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Do Central Antiadrenergic Actions Contribute to the Atypical Properties of Clozapine?

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Full neuropharmacological understanding of the atypical antipsychotic agent clozapine remains elusive. Antidopaminergic actions of most neuroleptics probably contribute to their antipsychotic benefits, but also to neurological side-effects. Clinical evidence of abnormalities of dopamine (DA) and serotonin (5-HT) in psychotic disorders is inconsistent, but there is substantial metabolic and post-mortem evidence for hyperactivity of noradrenalin (NA). Clozapine is only weakly antidopaminergic but is a potent antagonist at brain α_1-adrenergic, 5-HT_2-serotonergic, and muscarinic receptors. Its apparent limbic-over-extrapyramidal neurophysiological selectivity can be mimicked by combining a typical neuroleptic with a central α_1 antagonist. Clozapine strongly upregulates α_1, but not DA, receptor abundance, and may supersensitise α_1 but not DA receptors in rat brain. Clozapine also selectively increases activity of NA neurons and metabolic turnover in NA more than DA areas of rat brain, and also increases NA, but not DA or 5-HT, metabolites in human CSF. Potential psychotropic effects of selective central antiadrenergic agents may deserve reconsideration.

Clozapine exerts antipsychotic actions without the prominent neurological extrapyramidal side-effects (EPS) typical of most other clinically effective neuroleptic agents (Baldessarini, 1990; Baldessarini & Frankenburg, 1991). This pattern, at least partly, may reflect its potent antinoradrenergic (anti-NA) activity (Peroutka *et al*, 1977; Robinson *et al*, 1979). Traditionally, anti-NA activity has been considered to mediate sedative and hypotensive effects of psychotropic agents, and thus to be avoided as a nuisance (Cohen & Lipinski, 1986*a*). Even though the antidopaminergic (anti-DA) activity of clozapine is relatively weak (Baldessarini & Frankenburg, 1991), disproportionate attention has been given to it. Nearly all other effective neuroleptics were brought to clinical trials – largely through circular logic – *because* they showed anti-DA activity (Baldessarini, 1992). While many extrapyramidal neurological side-effects of typical neuroleptics probably can be ascribed to anti-DA actions, it is not proven that these actions are sufficient or uniquely required for clinically useful antipsychotic activity (Cohen, 1988; Baldessarini, 1990, 1992). Before considering the adrenergic pharmacology of clozapine further, it may be useful to emphasise that there is substantial evidence that such activity may contribute to the pathophysiology of psychotic disorders, including schizophrenia and severe affective disorders.

Clinical evidence of noradrenergic overactivity in psychotic patients

A vigorous search for clinical metabolic and post-mortem evidence of abnormalities of central DA or serotonin (5-HT) neurotransmission as an important component of the pathophysiology of idiopathic psychotic disorders has been strongly encouraged by partial knowledge of the actions of antipsychotic agents on these monoamines (Baldessarini, 1992). This 40-year search has led to some suggestive, but generally weak or inconsistent, support for the involvement of DA or 5-HT in the pathophysiology of psychotic disorders (Meltzer & Stahl, 1976; Gerner *et al*, 1984; Lindström, 1985; Carlsson, 1988; Gelernter & van Kammen, 1988; van Kammen *et al*, 1990). On the other hand, adrenergic overactivity has some modest support in major affective disorders, particularly in mania and agitated depression (Baldessarini, 1983; Koslow *et al*, 1983; Lipinski *et al*, 1987; Goodwin & Jamison, 1990). The substantial (albeit not totally consistent) evidence of similar overactivity in schizophrenia, including chronically psychotic patients, is less widely discussed (Hornykiewicz, 1982; van Kammen & Antelman, 1984; Lindström, 1985; van Kammen & Gelernter, 1987).

This evidence includes above-normal concentrations of NA (Farley *et al*, 1978; Bird *et al*, 1979; Crow *et al*, 1979; Hornykiewicz, 1982; van Kammen & Gelernter, 1987), or its major metabolite 3-methoxy-4-hydroxyphenethyleneglycol (MHPG; Kleinman *et al*, 1982), in post-mortem human brain tissue of patients with a history of schizophrenia or other psychotic disorders. In living psychotic patients, there is fairly consistent evidence of elevations of cerebrospinal fluid (CSF) concentrations of NA (Gomes *et al*, 1980; Lake *et al*, 1980; Zander *et al*, 1981; Gattaz *et al*, 1983; Jeste *et al*, 1984; Kemali & Maj, 1986;

van Kammen *et al*, 1990) or of MHPG (Pickar *et al*, 1990; van Kammen *et al*, 1990); there is additional evidence of elevated plasma concentrations of NA (Naber *et al*, 1980; Albus *et al*, 1982; Castellani *et al*, 1982; Breier *et al*, 1990). Some of these findings may reflect non-specific systemic sympathetic arousal or effects of psychotropic medication. Interestingly, whereas CSF levels of NA or MHPG typically have been elevated in schizophrenic patients, there have been variable, but sometimes normal or even decreased, corresponding concentrations of DA or its major metabolite, homovanillic acid (HVA) in several studies, including some with nominally drug-free patients (Lindström, 1985; Kemali & Maj, 1986; Karoum *et al*, 1987; Davidson & Davis, 1988; Pickar *et al*, 1990).

Pharmacological probes of NA metabolism in psychotic patients have yielded additional evidence of dysregulation: acute treatment with the pre-synaptic α_2 agonist clonidine (centrally antiadrenergic) led to smaller reductions of plasma MHPG concentrations in schizophrenic than in normal subjects (Sternberg *et al*, 1982), whereas similar probing with the α_2 antagonist yohimbine (an indirect adrenergic agonist) provoked abnormally large increases in the same measure, as well as clinical worsening in some patients (Glazer *et al*, 1987). It was found after three weeks of treatment of chronic schizophrenic patients with clozapine (at an average daily dose of 400 mg, yielding a drug concentration of 300 ng/ml in plasma) that CSF concentrations of monoamines and their metabolites showed a selective, significant, elevation of NA by 66%, but no change or a minor decrease (by 3–5%) of HVA or of the main serotonin metabolite, 5-hydroxy-indoleacetic acid (5-HIAA) (Lieberman *et al*, 1991).

Several therapeutic interventions in psychotic or manic patients with centrally active anti-NA agents other than clozapine have led to less convincing results. These include putative additional benefits from adding reserpine (a non-specific monoamine-depleting agent) to neuroleptic treatment regimens, especially in affective psychoses (Berlant, 1986), as well as long-standing but still inconclusive reports that high doses of the centrally active β-adrenergic antagonist propranolol may have benefit when added to standard neuroleptic treatments (Berlant, 1987; van Kammen & Gelernter, 1987; Lader, 1988). The centrally active direct α_1 antagonist prazosin was found to be ineffective in treating schizophrenia in one small study (Hommer *et al*, 1984), but it has not been combined with neuroleptics to seek additional benefit or reduction of neurological side-effects. Treatment with clonidine has not been studied extensively, but has provided modest benefit to some symptoms in schizophrenic patients, apparently independently of obvious sedative or hypotensive actions (Freedman *et al*, 1982; van Kammen & Gelernter, 1987), and may have at least minor or short-lived antimanic activity (Jouvent *et al*, 1980; Giannini *et al*, 1986; Goodwin & Jamison, 1990).

Antiadrenergic activity of clozapine

In comparison with other typical neuroleptics, the D_1 and D_2 dopaminergic receptor affinity of clozapine is about three to eight times lower than that of chlorpromazine, a typical neuroleptic of similarly low potency, and its D_2 affinity is about 30 times lower than that of haloperidol, a typical neuroleptic of high potency (Baldessarini & Frankenburg, 1991). In contrast, clozapine has very high affinity at α_1-adrenergic receptor sites in brain tissue (average K_i approximately 6 nM), as does chlorpromazine (6 nM), whereas haloperidol is three times less potent (18 nM); clozapine has much lower affinity at α_2- and β-adrenergic receptors (160 and 60 nM, respectively). It also interacts relatively potently at serotonergic (5-HT_2, 5 nM) as well as histaminergic (H_1, 3 nM) and acetylcholinergic-muscarinic (ACh_m, 21 nM) sites – all of which may contribute to its complex neuropharmacological activity.

After repeated treatment, virtually uniquely among antipsychotics, clozapine fails to increase the abundance of DA receptors or sensitivity to a DA agonist such as R(−)-apomorphine (Baldessarini & Frankenburg, 1991). When Cohen & Lipinski (1986*b*) repeatedly administered a series of typical neuroleptic agents or clozapine to rats, they expected and found moderate upregulation of D_2 receptor sites (usually by 10–30%) *except* with clozapine. Remarkably, however, all agents tested, including clozapine, *increased* α_1 receptor sites in rat forebrain tissue labelled with nM concentrations of ^{3}H-prazosin; with clozapine (three days after 25 mg/kg, i.p. daily for four weeks), this increase was 68%. Increased abundance of adrenergic receptor sites can, therefore, follow treatment with various antipsychotic agents. Furthermore, upregulation of α_1 but not D_2 receptors, apparently reflecting the ratio of potent antiadrenergic over weak antidopaminergic activity of clozapine, may help to differentiate clozapine from typical neuroleptics, and account for its antipsychotic activity with an atypically low risk of EPS. Similar upregulation of α_1 receptors in rat brain tissue assayed with radiolabelled BE-2254 (2-[β-(4-hydroxyphenyl)ethylaminomethyl]tetralone) has been reported after repeated treatment with other antiadrenergic agents, including prazosin and the NA-depleting agents reserpine and DSP-4 (a NA-neurotoxin, *N*-[2-chloroethyl]-*N*-ethyl-2-

bromobenzylamine); moreover, the DSP-4 treatment resulted in increased *functional* activity as measured by α-adrenergic receptor-mediated formation of inositol phosphates and cyclic-AMP (Johnson *et al*, 1987).

We are pursuing the observation of upregulation of central α_1-adrenergic sites by clozapine and other agents to seek evidence of functional *supersensitivity* of central adrenergic function. Initially, we applied a previously reported method of inducing behavioural arousal with the selective α_1 agonist (−)-phenylephrine injected directly into the brain (i.c.v.) through an in-dwelling lateral cerebroventricular cannula (Heal, 1984). At three days after three weeks of daily pre-treatment with haloperidol (0.5 mg/kg/day, i.p.) as a representative neuroleptic, we found a 32.9% (s.d. 8.6) increase ($n=6$; $P<0.001$) in behavioural response to a 100 μg dose of phenylephrine given i.c.v. to rats in a state of low basal behavioural arousal. The introduction of several novel centrally active α_1 agonists (Menon *et al*, 1990) encouraged us to apply them to the problem; a new Sandoz compound 210-085 (or NVI-085) has high α_1 affinity and selectivity and induces behavioural arousal in rats after systemic administration (Vigouret & Herrling, 1990). Since central adrenergic agonists induce much less locomotor response than is typical of DA agonists, we developed a behavioural rating method which assesses how drug-induced arousal counters normal behavioural adaptation and sleep onset, typically, at 60–120 min after introducing rats into a novel experimental environment near the end of a daily 12-hour lights-on cycle. This convenient method yields a more reliable and precisely quantifiable, dose-dependent, behavioural response (ED_{50} of SDZ-210-085 = 5.2 (s.d. 0.8) mg/kg, i.p.). We are using it to evaluate the ability of clozapine and other antipsychotic agents to induce functional central adrenergic supersensitivity (Huston-Lyons, D., Campbell, A. & Baldessarini, R. J., unpublished observations, 1991).

In additional studies aimed at evaluating the effects of clozapine and comparison agents on catecholamine synthesis (tyrosine hydroxylation) in NA- v. DA-rich regions of rat brain, we measured the rate of accumulation of L-dihydroxyphenylalanine (DOPA) assayed by high-performance liquid chromatography (HPLC, with electrochemical detection) after inhibition of its decarboxylation with *m*-hydroxyphenylhydrazine (NSD-1015; Baldessarini *et al*, 1990). Tissue dissected from pons-medulla containing the locus coeruleus is respresentative of NA neurons, whereas that from striatum is representative of DA neurons. The regional neurochemical selectivity was confirmed by HPLC analysis of the relative content of DA and NA in these areas. In preliminary observations with such tissue samples, clozapine produced a significantly greater increase in DOPA in the NA region than in the DA region. Chlorpromazine had the opposite effect (Huston-Lyons, D., Marsh, E., Baldessarini, R. J., *et al*, unpublished observations, 1991). This finding is consistent with the hypothesis that clozapine has a selective effect on central NA neuronal function, and with the recent clinical finding by Lieberman *et al* (1991) of selective increases of NA in CSF after treatment with clozapine.

Among rare replicated findings supporting the impression that clozapine may be an anti-DA agent of a special, regionally selective type are late reductions of DA-neuron firing rates observed in midbrain cells (tegmental A10 neurons) which project to the limbic system but, unlike typical neuroleptics, not in neurons (nigral A9 units) projecting to the extrapyramidal basal ganglia (Chiodo & Bunney, 1983; White & Wang, 1983). While this phenomenon has been taken as evidence of putative 'limbic antidopaminergic selectivity' of clozapine, it may reflect he central antiadrenergic actions of this atypical agent. Thus, co-administration of the α_1 antagonist prazosin with the typical neuroleptic haloperidol led to a pattern of neurophysiological responses in A9 and A10 that was indistinguishable from that of clozapine alone – that is, showing evidence of selective depolarisation inactivation in the A10 (limbic), but not the A9 (extrapyramidal) DA neurons (Chiodo & Bunney, 1985). Since combining an antimuscarinic agent with haloperidol also had a similar effect, it is not certain that the antiadrenergic action of clozapine uniquely accounts for its apparent functional selectivity for limbic DA neurons (Chiodo & Bunney, 1985). A further observation that adds to the distinction between neuroleptic actions on DA and NA neurons is that repeated administration of clozapine increased firing rates of NA neurons in rat locus coeruleus, while haloperidol induced inconsistent effects at that site (Ramirez & Wang, 1986); this activation may be secondary to blockade of post-synaptic α_1, or presynaptic α_2, receptors and may underlie the increase of NA in CSF found with clozapine treatment (Lieberman *et al*, 1991).

Additional evidence against a putative limbic-selective post-synaptic anti-DA action of clozapine is provided by our investigations into the ability of systemically administered clozapine and its experimental analogue ICI-204-636 to block the behavioural effects induced by DA applied stereotaxically in μg doses to a limbic (nucleus accumbens septi) or

extrapyramidal (central striatum) target site in rat brain, locomotion or head-deviation, respectively (Campbell *et al*, 1991). In these experiments, clozapine and its congener were much less potent than haloperidol, but all three compounds produced a dose-dependent blockade of DA in both regions, with a tendency towards greater potency in the extrapyramidal site.

Conclusions

Taken together, the evidence reviewed here suggests that central noradrenergic function may be more relevant to the pathophysiology of psychotic disorders than is generally acknowledged. Rather, there has been a preoccupation with the antidopaminergic actions of typical neuroleptic antipsychotic agents that have characteristic EPS, and an inference that all antipsychotic agents produce their beneficial effects via DA antagonism. The evidence surveyed suggests that clozapine is distinguished markedly from other antipsychotic agents by its ratio of relatively potent central antiadrenergic actions and low antidopaminergic activity. It may be worth considering further development and testing of selective, centrally effective, anti-NA agents, as well as anti-serotonin or other actions, in the search for additional 'atypical' antipsychotic agents with a low risk of inducing unwanted and often troublesome neurological side-effects.

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