GENERAL DISCUSSION

An established strategy in medicinal chemistry to develop agonists and/or antagonists of biologically active substances, such as neurotransmitters and hormones, which exert their effects through the interaction with specific receptors, is the rigid analogue approach. This approach involves the creation of conformationally restricted analogues of flexible biologically active substances [1]. Due to their conformational restraint, conformationally restricted analogues may show selectivity for a certain receptor subtype of the biologically active substance they are mimicking. These conformationally restricted analogues can be used as pharmacological tools to gain more information about the mode of action of these biologically active substances. Moreover, they can ultimately lead to clinically applicable drugs.

THE SEMI-RIGID 2-AMINOTETRALIN SYSTEM:
A STRUCTURAL BASE FOR ANALOGUES OF BIOLOGICALLY ACTIVE SUBSTANCES

Considering the molecular structure of the important CNS neurotransmitter dopamine (1), it can be seen that this structure contains a flexible ethylamine side chain. A well-known method to rigidify this structure is the incorporation into a semi-rigid 2-aminotetralin system. This system has been suggested to be the dopaminergic pharmacophore in the classical dopamine-receptor agonist (6αR)-(−)-apomorphine [2]. The 2-aminotetralin system fixes the flexible side chain in an extended trans conformation with the amino group close to the plane through the aromatic ring. Two such dopamine analogues, representing the two possible conformational extremes of the trans coplanar form of dopamine, i.e. 5,6-dihydroxy-2-aminotetralin [5,6-(OH)₂-AT, 2] and 6,7-dihydroxy-2-aminotetralin [6,7-(OH)₂-AT, 3], exert moderate activity at central dopamine receptors (for reviews, see ref. 3-6).

![Chart GD.1 Rigidification of rotameric conformers of dopamine (1) through incorporation into a semi-rigid 2-aminotetralin system.](image-url)
Previous SAR studies with analogues of these two 2-aminotetralins revealed that minor changes can lead to 2-aminotetralins displaying a certain dopamine-receptor subtype selectivity. In relation to the classical biochemical/pharmacological classification of dopamine receptors in two subtypes, i.e. D₁ receptors and D₂ receptors [7], it was shown that 5,6-dihydroxy-2-(N,N-di-n-propy1amino)tetratin [5,6-(OH)₂-DPAT, 4] and 6,7-dihydroxy-2-(N,N-di-n-propy1amino)tetratin [6,7-(OH)₂-DPAT, 5] act as mixed D₁/D₂-receptor agonists, whereas 5-hydroxy-2-(N,N-di-n-propy1amino)tetratin (5-OH-DPAT, 6) and 7-hydroxy-2-(N,N-di-n-propy1amino)tetratin (7-OH-DPAT, 7) display selectivity for D₂-receptors in comparison to their catechol analogues [6,8-10].

Moreover, N-0434 (8) and N-0437 (9), 5-hydroxy-2-aminotetralins with a N-aryl-ethyl substituent, appeared to be extremely potent and selective D₂-receptor agonists [10-13]. In contrast, 8-chloro-6,7-dihydroxy-2-aminotetralin (10) and 8-fluoro-6,7-dihydroxy-2-aminotetralin (11) were found to be relatively selective D₁-receptor agonists [14].
Keeping the pharmacological profiles of the above-mentioned 2-aminotetralins in mind, it is not surprising that 5,6-dihydroxy-2-[N-n-propyl-N-2-(2-thienyl)ethylamino]tetralin [5,6-(OH)2-PTAT, 12] turns out to be a potent mixed D1/D2-receptor agonist [15]. The fact that this compound, like all other 2-aminotetralins, contains an asymmetric C-2 atom should not be overlooked. It is not only very common that a certain pharmacological activity of a 2-aminotetralin mainly resides in one enantiomer, but it is also possible that the enantiomers have different pharmacological profiles, e.g. opposite effects. For example, the dopamine-receptor agonist activities of 5,6-(OH)2-DPAT (4) and 5-OH-DPAT (6) mainly reside in the (2S)-(−)-enantiomers, whereas the (2R)-(+) -enantiomers are the eutomers of 6,7-(OH)2-DPAT (5) and 7-OH-DPAT (7) [3-6]. In the case of N-0437 (9), the (2S)-(−)-enantiomer is the more active one [16,17]. Interestingly, the (2R)-(+) -enantiomer of N-0437 (9) behaves pharmacologically as a partial agonist at the D2 receptor [18]. Thus, this enantiomer can antagonize some dopamine-receptor agonist effects of the (2S)-(−)-enantiomer. In analogy, the more active enantiomer of 5,6-(OH)2-PTAT (12) has most likely the 2S absolute configuration. However, this suggestion can only be confirmed by the resolution of 5,6-(OH)2-PTAT (12) in its enantiomers and the subsequent pharmacological evaluation of the individual enantiomers.

![Chemical structure of 5,6-(OH)2-PTAT (12).](chart)

Previous SAR studies disclosed also that the semi-rigid 2-aminotetralin system is not only a structural template for conformationally restricted analogues of dopamine, but also for conformationally restricted analogues of the other catecholamines noradrenaline (13) and adrenaline (14). Particularly, 5,8-dimethoxy-2-aminotetralin (15) was shown to be a selective α1-receptor agonist, possessing greater potency than the prototypical α1-receptor agonist methoxamine (16) [19]. Likewise, 1,5,6-trihydroxy-2-(N-i-propylamino)tetralin (17), a semi-rigid analogue of the mixed β1/β2-receptor agonist isoprenaline (18) through the addition of an ethylene bridge, appeared to be a potent mixed β1/β2-receptor agonist [20].

![Chemical structures of the catecholamines noradrenaline (13) and adrenaline (14).](chart)
More surprisingly, it was found that 8-hydroxy-2-(N,N-di-n-propy1amino)tetratin (8-OH-DPAT, 20) acts as an agonist of the indolamine serotonin (5-hydroxytryptamine, 19) [21]. The 2-aminotetralin 8-OH-DPAT (20) can be taken as a molecular structure formed from serotonin by rigidification through the addition of a methylene bridge, followed firstly by molecular dissection of the pyrrole part of the indole nucleus, and secondly, by structural modification via N,N-di-n-propylation. Molecular dissection and structural modification are other strategies to develop biologically active agents. In particular, 8-OH-DPAT (20) is a potent, selective 5-HT_1A-receptor agonist [22]. This finding indicates that it is not always necessary to incorporate all the functional groups of a biologically active substance in a conformationally restricted analogue to mimic some of its activities.

In accordance with this line of reasoning, the 2-aminotetralin derivative 8-methoxy-2-(acetamido)tetratin (8-MeO-AAT, 22) was developed as a conformationally restricted analogue of melatonin (N-acetyl-5-methoxytryptamine, 21). 8-MeO-AAT (22) appeared to be a melatonin-receptor agonist of moderate potency [23-26]. Subsequently, 8-MeO-AAT (22) was used as a lead compound for a series of 8-methoxy-2-amidotetralins with melatonin-receptor agonist properties. It was also shown that the (-)-enantiomer of 8-MeO-AAT (22), possessing most likely the 2S absolute configuration, is more active at
the retinal melatonin receptor than its (+)-enantiomer. A very common approach to develop antagonists of a biologically active substance is the appendage of a bulky lipophilic group to an agonist or partial agonist of that specific, biologically active substance. This approach led to the development of 4-aryl-2-amidotetralins as potential melatonin-receptor antagonists [23,27]. These compounds possess two asymmetric ring carbon atoms. Hence, cis/trans isomerism as well as optical isomerism is involved. Racemic cis-4-phenyl-2-(acetamido)tetralin (23) is a conformationally restricted melatonin-receptor antagonist of reasonable affinity [23,24,26,27]. This nonindolic melatonin-receptor antagonist, based on the semi-rigid 2-aminotetralin system, is 10 times more potent than the indolic melatonin-receptor antagonist luzindole (N-acetyl-2-benzytryptamine, 24).

In conclusion, the semi-rigid 2-aminotetralin system can serve as a structural base for the development of conformationally restricted analogues of various biologically active substances, including the catecholamine dopamine (1) and the indolamide melatonin (21).

REFERENCES


(9) Seiler MP, Markstein R (1984) Further characterization of structural requirements for agonists at the striatal dopamine D2 receptor and a comparison with those at the striatal dopamine D1 receptor. Studies with a series of monohydroxyaminotetralins on acetylcholine release from rat striatum. Mol Pharmacol 26, 452-457.


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