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Dopamine Receptor Agonists: Intrinsic Activity vs. State of Receptor

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With 1 Figure

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Summary

Based on observations with the novel dopamine-receptor agonist 3-(3-hydroxyphenyl-)-N-n-propylpiperidine, 3-PPP, especially its levorotatory enantiomer, it is proposed that the intrinsic activity of a receptor agonist depends in part on the responsiveness of the receptor; this in turn is determined by the degree of previous agonist occupancy on the receptor. A change in occupancy will induce a slow conformational change, influencing the responsiveness. This may constitute an important aspect of receptor adaptation and may help to explain otherwise puzzling phenomena, *e.g.* that compounds such as (−)-3-PPP or transdihydrolisuride can act as strong dopamine-receptor agonists in some locations and as antagonists in others.

The observations discussed in the present paper may be interpreted to indicate that the dopamine receptors in different locations are, in fact, derived from a homogeneous receptor population, though in a varying state of adaptation. Thus it may prove worth-while to reconsider the various subclassifications of DA receptors proposed so far.

Introduction

The adaptation of receptors to agonist occupancy, as manifested *e.g.* in denervation supersensitivity, is often ascribed to a change in the number of receptor molecules; the affinity of the receptor for the agonist is generally considered to remain unchanged. Such conclusions, mainly based on "receptor"-binding data, have been drawn *e.g.* for dopamine (DA) receptors in the CNS (see review by *Seeman,* 1980).

However, the change in number of receptor molecules following *e.g.* denervation is often modest compared to the striking changes in physiological responses to an agonist. For example, after destruction of central dopaminergic pathways the increase in binding sites is only about 50 per cent (*Seeman,* 1980). Even though *Seeman* (1980) has proposed that a 40 percent increase in the number of DA receptors can account for a 4-fold increase in DA sensitivity, it may prove worthwhile to look for an alternative explanation.

Theoretically, the response to an agonist could depend not only on the number of receptor molecules and on their affinity for the agonist, but also on the responsiveness of the receptor. As is well known, agonists may differ in intrinsic activity, *i.e.* in the degree of maximum reponse elicited. In this presentation the possibility will be discussed that the intrinsic activity of an agonist depends not only on its molecular structure but also on the state of the receptor. The hypothesis is put forward that a given receptor molecule or receptor complex may adapt itself to a varying agonist occupancy by a conformational change that will influence the response to an agonist; this adaptation does not necessarily involve any change in the number of receptor molecules or in affinity. Synthesis of new receptor molecules may or may not be a prerequisite for the adaptive response.

Observations

The discussion will be based mainly on observations made with the novel dopamine receptor agonist (−)-3-(3-hydroxyphenyl)-N-n-propylpiperidine, in the following referred to as (−)-3-PPP. In several instances a comparison between the two enantiomers of 3-PPP has been useful.

Our first experiments were made with the racemic mixture of 3-PPP. This compound exhibits the profile of a dopaminergic agonist, acting selectively on the presynaptic dopamine receptors, so-called autoreceptors, in the rat forebrain, while leaving the postsynaptic dopamine receptors unchanged. Since activation of DA autoreceptors causes inhibition of presynaptic dopaminergic activity, *i.e.* firing and transmitter synthesis, release and metabolism, the most striking physiological change induced by such a compound will be inhibition of motility, especially exploratory behaviour (*Hjorth et al.,* 1981).

When later on the two enantiomers of 3-PPP became available, they were found to have different profiles. While the (+)-form behaved essentially like a classical DA-receptor agonist such as apomor-

phine, *i.e.* preferential activation of autoreceptors in low dosage and activation also of postsynaptic receptors in higher dosage, the (−)-form caused activation of DA autoreceptors to almost the same extent as the (+)-form but behaved as an antagonist on the postsynaptic receptors (*Hjorth et al.*, 1983).

We have subsequently extended our studies to DA receptors in other localities. The pattern thus emerging forms the basis of the present discussion. The most pertinent data will first be summarized.

1. Action of (−)-3-PPP on Postsynaptic Receptors of the Intact Rat Forebrain: Predominantly Antagonist Properties with at Most a Slight Intrinsic Activity

In normal rats (−)-3-PPP inhibits exploratory activity. In contrast to a classical DA receptor agonist, such as apomorphine, this agent exhibits no stimulating properties, *e.g.* increase in motility and sterotyped behaviour, even after high doses. It thus seems to be devoid of stimulating action on postsynaptic DA receptors. This assumption is strengthened by the fact that in reserpine-treated animals (−)-3-PPP causes at most a very slight increase in motility. Thus, if this agent has any intrinsic activity on postsynaptic DA receptors in the rat forebrain, it amounts to only a few percent of the maximum response elicited *e.g.* by apomorphine (*Hjorth et al.*, 1983).

2. Effect of 3-PPP on Presynaptic DA Receptors (Autoreceptors) in the Rat Forebrain

Both enantiomers of 3-PPP are strong agonists on DA autoreceptors, as indicated by reduced dopa formation and DA metabolite levels under conditions precluding the influence of feedback loops (pretreatment with gamma-butyrolactone or reserpine, *Hjorth et al.*, 1983, or after axotomy, *Magnusson et al.*, 1983).

3. Effect of 3-PPP on Prolactin Secretion

Both enantiomers of 3-PPP act as equipotent, strong agonists on the DA lactotroph receptors in the anterior pituitary (*Eriksson et al.*, 1983).

4. Effect of 3-PPP on DA Receptors of the Emetic Trigger Zone

Both enantiomers of 3-PPP elicit emesis after intravenous injection to dogs (*Martin et al.*, 1981, *Arnt et al.*, 1982). However, the

response appears to be less pronounced than after apomorphine treatment. Certain observations suggest that the (−)-form is less potent than the (+)-form (*G. Paalzow,* personal communication).

5. Effect of 3-PPP on Postsynaptic DA Receptors in the Rat Forebrain After Denervation by Intranigral 6-OH-DA Injection

After unilateral destruction of the nigrostriatal DA pathway by intranigral injection of 6-OH-DA, both enantiomers of 3-PPP elicited contralateral turning of an intensity comparable to apomorphine. The two enantiomers were approximately equipotent. The effects were blocked by DA-receptor antagonists (*Arnt et al.,* 1983).

The conventional interpretation of these findings would be that both enantiomers of 3-PPP act as full agonists on denervated DA receptors in the striatum. However, this conclusion should be regarded as tentative, in view of the shortcomings of this model (see *e.g. Costall et al.,* 1983). Further studies, *e.g.* on bilaterally denervated animals, are necessary to rule out an interference by DA receptors on the intact side.

Observations somewhat similar to those summarized above have been reported in an investigation on transdihydrolisuride (*Wachtel* and *Dorow,* 1983). This compound appears to be rather similar to (−)-3-PPP, at least as regards the actions described under points 1, 3, 4, and 5. The data published thus far do not permit any conclusions concerning the action of this agent on DA autoreceptors, *i.e.* with respect to point 2 above.

Discussion: Intrinsic Activity vs. State of Receptor

In the investigations summarized above control experiments were performed in order to ensure that the effects observed were indeed mediated via DA receptors, *e.g.* by treatment with DA receptor antagonists. Moreover, several observations support the view that 3-PPP and its enantiomers have no appreciable action on *e.g.* alpha-adrenergic or serotonergic receptors (for review, see *Hjorth,* 1983).

It is evident from the data referred to above that (−)-3-PPP behaves as an apparently full DA-receptor agonist in some locations and as a DA-receptor antagonist with a very slight, if any, intrinsic activity in other locations.

Moreover, the data suggest that there exists a relationship between the intrinsic activity of (−)-3-PPP and the degree of previous agonist occupancy on the receptor. On the normal postsynaptic DA receptor in the rat forebrain, where the agonist occupancy can be assumed to be high, (−)-3-PPP acts as an antagonist with at most a

slight intrinsic activity. Not even after reserpine pretreatment 18 hours beforehand, which can be assumed to induce a certain, albeit slight degree of receptor supersensitivity, did (−)-3-PPP show more than a trace of intrinsic activity.

On the other hand, on receptors where the agonist occupancy can be assumed to be low, since these receptors are largely or entirely located outside the synaptic cleft, (−)-3-PPP showed up as a potent and strong agonist with an intrinsic activity approaching that of its dextrorotatory enantiomer and apomorphine. This is true of DA autoreceptors, lactotroph receptors, and denervated postsynaptic receptors. In the emetic trigger zone, which may or may not receive a small dopaminergic input, (−)-3-PPP appears to behave like a partial agonist.

These data invite the speculation that the DA receptor molecules are basically the same in all the locations mentioned; their different responsiveness to an agonist such as (−)-3-PPP is a result of the adaptability of the receptor molecule, or of a component in the receptor complex (see Fig. 1). A change in agonist occupancy on the receptor will induce a slow conformational change influencing the responsiveness of the receptor. In this way one and the same receptor agonist will show a varying intrinsic activity, depending on the state of the receptor.

If the hypothesis proposed above is correct, it will have several important consequences. For example, if a receptor is adapted to a low occupancy (*e.g.* autoreceptors, lactotroph receptors, emetic receptors) it would be expected to manifest its adaptability mainly in

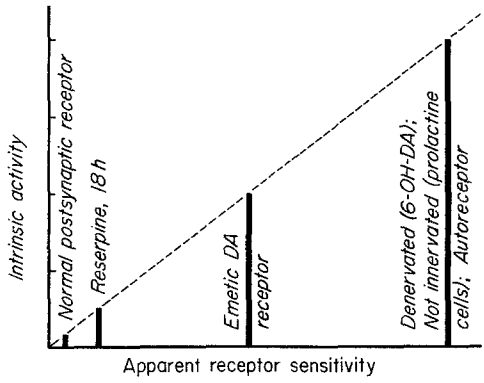

Fig. 1. Intrinsic activity of (−)-3-PPP in different localities: a possible function of the adaptive state of the dopamine receptor

response to an increased agonist occupancy. On the other hand, receptors adapted to a high agonist occupancy, such as the normal postsynaptic DA receptors of the CNS, would show their greatest adaptability in response to a reduced agonist occupancy. During chronic treatment with an agonist, *e.g.* L-dopa in Parkinson's disease, adaptation of DA autoreceptors and denervated, supersensitive postsynaptic receptors would predominate and lead to reduced sensitivity of these receptors, whereas any remaining innervated, normosensitive postsynaptic receptors would show less marked changes. This might contribute to the "on-off" problems during chronic L-dopa treatment (cf. *Carlsson,* 1983). On the other hand, the prompt adaptation of the emetic DA receptors to increased agonist occupancy is an obvious advantage.

Moreover, the various subclassifications of DA receptors proposed so far, *e.g.* into D-1, D-2, D-3 etc., many have to need revision; the possibility should be considered that we are dealing with a homogeneous receptor population, though in different states of adaptation.

A unitary DA-receptor concept has been proposed earlier, though on different grounds (*Laduron,* 1981).

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