

CHAPTER 10

DISCUSSION

Potential therapeutic DA agents

The aim of the research described in this thesis is to gain more insight into factors that determine the activity at dopaminergic and serotonergic receptors and to use this knowledge for the development of new more selective dopaminergic and serotonergic agents.

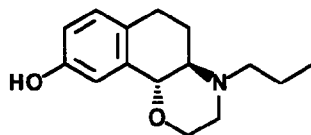
10.1 DA Agonists

Until recently, the main interest in developing new and efficient DA agonists was for the treatment of Parkinson's disease. This development is still important, because at this moment there are only a few centrally active compounds on the market. However, with these drugs (L-DOPA, bromocryptine, lisuride), psychotropic side effects are observed.

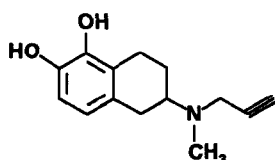
The 2-aminotetralins, being one of the most important group of compounds, have increased our understanding of the neurobiology of the dopaminergic systems. The two most studied and potent DA receptor agonists 5-OH-DPAT and 7-OH-DPAT were resolved, and it was shown that the active enantiomers have the (S) and (R) configuration, respectively. This has led to the McDermed receptor concept [1] which is the basis for the development of almost all the compounds synthesized in this thesis.

The most potent DA agonist we have prepared is the 4-propyl-9-hydroxyhexahydronaphthoxazine (PHNO/N-0500). This compound has been shown by ourselves and others [2] to be a very potent D₂ agonist in various *in vitro* and *in vivo* test systems. In addition, its activity at various other receptors (α , 5-HT, NE) is low. The activity resided, as expected, in the (R)-(+)-enantiomer. Martin et al. [3] have stated that the (R)-(+)-enantiomer is "the most active DA agonist yet discovered". The compound has reached the clinic and, unlike the phenolic aminotetralins (e.g. N-0437), it is readily absorbed in primates when given either transdermally or subcutaneously, as well as orally.

The discovery that the selective MAO-B inhibitor Selegiline[®] is free of the



tyramine effect and is able to prevent the toxicity of MPTP, has led to the reassessment of Selegiline® and it is now widely used in the early management of Parkinson's disease. Therefore we have introduced some MAO inhibiting properties within the dopaminergic 2-aminotetralins to try to combine the benefits of both properties. The results we have indicate that, at least for the 2-aminotetralins, it is very difficult to obtain a high degree of both properties in one and the same molecule. The dopaminergic effect dominates in the catechols, whereas the MAO-inhibitory effects are stronger in the non- and monohydroxylated compounds. The catechols have in some models potencies, comparable with those of apomorphine. New delivery systems have lead to the rediscovery of apomorphine in the treatment of Parkinson's disease [4]. In combination with domperidone, a peripheral DA antagonist that blocks peripheral side effects, the compound significantly reduces daily "off" periods in Parkinsonian patients.



5,6-(OH)₂-N-methyl-N-propargyl-ATN

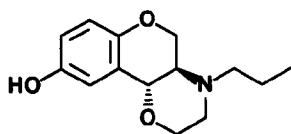
consequences have yet resulted from these observations. 5,6-Dihydroxy-2(N-methyl-N-propargylamino)tetralin has a moderate but 4-5 fold selectivity for MAO-A, leaving in the periphery enough MAO-A/B intact to metabolize ingested tyramine. The levels of NE, 5-HT and to a certain degree DA, can be increased by these MAO inhibiting properties.

This make these dopaminergic catecholamines with MAO-inhibiting properties interesting for further research in relation to Parkinson's disease. Reduced neurotransmitter concentrations have also been described for non-dopaminergic systems, e.g. 5-HT and NE, in several parts of the CNS [5]. It is noteworthy that no practical

10.2 DA autoreceptor agonists

Many DA receptor antagonists have become efficient medicines for treating psychoses. However, most of them induce severe extrapyramidal side effects akin to Parkinsonian symptoms and tardive dyskinesias. The main interest in developing selective autoreceptor agonists is based on the idea that they may be useful in treating schizophrenia [6]. Thus if the latter diseased state is due to an overactivity in one or several of the DA systems in the CNS, then selective stimulation of the autoreceptor should reduce DA synthesis and/or release and lead to improvement of the symptomatology of the disease.

On the basis of data indicating that the *trans*-hexahydronaphthoxazines and 8-hydroxy-chromanamines possess good biological activity, we have synthesized, as a structural extension of these compounds, the *trans*-tetrahydrobenzopyranoxazines.



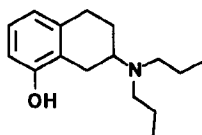
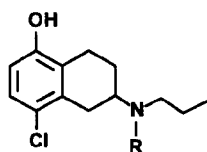
Benzopyranoxazine

Surprisingly these compounds have weak to modest activity for D₂ receptors. This weak activity cannot readily be explained on the basis of molecular conformations. The inspection of the molecular models of the 2-aminotetralins, naphthoxazines, chromanamines and benzopyranoxazines reveals a close similarity in size and

shape, as well as in location of the hydroxyl and amino functions. We have found that all compounds are lipophilic enough to pass the blood brain barrier. The only demonstrable difference was the degree of protonation of the nitrogen atom under physiological conditions. The benzopyranoxazines were only protonated to an extent of 2-4%. We therefore conclude that the unexpectedly low activity is a consequence of the low pK_a values. This suggestion is supported by studies of Miller et al. [7] and Seeman and Guan [8] who showed that permanently charged residues have affinity for, and can activate D₂ receptors. However, the 9-hydroxy derivative has demonstrated DA autoreceptor activity [9]. Because some partial DA agonists can produce antipsychotic-like effects, Arndt and Hyttel [10] have stated, that the apparent autoreceptor selectivity of many DA agonists stems from low intrinsic activity at D₂ receptors rather than absolute affinities for presynaptic versus postsynaptic DA receptors. Hitherto, the most used methods to produce an autoreceptor selective profile were i) introduction of steric bulk, which is likely to bring about some degree of steric hindrance at the drug receptor interaction; ii) variation of the position of the aromatic hydroxyl groups; iii) variation of the N-substituents [11]. From the results presented in Chapter 7 it seems a sound strategy to diminish the intrinsic efficacy of full agonists by manipulation of the pK_a value of the nitrogen atom making them only active at the more sensitive presynaptic receptors. However, several other possible strategies might work as well.

10.3 DA / 5-HT_{1A} Balance

The 5-HT_{1A} receptor has greater homology with dopaminergic receptors than with the other serotonergic subtypes. The pharmacological results of the 8-chlorinated



8-OH-DPAT

5-hydroxy-2-aminotetralins indicate that a small modification within dopaminergic molecules can give compounds which have affinity also for the 5-HT_{1A} receptor. So, it is likely that there is a delicate balance between the SAR of dopaminergic and serotonergic (5-HT_{1A})

compounds. In 8-OH-DPAT the hydroxyl function can act as hydrogen bond donor. Obviously, H-bond acceptance by the chlorine atom is sufficient for inducing 5-HT_{1A} interaction. The stereoselectivity is low, the R-enantiomers have a slightly higher affinity for the 5-HT_{1A} receptor than the S-enantiomers. The (R)- and (S)-enantiomers of 8-Cl-5-OH-DPAT are equipotent. However, there seems to be a trend to higher enantiomeric differences when one n-propyl group is replaced by a larger substituent like phenylethyl.

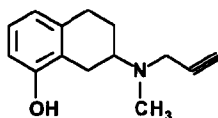
All the chlorinated compounds display affinity for the D₁ and D₂ DA receptor sites. However, the chlorinated compounds have lower affinities than their non-chlorinated analogues. Surprisingly, for the enantiomers of 8-chloro-N-0434 (R = phenylethyl), the K_i values for [³H]-spiperone displacement were not significantly different. This is in agreement with results found in competition experiments with the enantiomers of the non-chlorinated compound and with the DA agonist [³H]-N-0437 as the radioligand [12]. In these experiments, the (S)-(-) and (R)-(+)-enantiomers both display a high affinity for the D₂ receptor, IC₅₀ values of 0.5 and 5.5 nM, respectively.

The effect of chlorination was also remarkable in the presynaptic brain microdialysis model. While (±)-N-0434 shows a decrease in DA release, racemic 8-chloro-N-0434 and its (R)-(+)-enantiomer showed an increase, indicating that these compounds have DA antagonistic effects. (R)-(+)-8-chloro-N-0434 exhibited in the postsynaptic 6-OHDA model no contralateral turning, so the compound behaves as a real antagonist.

8-Cl-N-0437 gave, after infusion, a decrease in DA release in the brain microdialysis model, whereas no activity was displayed in the 6-OHDA model. An explanation for this discrepancy between the two models could be the higher speed of glucuronidation [21].

A New 8-OH-DPAT Analogue with Combined MAO-inhibiting and 5-HT_{1A} Agonistic Activities

The advent of selective 5-HT_{1A} receptor agonists, showing antidepressant activity, has focussed increased attention on serotonergic mechanisms as being central to the pathophysiology of mood disorders. Further it is believed that there is a beneficial effect of MAO-A inhibition in depression. It is assumed that MAO-inhibitors exert their therapeutic effect through a central mechanism [14]. To acquire site selectivity two structural analogues of the 5-HT_{1A} receptor agonist 8-OH-DPAT were synthesized.



8-OH-N-methyl-N-propargyl-ATN

The first studies in the brain microdialysis model indicate that, compared with the selective MAO-A inhibitor clorgyline, there is a shift in the ratio for the increase in 5-HT over DA extracellular concentrations. However, further research is needed to elucidate this selectivity. The compounds also induced the 5-HT syndrome. Therefore, these results suggest that, possibly through the similarity with the 5-HT_{1A} receptor agonist 8-OH-DPAT, site-selectivity is introduced which resulted in a relative stronger inhibition of MAO-A.

General Remarks

The results of several years of chemical and pharmacological studies of dopaminergic agonists permit some general conclusions to be drawn.

i) Many of the structure-activity relationships that have been made in the past by us, as well by others, do not necessarily reflect the true nature of the agonist receptor interactions. However, these correlations can be used to stimulate the creativity in design of new biologically active compounds.

ii) The results obtained with the enantiomers of 8-Cl-N-0434 and with the enantiomers of several other aminotetralins [13], emphasize the importance of testing enantiomers instead of racemic mixtures.

iii) Differences in metabolic fate of isomeric aminotetralins emphasize the need for a greater consideration of metabolic factors in design of new candidate molecules for DA/5-HT_{1A} activity. In the 2-aminotetralins, differences in metabolic pathways seem to be an important factor in determining spectrum and sites of dopaminergic effects.

It is recommendable therefore, that bioavailability studies should be carried out as early as possible since lack of the desired response may be attributable to an agent's ability to reach therapeutic concentration in the circulation. Such finding could warrant the synthesis of suitably modified derivatives or the development of alternative dosage formulations to maximize bioavailability.

iv) Because the receptors coupled with G-proteins share a variety of structural and functional similarities, it is therefore not surprising that also ligands possess structural similarities. In this respect the aminotetralins are many-faced compounds, showing activities on various receptors or receptor subtypes. In Figure 10.1 a collection of different aminotetralins is taken from literature [1,15-20].

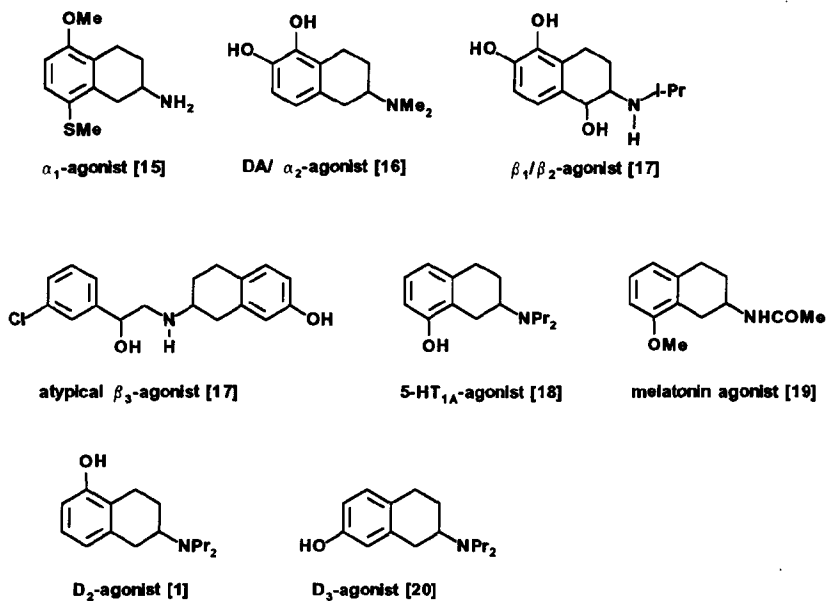


Figure 10.1. Various aminotetralins interacting with different G-protein coupled receptors

10.4 References

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