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Partial dopamine agonists in the treatment of psychosis

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Summary. The discovery and characterization of dopamine in the mammalian brain earned Dr. Arvid Carlsson the Nobel Prize in 2000. Along with his many insights about dopamine pharmacology, came his proposal of the existence and critical role of dopamine autoreceptors in the overall regulation of dopamine-mediated neurotransmission. In this paper, the rationale, the putative mechanisms, and pertinent clinical data are reviewed to support the idea of the clinical relevance of dopamine agonists, especially partial agonists, in the treatment of psychosis. Evidence was gathered for the usefulness of this strategy in schizophrenia in early trials with apomorphine and N-propylnoraporphine (NPA). But clinical relevance was not a reality before the application of (−)-3PPP. These clinical results are presented. Moreover, now a partial dopamine agonist, aripiprazole, has been developed and will likely be marketed by BMS and Otsuka for the treatment of psychosis and will be the first drug in this class to be commercially available. Partial dopamine agonists represent the next new class of antipsychotic drugs, effective in treating schizophrenia.

Keywords: Dopamine, (−)-3PPP, schizophrenia, apomorphine, N-propylnorapomorphine.

Introduction

The award of the Nobel Prize in Medicine in December, 2000 to three eminent neuroscientists, drew deserved recognition to progress in the field of neurobiology and neuropharmacology. That one of those scientist was Arvid Carlsson, gave recognition to the seminal discoveries he has made over his extraordinarily productive career and to the application of these discoveries to advances in the treatment of brain diseases, including schizophrenia, Parkinson's and Alzheimer's diseases. Not only did Dr. Carlsson identify dopamine and its neurotransmitter function, in brain but he also explicated the importance of the substance for normal brain function and its potential relevance to several important human diseases. The most successful current

treatments for schizophrenia and for Parkinson's disease are based on pharmacologic manipulation of dopamine neurotransmission in brain. But, Dr. Carlsson's were not one-time contributions or advances for a single disease in these fields. Rather, his contributions were broad, sustained over time, modified and updated with basic neuroscience information as the fields expanded, and applied to theory and treatment development in a repeated and vigorous way. Dr. Carlsson's talent, insight, and understanding of mammalian brain mechanisms and techniques for relevant function evaluation have resulted in a tremendous legacy of brain science that will be an intellectual substrate for years to come.

One aspect of Dr. Carlsson's formulations that has found application in schizophrenia therapeutics has been his discovery of the role that dopamine autoreceptors play in modulating dopaminergic transmission. Several laboratories proposed autoreceptor regulation of monoamine neurotransmission (Farnebo and Hamberger, 1971; Langer, 1980). The postulate that dopamine neurons bear autoregulatory receptors sensitive to dopamine itself (Carlsson, 1975, 1976, 1983), coupled with early observations showing a therapeutic effect of dopamine agonists in psychosis (Douglas, 1900; Tamminga et al., 1978; Corsini, 1981), grew into a productive collaboration between Dr. Carlsson and myself to treat schizophrenic psychosis with partial dopamine agonists. The story of that background and those collaborative studies are presented here.

Schizophrenia is a psychiatric illness most successfully treated today with D_2 dopamine receptor blockers, using either the traditional drugs or the new antipsychotics with their lower motor side effects and possibly broader action (Klein and Davis, 1969; Tamminga et al., 2001). Although the discovery that dopamine receptor blockers are selective antipsychotic drugs was serendipitous (Delay et al., 1952), their mechanism of action was quickly identified (Carlsson and Lindquist, 1963; Anden et al., 1970) as antimonoaminergic, then antidopaminergic. This series of discoveries was the basis for not only the effective antipsychotic treatment agents we have today, but also for dopamine hypothesis of schizophrenia pathophysiology, suggesting that abnormalities in dopaminergic neurotransmission may underlie schizophrenia manifestations (Seeman et al., 1975; Creese, 1976).

Dopamine autoreceptors

Dopamine neurons bear D_2 and D_3 dopamine receptors sensitive to the neurotransmitter dopamine and its agonists, which function to regulate the synthesis and the release of dopamine. These dopamine autoreceptors, when stimulated reduce tyrosine hydroxylase activity and modulate the release of dopamine at the synapse, hence reduce dopamine-mediated neural transmission (Kehr et al., 1972; Walters et al., 1975; Carlsson, 1975). This pharmacologic action could theoretically be therapeutic in illnesses where dopamine receptor antagonists reduce symptoms. And because dopamine transmission is reduced but not blocked entirely, the possibility exists of reduced side effects with dopamine agonist treatment.

Dopamine agonists with high intrinsic activity (full agonists) behave as agonists at all dopamine receptors, both autoreceptors and postsynaptic sites (Ariens, 1983; Kenakin, 1993). However, the field has more recently developed and applied partial dopamine agonists in brain diseases, (−)-3PPP being the prototypical partial dopamine agonist (Carlsson, 1984). Ariens has described the steps of drug action at a receptor:

> "The affinity is the probability of a drug molecule binding to a free drug receptor at any given instant. The intrinsic efficacy of a drug is that inherent property that imparts the biological signal to the drug receptor (and this to the cell) to result in a biological response. . . . Thus, the affinity gets the drug to the receptor, and the intrinsic efficacy determines what it does when it gets there (Ariens, 1954)."

Partial agonists at the dopamine receptor are those drugs which have full affinity but limited intrinsic activity at that receptor. Unlike full agonists, partial agonists can behave as an agonist or as an antagonist, depending on the target receptor population and the local concentrations of the natural neurotransmitter dopamine.

Whereas full agonists reduce the resting, unstimulated levels of dopamine synthesis and release, partial dopamine agonists (PDAs) only reduce dopamine synthesis and release under circumstances of basal elevation, e.g. with gammabutyrolactone (GBL) block, reserpine treatment, or dopaminergic denervation (Clark et al., 1985a,b). At the postsynaptic receptor, especially those sites where the concentrations of dopamine itself are high, the PDAs characteristically behave as antagonists. They occupy the postsynaptic receptor, without having the full intrinsic activity of the natural neurotransmitter dopamine, thus deliver a lesser signal. PDA treatment usually increases dopamine synthesis and release, presumably through long loop feedback pathways, representing relative antagonist activity. PDAs exhibit variable intrinsic activity at different dopamine receptor populations. Carlsson (1983) proposed that the degree of intrinsic activity displayed by a PDA at a particular receptor population is dependent on the degree of usual agonist occupancy of the dopamine receptor at that site.

Thus, the strategy of using partial dopamine agonists as antidopaminergic antipsychotic agents is based on several sets of pharmacologic observations. Dopamine neurons have autoreceptors sensitive to dopamine itself and to its agonists and these function to decrease dopamine synthesis, release and neuronal firing under certain circumstances. And, partial agonists have full affinity but reduced intrinsic activity at postsynaptic dopamine receptors, consequently they exert relatively lower receptor stimulation in comparison with the natural neurotransmitter, dopamine and consequently behave as an antagonist. PDAs are agonists at autoreceptors and can behave as antagonists at postsynaptic receptors, blocking dopamine. Despite behaving as antagonists, the PDAs still retain a measure of agonist action at the receptor, hence having a lower tendency (or none at all) to upregulate that receptor as an antagonist would do.

Partial agonists at a given receptor can result from a combination of full agonist and full antagonist, as has been demonstrated by Kroosgard-Larson

with isomers of APPA at the AMPA receptor (Krogsgaard-Larsen, 1994). Likewise, the intrinsic activity of a dopamine agonist, can be modified along a range by combining it with low doses of an antagonist. We have demonstrated that the intrinsic activity of (−)-3PPP can be modified by low concentrations of haloperidol or clozapine (R.A. Lahti, personal communication). This combination of a PDA with low doses of an antagonist produces a flexible intrinsic activity PDA, potentially more broadly applicable to different disease conditions because of its adjustable intrinsic activity.

Schizophrenia studies with dopamine agonists

The early testing of dopamine agonist treatment approaches in schizophrenia began from this theoretical perspective. Progress in this area has been limited by the clinical necessity for specific agonist characteristics in effective compounds. Whereas dopamine receptor antagonists deliver their actions by simply blocking the receptor protein (denying access of the natural neurotransmitter), drugs which are agonists manifest their actions through the receptor, by altering the receptor protein. This is a more complex and consequential process. Pharmacologic characteristics of agonists, like their receptor affinity profile, specificity, and intrinsic activity all determine the acute drug action and can result in attenuation with repeated treatment. Moreover, agonists which are potent or have a prolonged half life or delivery will be prone to alter (i.e. desensitize) the dopamine receptor.

Apomorphine

Apomorphine was tested for the treatment of schizophrenic psychosis on the hypothesis that stimulation of the dopamine autoreceptor would reduce dopamine synthesis and release, reduce dopamine-mediated neurotransmission, and thereby improve psychotic symptoms (Tamminga et al., 1978). The initial selection of apomorphine as the pharmacologic probe was based on its clinical availability and its dopamine agonist pharmacology (Cotzias et al., 1976). Treatment was tested in hospitalized schizophrenic persons with active symptoms who were partially treated with traditional antipsychotic drugs. The group of 18 volunteer patients included paranoid, undifferentiated, and schizoaffective subtypes. Volunteers each received a single dose of apomorphine and placebo in random order one week apart with psychosis ratings for 8 hours after each drug administration. The change in positive psychotic symptoms after apomorphine was compared to the change after placebo.

The reduction in psychosis after apomorphine was -6.22 ± 0.4 compared with a change of $+1.67 \pm 09$ after placebo as rated on a modified New Haven Schizophrenia Scale (M-NHSS) ($p < .02$). Detailed individual analysis showed that 9 out of 18 patients had a 20% to 50% symptom reduction, whereas 4 out of the 18 showed no change and 5 out of 18, a slight worsening (clinically insignificant). These differences were not explained by age, sex, concomitant medication, or illness subtype. The clinical response in the

volunteers who improved was remarkable in its breadth, including cognitive reorganization as well as psychosis reduction. In retrospect, based on current knowledge of partial agonist action, and the combination in that study of a full agonist (apomorphine) with various antagonists (the traditional treatments), the differential response across patients may have been due to the dose (not type) of the concomitant antagonist, hence the variable intrinsic activity of the combination.

Thereafter, several additional dopamine agonists, including bromocriptine, were tested without any indication of an antipsychotic effect (Tamminga and Chase, 1980; Tamminga, 1980). Those agonists with high affinity for the serotonin receptor frequently caused motor hyperactivity in the volunteers and eventual study failure. No overall consensus developed to explain why some agonists were effective and others not, other than a broad monoaminergic activity.

N-propyl-norapomorphine

N-propyl-norapomorphine (NPA) is an apomorphine congener originally synthesized for the treatment of Parkinson's disease. It was tested in schizophrenia as a follow up to the apomorphine trial, in an attempt to find a practical treatment, based on the autoreceptor rationale and the apomorphine data (Tamminga, 1986). All volunteers were free from antipsychotic medication for four-weeks and received NPA daily in a single administration over a rising dose range from 25–40 mg or placebo in random design with outcome evaluated by blind raters at 2 and 4 hours after drug.

After acute administration, NPA significantly reduced psychosis in the schizophrenic volunteers (-6.9 ± 1.7) compared to placebo (-2.1 ± 0.09) across a range of doses. The overall group response was significant ($p < 0.02$), but individuals who were antipsychotic drug responders showed the greatest psychosis reduction (-9.7 ± 1.2 NPA vs -2.4 ± 1.1 placebo), especially in positive symptoms compared with neuroleptic treatment non-responders. Because the development of a practical treatment regimen was the goal of this work, repeated administration studies directly followed the initial encouraging acute results. However, subchronic NPA administration showed no efficacy at all when evaluated at the end of seven days in individual volunteers, whether in persons with a good history of treatment response or not.

These data suggested that the ability of a dopamine agonist to cause receptor desensitization with repeated administration could interfere with the therapeutic response and might be dependent on the intrinsic activity and the dosing schedule of the compound. It was clear from the agonist studies conducted thus far, that a dopamine agonist with special characteristics would be required for antipsychotic efficacy based on this model.

(−)-3PPP

Partial agonists at any receptor are those drugs which have full affinity for the receptor but limited intrinsic activity. Partial agonists are attracted to a receptor and bind to it, with an affinity similar to the natural ligand, but, once

bound, have a lesser activity (Ariens, 1983; Kenakin, 1993). Depending on the state of occupancy of that receptor, and the drug's intrinsic activity, these partial agonists can have an overall antagonist or agonist action on neurotransmission at that synapse (Carlsson, 1983). Partial agonists can have a high level of intrinsic activity (approaching the 100% activity of the natural agonist) and act much like a full agonist; or, they can have a low level of intrinsic activity (perhaps of 10%–20%) and act nearly like an antagonist. In between, partial agonists have widely varying levels of intrinsic activity, and differing behavioral actions. The resultant pharmacologic action of these medium-intrinsic activity agonists depends on the state of the target system; and, their actions in humans need to be explored experimentally. Over the last twenty years, considerable work has been done testing dopamine agonists in schizophrenia, as reviewed above; but, only recently have partial agonists been available for study (Olbrich, 1988; Murasaki et al., 1988; Benkert, 1992). Of the partial agonists studied recently, (−)-3PPP is one which is relatively selective for dopamine receptors and lacks activity at other monoamine receptors (Carlsson, 1975).

3-(3-hydroxyphenyl)-N-n-propylpiperidine (3PPP) (Figure) is a partial dopamine (DA) agonist at the D_2 receptor, with its negative and positive enantiomers having very different intrinsic activities. 3PPP exerts agonist or antagonist actions at its receptor, dependent on the receptor type and the experimental conditions. (−)-3PPP is a lower intrinsic activity partial agonist than the (+) isomer. (−)-3PPP is at least a partially limbic-selective PDA at the D_2 autoreceptor and at higher doses has antagonist effects at the normosensitive postsynaptic D_2 site (Clark et al., 1985a,b). Specifically, (−)-3PPP reduces locomotor activity in rats and mice (Hjorth, 1983) and, it reduces open field exploratory behavior in rats following injection into nucleus accumbens, but not into striatum (Svensson and Ahlenius, 1983). (−)-3PPP partially reverses the GBL-induced increase in dopamine synthesis (Clark et al., 1985a; Pugsley et al., 1995) and the increase in dopamine metabolism produced by lesioning the nigrostriatal pathway (Magnusson, 1983), both putatively due to actions at the autoreceptor. In contrast, (−)-3PPP decreases, rather than stimulates, acetylcholine release in vivo, a postsynaptic dopamine receptor antagonist action. And, at higher doses, the drug mimics the systemic action of haloperidol on globus pallidus neuronal firing. Recently, (−)-3PPP has been shown to also possess affinity for the dopamine D_3 receptor subtype, with an approximately 3-fold preference for this receptor subtype in relation to D_2 and has high affinity for D_4 receptor.

In initial clinical studies (−)-3PPP was given in single, increasing doses to six schizophrenia volunteers, with placebo in a modified double blind design to evaluate safety and suggest any clue of efficacy. An antipsychotic effect was noted over the six hours following drug administration. Side effects were minimal, with only nausea and mild hypotension occurring only at the highest acute dose (Tamminga et al., 1992). Thus, safety in humans was confirmed and the possibility of efficacy was encouraged.

Consequently, a three week placebo-controlled double blind cross-over design was begun to test the effect of this PDA on psychosis. The data

showed a positive and significant antipsychotic effect at the first ratings after chronic dosing began (7 days) (a 21% BPRS decrease from placebo) but no effect at the end of the second or third weeks (Lahti et al., 1998). A detailed analysis of the 7 day response indicated a brisk response of positive symptoms without any measurable parkinsonism in any volunteer (all were drug-free at study start); negative symptoms improved as well, as other reports have suggested (Wetzel et al., 1994). Cognitive performance was not tested but interpersonal affect tended to improve. It was our clinical impression that if this clinical action were allowed to develop, it might be unusually broad. The observation that this therapeutic effect attenuated, suggests that tolerance occurs to the effects of (−)-3PPP gradually over the first two weeks of dosing to obviate the therapeutic action over time. Tachyphylaxis with agonist-stimulated behaviors is common, as we had already encountered with NPA. However, examination of the NPA and (−)-3PPP results side-by-side suggested that the lower the intrinsic activity of the agonist (40% for (−)-3PPP) the longer its duration of action. We concluded that a mechanism to modify agonist intrinsic activity was necessary to develop this psychosis treatment further.

This set of observations led to the idea of using a lower intrinsic activity agonist to avoid tolerance to treatment. Since producing a lower intrinsic activity agonist was cost and time prohibitive, we chose to lower the effective intrinsic activity of (−)-3PPP by combining the agonist with a small amount of dopamine receptor antagonist. The ability of small concentrations of receptor antagonist, mixed with the receptor agonist to produce partial agonist activity had already been demonstrated for AMPA receptors (Krogsgaard-Larsen, 1994). P. Krosgaard-Larson studied AMPA agonists, and synthesized the phenyl-analogue of AMPA called APPA. This drug was initially characterized as a selective partial agonist at the AMPA receptor. However, when Krosgaard-Larson resolved APPA into its two steroisomers, they each had an opposite action at the AMPA receptor, with one isomer being a full agonist and the other isomer a full antagonist. By varying the proportion of each isomer in resultant mixes, Krosgaard-Larson could control the level of intrinsic activity of the racemic mixture. We have already demonstrated for dopamine receptors that the intrinsic activity of (−)-3PPP at the cloned $D_{4.4}$ dopamine receptor in CH0 cells is reduced by low nanomolar concentrations of haloperidol or clozapine (R. Lahti, personal communication). Moreover, in piloting this idea clinically, at haloperidol doses of 1 mg bid in schizophrenic volunteers, (−)-3PPP was shown (in preliminary analysis), to have a longer antipsychotic effect in combination with haloperidol than without. Since this was only a preliminary and incomplete test of this strategy, we are now testing both haloperidol (0.5 mg bid) with (−)-3PPP (300–600 mg bid, p.o.) and clozapine (25 mg bid) with the same dose of (−)-3PPP for efficacy and side effects over four week treatment periods. These are ongoing clinical studies.

Motivation to follow through with this therapeutic approach is multi-determined. First, a single compound like (−)-3PPP could function over a range of intrinsic activities by varying the amount of accompanying antago-

nist, producing an adjustable intrinsic activity PDA. Second, the side effect profile of (−)-3PPP is very favorable. Motor side effects are not only minimal, but not detectable. This is of great therapeutic benefit to treated persons. Third, we suspect that this low intrinsic activity dopamine agonist treatment may treat the pathologic features of schizophrenia more broadly. Both the primary negative symptoms and the cognitive features of schizophrenia have responded to PDA treatment. We are currently evaluating this prediction in our ongoing therapeutic trials.

Another PDA, called aripiprazole, has been introduced by Otsuka and is being brought to market by Otsuka and BMS together. Although clearly a PDA with low intrinsic activity, its exact relative intrinsic activity, compared to dopamine and other agonists has not yet been determined. This drug has potent antipsychotic activity in acutely psychotic persons with schizophrenia and bipolar illness. Negative symptoms respond as well; but, trials in predominantly negative symptom schizophrenics have not been done yet. Motor side effects are low; any EPS detected, however, needs to be differentiated from a residual antipsychotic effect. Other side effects are minimal. This drug is an attractive antipsychotic candidate having the potential of full action against psychosis coupled with blunted motor and negative cognitive side effects. Therapeutic cognitive actions of aripiprazole in schizophrenia are under study.

It is likely that PDAs will contribute meaningfully to schizophrenia treatment. The rationale for their mechanism of action is clear. Early data with (−)-3PPP are encouraging. And commercial development is proceeding with this class of drugs – the partial dopamine agonists (PDAs) in the form of aripiprazole. That this strategy is a novel approach to treating schizophrenic psychosis is popular in the area of schizophrenia therapeutics and holds promise for broad clinical action in schizophrenia.

This line of clinical research developed from Dr. Carlsson's original insight that dopaminergic autoreceptors exist and are functionally important to the regulation of dopamine-mediated neurotransmission. The clinical application of this idea has been challenging but is now generating novel therapeutics in psychosis.

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