hydroxyl substituent, on the other hand, demonstrate a high degree of selectivity for dopamine autoreceptors as compared to postsynaptic dopamine receptors, and the 7-hydroxylated N,N-di-n-propyl-substituted derivative DP-7-AT emerged as the most potent and selective dopamine autoreceptor agonist of the series investigated.
Chapter XI starts with a further elaboration of the results obtained in measuring normal dopamine synthesis rate and the influence of drug treatments upon this parameter. Some calculations are presented that possibly allow the determination of the extent to which synthesis-regulating dopamine autoreceptors are normally stimulated by endogenous dopamine in the rat corpus striatum and tuberculum olfactorium. A comparison is made between some frequently-used biochemical test models for the assessment of dopamine autoreceptor stimulating potency. Data of some comprehensive literature reports on the effectiveness of a large number of dopamine agonists in these test models are summarized and briefly discussed. A summary is also given of what is known about the effectiveness of the two most widely investigated monohydroxylated derivatives of 2-aminotetralin i.e. DP-5-AT and DP-7-AT in stimulating dopamine receptors and α-adrenoceptors. A schematic presentation is given of the relationships between the chemical structures of hydroxylated 2-aminotetralin derivatives and their stimulating activities at dopamine receptors and α_2-adrenoceptors. DP-5-AT and DP-7-AT appear to be the derivatives with the highest selectivity for dopamine receptors as compared to α_2-adrenoceptors. It is demonstrated that both these compounds are ineffective in stimulating rat central α_2-adrenoceptors at a dose that produces a maximal stimulation of dopamine autoreceptors. Finally it is concluded that DP-5-AT and DP-7-AT may be designated as selective dopamine receptor agonists; DP-5-AT is capable of stimulating both dopamine autoreceptors and postsynaptic dopamine receptors, whereas DP-7-AT exhibits a selective stimulatory influence upon dopamine autoreceptors.