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Clinical studies on the mechanism of action of clozapine: the dopamine-serotonin hypothesis of schizophrenia

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Abstract. Clozapine administration to schizophrenic patients was found to produce dopamine$_2$ (D-2) and serotonin$_2$ (5-HT$_2$) receptor blockade, as evidenced by the ability to block the increases in growth hormone and cortisol secretion produced by apomorphine and MK-212, respectively, direct acting dopamine (DA) and 5-HT$_2$ agonists. Clozapine did not increase plasma prolactin (PRL) levels nor did it block the apomorphine-induced decrease in plasma PRL concentration, as would be expected from a D-2 receptor antagonist. These PRL results are consistent with the observation that clozapine may increase DA release. Clozapine also decreased plasma tryptophan, plasma homovanillac acid (HVA) and basal plasma cortisol levels. Rodent studies suggest clozapine also increases 5-HT release. We hypothesize that antagonism of D-2 and 5-HT$_2$ receptors and enhancement of DA and 5-HT release are critical elements in the action of clozapine to minimize both positive and negative symptoms without producing significant extrapyramidal symptoms or plasma PRL increases. It is proposed that schizophrenia may also involve a dysregulation of 5-HT$_2$- and D-2-mediated neurotransmission, and that a more normal balance in serotonergic and dopaminergic neurotransmission is at least partially restored by clozapine.

Key words: Clozapine – Dopamine – Serotonin – Cortisol – Tryptophan

The efficacy of clozapine in the treatment of schizophrenia was clearly demonstrated in early clinical studies (Angst et al. 1971; Berzewski et al. 1969). Subsequent clinical experience suggested that clozapine might be a superior antipsychotic agent compared to classical neuroleptic drugs in some schizophrenic patients (Honigfeld et al. 1984). Such claims have often been made for other antipsychotic drugs, but they have never been satisfactorily verified. However, there is now increasingly convincing evidence from controlled studies, both with representative schizophrenic patients (Claghorn 1987) as well as neuroleptic-resistant schizophrenic patients (Kane et al. 1988; Meltzer et al. 1989a, b), that clozapine is a more effective antipsychotic than typical neuroleptic drugs. Retrospective studies of the effect of clozapine also support the greater efficacy of clozapine in treatment resistant schizophrenic patients (Juul Povlsen et al. 1985; Kuha and Miettinen 1986; Lindström 1988). This appears to represent the first reliable body of evidence that one antipsychotic drug is superior for the treatment of schizophrenia to any other (Meltzer 1988). Clozapine also differs from typical antipsychotic drugs in: a) producing a significantly lower incidence of extrapyramidal side effects (EPS) (Meltzer et al. 1984; Kane et al. 1988); b) very likely no tardive dyskinesia (Meltzer and Luchins 1984; Marder and Van Putten 1988; Casey 1989), although this claim has not been, and may never be, tested in a controlled study; and c) unique neuroendocrine effects [e.g. absence of plasma prolactin (PRL) elevations (Meltzer et al. 1979)], which will be described subsequently.

I have drawn two major conclusions from these findings: 1) it is likely that all of clozapine's clinical advantages: increased efficacy and unique profile of acute and chronic EPS, as well as neuroendocrine profile, are related to the same common core of biological properties which differentiate it from typical antipsychotic drugs (Meltzer 1989a); and 2) identification of how clozapine produces its unique clinical effects may well provide a means of clarifying the biological basis of schizophrenia itself (Meltzer 1989a). In this paper, we will propose the hypothesis that the mechanism of action of clozapine involves its ability to alter the dopaminergic and serotonergic system in an integrated manner and use it to advance the hypothesis that the etiology of schizophrenia could itself involve an abnormality in the interaction of the dopaminergic and serotonergic system rather than either system itself.

Dopaminergic mechanisms

The antipsychotic action of neuroleptic drugs has been attributed to blockade of mesolimbic or mesocortical dopamine (DA) D-2 receptors (Carlsson and Lindquist 1963; Meltzer and Stahl 1976), the DA receptor negatively coupled or not coupled to DA-sensitive adenylate cyclase (Kebabian and Calne 1979). Until recently, the DA D-1 receptor, the DA receptor positively coupled to adenylate cyclase, has been thought to play little or no role in the action of antipsychotic drugs. This view has now dramatically changed (see Clark and White 1988 for review). In particular, it has now been proposed that the action of clozapine and other atypical antipsychotic drugs at D-1 receptors is an important differential component of the action of these drugs (Andersen and Braestrup 1986; Andersen et al. 1986; Altar et al. 1988; Gudelsky et al. 1989).

Clozapine has traditionally been thought to produce weak, reversible D-2 receptor blockade, at least in the stria-

tum (Bartholini et al. 1972). More recently, Farde et al. (1988, 1989), on the basis of positron emission tomographic (PET) studies of the ability of clozapine and typical neuroleptics to block the binding of ^{11}C-SCH 23390, a putative D-1 ligand, and ^{11}C-raclopride, a putative D-2 ligand, in a small number of antipsychotic drug-treated schizophrenic patients, proposed that clozapine differs from the typical neuroleptic drugs in producing relatively more potent D-1 receptor occupancy and relatively weaker D-2 receptor blockade.

The attempt to understand the uniqueness of clozapine has, until recently, focused entirely on understanding why it produces fewer EPS or no plasma PRL elevations in man and not on its superior efficacy. Studies relevant to EPS and PRL secretion could be carried out in laboratory animals, including rodents, since the physiological processes regulating motor and endocrine function have been largely conserved throughout the mammalian phyla. The concept that clozapine has a selective effect on limbic mechanisms, leaving the striatal system intact, and thus producing an antipsychotic effect and low EPS, is supported by biochemical (Andén and Stock 1973) and electrophysiological studies (Chiodo and Bunney 1983, 1985) in rodents. However, not all studies have found such selectivity (Waldmeier and Maitre 1976; Souto et al. 1979). Furthermore, the need for caution, with regard to extrapolation from rodent studies to man, became evident after neuroendocrine studies demonstrated that clozapine markedly increased plasma PRL levels in rats (Meltzer et al. 1975), although with a time course that was significantly shorter than that of typical drugs (Gudelsky et al. 1987). The brief plasma PRL surge in rats appears to be due to blockade of D-2 receptors at the pituitary, followed by a rapid increase in the synthesis and release of DA from the tuberoinfundibular dopaminergic (TIDA) neurons, overcoming the blockade of the pituitary D-2 receptors (Gudelsky et al. 1987). No tolerance to this effect of clozapine develops after 21 days' treatment (Gudelsky and Meltzer, in preparation). Other discrepancies between rodent and human effects of clozapine will be discussed below. These discrepancies emphasize the need to conduct studies of the mechanism of action of clozapine, wherever possible, on humans and in particular, in schizophrenic patients.

The ability of clozapine to act as a serotonin (5-HT) antagonist (Lai et al. 1980; Fink et al. 1984; Friedman et al. 1985) has also been suggested to be relevant to its low EPS, since lesions of the serotonergic system or pretreatment with para-chlorophenylalanine (PCPA), which inhibits 5-HT synthesis, have been shown to decrease neuroleptic-induced catalepsy in rodents (Kostowski et al. 1972). The serotonin antagonist ritanserin has been reported to decrease EPS in neuroleptic-treated patients (Bersani et al. 1986). Studies to be reviewed below suggest that clozapine is a potent 5-HT$_2$ antagonist. As will be discussed below, there is evidence that clozapine is a more potent 5-HT$_2$ antagonist in vivo than would be predicted on the basis of its in vitro affinity for the 5-HT$_2$ receptor (Nash et al. 1988; Meltzer 1989a). The effect of clozapine on the serotonergic system can be assessed in patients using biochemical and endocrine methods (Meltzer and Lowy 1987).

Human studies of the mechanism of action of clozapine are also indicated to generate additional hypotheses about the mechanism of action of clozapine. For example, evidence will be presented that chronic clozapine treatment in man may decrease plasma cortisol levels, an effect that was not predicted from its preclinical pharmacology, since acute clozapine treatment increases plasma corticosterone levels in rats.

Human studies

There has been only limited study of the effect of clozapine treatment in man. These studies have mainly focused on: 1) the dopaminergic system, including PRL and growth hormone (GH) secretion, indirect measures of dopaminergic activity; and 2) the serotonergic system. These studies will be reviewed and then some recent studies from our laboratory will be presented.

CSF homovanillac acid

Clozapine has been reported to have no effect on the concentration of urinary homovanillac acid (HVA), the major metabolite of DA (Ackenheil et al. 1974). However, it increased cerebrospinal fluid (CSF) concentrations of HVA in six schizophrenic patients by 114% and by 25% in three manic patients after 10 days of treatment (Ackenheil et al. 1974). On the other hand, Gerlach et al. (1975) reported that at 4 and 21 days of treatment, clozapine treatment decreased CSF HVA levels. The factors which influence CSF HVA concentrations are still poorly understood. At one time, CSF HVA levels were thought to mainly reflect the release of DA from the basal ganglia, which has the most dense concentration of DA terminals of any region of the brain. However, a recent study suggests that the frontal cortex, which contains the terminals of the most rapidly firing DA neurons, may be the most important source of HVA in the CSF of primates (Elsworth et al. 1987). Even if this is so, the significance of CSF HVA levels as an index of the functional effect of clozapine on the firing of DA neurons must be interpreted with caution, since HVA concentrations may reflect intraneuronal metabolism of DA rather than release of functionally significant DA (Ebinger et al. 1987). Future studies must examine the time course of the effect of clozapine on CSF HVA concentrations and its relationship to clinical response.

Plasma homovanillac acid

Plasma HVA levels have also been suggested to provide a measure of central dopaminergic activity (Bacopolous et al. 1979). A variety of experimental paradigms have suggested that about 25% of plasma HVA derives from the central nervous system (Maas et al. 1985). The central sources of plasma and CSF HVA are not necessarily the same. For example, we have found no significant correlation between CSF and plasma HVA concentrations in 19 unmedicated patients with major depression or bipolar disorder (Meltzer et al. unpublished data).

There is conflicting evidence concerning the effect of treatment with typical neuroleptics on plasma HVA in man. Plasma HVA levels have been reported to decrease following neuroleptic treatment (Pickar et al. 1984, 1986), to be increased (Harris et al. 1984), and to increase after 4 days' treatment but to return to normal after 28 days of treatment (Davila et al. 1988). We determined plasma HVA levels using high pressure liquid chromatography with electrochemical detection. As can be seen in Table 1, there was no signifi-

Table 1. Plasma HVA concentrations in unmedicated-, neuroleptic- and clozapine-treated schizophrenic-treated and normal controls

Group	*N*	Plasma HVA (nmol/l)
Normal controls	26	50.6±20.0
Schizophrenics		
Unmedicated	25	48.9±21.1
Clozapine-treated	28	37.3±14.5*

$P<0.02$ vs normal controls and schizophrenic patients

Table 2. Plasma prolactin concentrations in normal controls and schizophrenic patients

Group	*N*	Plasma PRL (μg/ml)
Normal controls	20	5.9±2.8
Schizophrenics unmedicated	69	6.6±3.3
Clozapine-treated	21	4.3±1.7*

$F=4.56$; $df=2,107$; $P=0.01$

* Significantly less than unmedicated schizophrenics

cant difference in plasma HVA levels in the unmedicated schizophrenic patients compared to normal controls. The duration of treatment was 65.8±70.8 days. There was a significant decrease in plasma HVA in the clozapine-treated patients. We have observed a similar effect in neuroleptic-treated schizophrenic patients (Meltzer, in preparation). The significance of the decrease in plasma HVA concentration is unknown.

Plasma prolactin concentration

We reported that clozapine did not increase plasma PRL levels in man (Meltzer et al. 1979), in contrast with the marked increase produced by all typical antipsychotic drugs, including thioridazine (Meltzer and Fang 1976). The lack of an increase in plasma PRL levels during clozapine treatment was also found in the Kane et al. (1988) study of treatment-resistant schizophrenics (Meltzer et al. unpublished data).

Previous studies of the effect of clozapine treatment on plasma PRL levels involved morning blood samples which were obtained by direct venepuncture. Samples obtained in this manner may be influenced by the effects of sleep and stress. We have recently measured plasma PRL level in normal controls, unmedicated and clozapine-treated schizophrenic patients, in samples obtained via indwelling venous catheters, 60 min after catheter placement. The unmedicated schizophrenic patients were drug free for a minimum of 7 days if they had received oral medication or for 4 weeks if they had received a long acting neuroleptic. The clozapine-treated patients had received clozapine for 4–8 weeks in doses of 200–900 mg/day. The method for determination of PRL levels has been described elsewhere (Lowy et al. 1988). Only the results from male patients are reported here because of the small number of females studied to date. As can be seen in Table 2, not only were plasma PRL levels in clozapine-treated patients not increased, they were significantly lower than those of the unmedicated schizophrenics, but not significantly different from normal controls. These PRL levels should be compared to the markedly elevated plasma PRL levels found in 43 male schizophrenic patients receiving typical neuroleptic drugs (19.2±16.2 ng/ml). This increase is in agreement with our previous results (Meltzer and Fang 1976). However, caution is necessary in interpreting the decreased PRL levels in the clozapine-treated patients because the plasma PRL levels in the unmedicated schizophrenic patients may have been influenced by previous treatment with neuroleptic drugs or stress and because different subjects are being compared. However, there was no relationship between the duration of the drug-free period and elevated plasma PRL levels in the unmedicated schizophrenic patients. Nevertheless, when we compared plasma PRL levels in 15 patients who had at least a 7-day washout before a drug-free catheter study followed by another study during clozapine treatment, the pre-post plasma PRL levels were not significantly different although there was a trend in this direction (data not presented). This may reflect a tendency for treatment-resistant schizophrenic patients to have lower plasma PRL levels even when not receiving clozapine. If clozapine did actually decrease plasma PRL levels in man, it would be relevant to the possibility that it produces sustained increases in the release of DA in the TIDA, and perhaps other neurons.

The lack of an increase in plasma PRL concentrations with clozapine would suggest that clozapine is not a potent D-2 receptor blocker in man, since the pituitary DA receptor which mediates the inhibition of PRL secretion is a D-2 receptor (Kebabian and Calne 1979). However, there is considerable evidence incompatible with this view. Nair et al. (1979) demonstrated that the apomorphine-induced increase in GH secretion was blocked by clozapine treatment. Apomorphine is a mixed D-1/D-2 agonist (Schechter and Greer 1987), although it has a more potent effect on D-2 mechanisms. The ability of apomorphine to stimulate GH is D-2 mediated, since it is blocked by molindone which has minimal affinity for the D-1 receptor (negative log of the Ki for striatal D-1 receptor =5.8, Meltzer et al., in preparation) and by low doses of haloperidol, which would not be expected to block D-1 receptors (Meltzer, unpublished observations). Other evidence for the conclusion that apomorphine stimulates GH secretion by a D-2 mechanism has been summarized by Zemlan et al. (1986). We have replicated the inhibitory effects of clozapine on the apomorphine-induced increase in plasma GH, comparing the GH responses to apomorphine 0.01 mg/kg SC in normal volunteers, clozapine-treated patients, 15 unmedicated and 10 typical neuroleptic-treated schizophrenic patients (Table 3). Plasma GH levels were determined as previously described (Meltzer et al. 1984).

We have also examined the effect of apomorphine, 0.01 mg/kg SC, on PRL secretion in 15 unmedicated, 10 neuroleptic-treated, and 11 clozapine-treated schizophrenic patients. Subjects had two catheter studies (one apomorphine, one saline) separated by 2–7 days (Meltzer et al. 1984b). The methodology has been described elsewhere (Meltzer et al. 1984b). Apomorphine, compared to placebo, significantly decreased the PRL area under the curve (120 min following apomorphine) in all three groups (Table 4). We have previously found that clozapine, like typical neuroleptic drugs, blocks the ability of DA to inhibit PRL

Table 3. Effect of clozapine and other neuroleptic-drugs on apomorphine-induced increase in plasma growth hormone levels

Group	*N*	Areas under the curve[a]
Normal controls	12	615.8±382.2
Schizophrenic patients		
Unmedicated	15	471.5± 54.6*
Neuroleptic-treated	9	175.5±216.0**
Clozapine-treated	11	97.4±117.6**

$F=10.12$; $df=3.42$; $P=0.0001$

[a] Mean±SD

* Trend for difference from normal controls after log transformation ($P=0.08$)

** Significantly less than normal controls and unmedicated schizophrenics after log transformation and covarying log basal GH

Table 4. Effect of clozapine and other neuroleptic drugs on apomorphine-induced change in plasma prolactin levels

Group	*N*	Area under curve[a]		Δ
		Placebo	Apomorphine	
Schizophrenic patients				
Unmedicated	15	558.5	470.9	87.6
Neuroleptic-treated	10	1407.8	1340.3	67.5
Clozapine-treated	11	467.0	380.8	86.2

Source	ANCOVA table		
	DF	*F*	*P*
Group	2	3.66	0.037
Drug	1	4.81	0.036
Group × Drug	2	0.03	0.97
Basal PRL		0.13	0.72

[a] 120 min following apomorphine, adjusted for sex and baseline PRL

release from rat hemipituitary glands in vitro (Meltzer 1989a, b). Thus, the blockade of pituitary D-2 receptors by clozapine in man is sufficiently weak that it can be overcome by both endogenous DA and apomorphine whereas the blockade by typical neuroleptic drugs can be overcome by apomorphine but not completely by endogenous DA. The demonstration by Fardé et al. (1988, 1989) that clozapine occupies striatal DA receptors that bind ^{11}C-raclopride is also consistent with D-2 blockade in man.

Why then does clozapine not increase plasma PRL levels in man? All other drugs which block D-2 DA receptors in the pituitary increase plasma PRL levels (Meltzer and Fang 1976). It could be that clozapine decreases PRL synthesis or release in man by some non-dopaminergic mechanism. However, the most likely explanation is that clozapine increases DA release from the tuberoinfundibular DA (TIDA) neurons in man just as it does in the rat (Gudelsky et al. 1987). This would account for its possibly lowering plasma PRL levels despite blockade of lactotrophe D-2 receptors.

There is considerable controversy as to whether clozapine increases DA release acutely or chronically in various rat brain regions. For example, Altar et al. (1988) proposed that the concentration of the DA metabolite 3-methoxytyramine (3-MT) provided a measure of DA release and found that single doses of clozapine did not, but haloperidol and chlorpromazine did, increase 3-MT concentrations. However, in vivo dialysis studies indicate that acute treatment with clozapine does increase DA release in the striatum, nucleus accumbens and frontal cortex (Imperato and Angelucci 1988; Ichikawa and Meltzer, in preparation). Furthermore, we have found that chronic clozapine administration also increases DA release in the striatum and nucleus accumbens (Ichikawa and Meltzer, in preparation). However, electrophysiological studies would suggest that chronic clozapine treatment decreases the firing of DA neurons in the ventral tegmentum (A10) and presumably DA release in the nucleus accumbens (Chiodo and Bunney 1983; White and Wang 1983). In vivo voltammetry also suggests clozapine decreased DA release in the nucleus accumbens (Blaha and Lane 1987). There is no explanation for these discrepancies at this time. It is also unknown which, if any of these effects, occurs in man. It is intriguing to speculate that D-2 DA receptor blockade in the mesolimbic system by clozapine accounts for its ability to block positive psychotic symptoms. This action of clozapine could also be based upon the synergistic effect of D-1 and D-2 DA receptor blockade in the mesolimbic system. At the same time, clozapine could increase DA release in the frontal cortex, striatum and TIDA neurons. These effects would account for its palliative effects on negative symptoms, extrapyramidal function and absence of plasma PRL increases, respectively. The role of the effect of clozapine on serotonergic function in mediating these effects could be crucial, as will now be discussed.

Clozapine as serotonin antagonist

There is extensive evidence that clozapine is a serotonin (5-HT) antagonist. For example, clozapine blocks the behavioral effects of quipazine, a 5-HT agonist (Friedman et al. 1985), as well as the serotonergic effects of lysergic acid diethylamide (Fink et al. 1984) and 2,5-dimethoxy-4-methylamphetamine (DOM) (Rasmussen and Aghajanian 1988). We have found that clozapine blocks the hyperthermic and hormone-stimulating effects of MK-212 (Nash et al. 1988), a 5-HT$_2$ agonist (Koenig et al. 1987). We have reported that clozapine treatment blocks the MK-212-induced increase in plasma cortisol secretion (Meltzer 1989a). These results have been confirmed as additional patients have been studied. Thus, the plasma cortisol area under the curve in clozapine-treated schizophrenic patients was significantly less than that of unmedicated and neuroleptic-treated schizophrenic patients (Table 5). There was a trend for the cortisol response in the clozapine-treated patients to be less than that of the normal controls as well. What is particularly intriguing is that the pK_i values for the ability of clozapine and chlorpromazine for 5-HT$_2$ receptors in rat frontal cortex are 8.3 and 8.7, respectively, (Meltzer et al., in preparation). Thus, chlorpromazine would be expected to block the MK-212-induced cortisol response at least as well as clozapine. The lack of effect of chlorpromazine raises the possibility that clozapine may be more effective in vivo as a 5-HT$_2$ antagonist than would be predicted

Table 5. Effect of MK-212 20 mg on plasma cortisol levels in normal controls and schizophrenic patients

Group	*N*	Area under curve 180 min[a]
Normal controls	10	1939±531
Schizophrenics		
Unmedicated	25	2066±630
Neuroleptic-treated	25	2218±770
Clozapine-treated	15	1281±540*

$F=10.28$; $df=4,70$; $P=0.0001$

[a] Mean±SD

* Significantly less than unmedicated ($P=0.03$) and neuroleptic-treated ($P=0.004$) schizophrenic patients; trend to differ from normal controls ($P=0.10$)

on the basis of the in vitro affinity data. Alternatively, the MK-212-induced cortisol responses in man may be due to stimulation of some other type of 5-HT receptor which is blocked by clozapine and not by chlorpromazine.

Other effects of clozapine on the serotonergic system in man

There is other evidence that clozapine affects the serotonergic system. Clozapine treatment has been reported to increase the levels of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT, in CSF in patients after 2 and 4 days of treatment, but not after 6, 10, 20 or 30 days (Banki 1978). Clozapine was also reported to non-significantly increase CSF 5-HIAA levels at 10 days in nine patients in another study in which it significantly increased urinary 5-HIAA levels by 29% (Ackenheil et al. 1975). However, in a third study of eight patients, it was found to significantly decrease mean levels of 5-HIAA in CSF after 4 and 21 days of treatment (Gerlach et al. 1975). Inspection of these data indicates that the decreases in CSF 5-HIAA levels were observed in only four of the eight patients studied. Blood 5-HT levels have also been reported to be markedly increased during clozapine treatment (Banki 1978). The 5-HT in blood is virtually all in the platelets.

There is some evidence that clozapine treatment affects plasma levels of tryptophan, the precursor of 5-HT. Clozapine administration has been reported to increase rat brain 5-HT synthesis as indicated by enhanced accumulation of ^{3}H-5-HT in the brain after IV infusion of ^{3}H-TRP (Ruch et al. 1976). This was associated with an increased concentration of plasma-free tryptophan but a reduced plasma concentration of total tryptophan. Increased plasma free tryptophan would be expected to enhance brain 5-HT synthesis, since the availability of tryptophan in the brain is believed to be the rate limiting step in 5-HT synthesis. Other investigators have also found that clozapine treatment increases the concentrations of rat brain 5-HT or 5-HIAA, or both (Maj et al. 1974; Ackenheil et al. 1975; Burki et al. 1975).

We have now studied the effect of clozapine treatment on plasma tryptophan levels and 5-HIAA (Table 6). Plasma tryptophan was measured by high pressure liquid chromatography (Koyama and Meltzer 1986). As can be seen, plasma tryptophan levels were significantly lower in the clozapine-treated schizophrenic patients than in the unmedicated

Table 6. Plasma tryptophan concentrations in normal controls and schizophrenic patients

Group	*N*	Plasma tryptophan[a] (ng/ml)
Normal controls	29	7.90±1.26*
Schizophrenics		
Unmedicated	26	10.05±1.81
Neuroleptic-treated	15	9.55±1.90
Clozapine-treated	25	8.06±1.97*

$F=9.51$; $df=3,90$; $P=0.0001$

[a] Mean±SD

* Significantly less than unmedicated or neuroleptic-treated schizophrenic patients

Table 7. Plasma 5-HIAA concentrations in normal controls and schizophrenic patients

Group	*N*	Plasma 5-HIAA
Normal controls	29	4.86±1.45
Schizophrenics		
Unmedicated	26	4.80±1.16
Neuroleptic-treated	16	4.85±2.18
Clozapine-treated	25	5.48±1.63

$F=1.06$; $df=3,92$; $P=0.37$

or neuroleptic-treated schizophrenic patients. We found no difference in plasma 5-HIAA levels in unmedicated schizophrenic patients and normal controls (Table 7). However, the relationships between plasma tryptophan and 5-HIAA concentrations were markedly different in the various groups. The correlation between tryptophan and 5-HIAA concentrations in plasma was significant in the neuroleptic-treated ($r=0.59$, $N=15$, $P=0.01$) and unmedicated schizophrenic patients ($r=0.37$, $N=42$, $P=0.015$) but was non-significant in the clozapine-treated patients ($r=0.28$, $N=22$, $P=0.20$). The correlation in 28 normal controls was also not significant ($r=-0.17$, $N=25$, $P=0.37$).

Further studies are needed to clarify the significance of the ability of clozapine to decrease plasma tryptophan to normal levels and to alter the correlation between plasma tryptophan and 5-HIAA levels in schizophrenic patients. These two effects may or may not be related to each other. The absence of a correlation between plasma tryptophan and 5-HIAA levels in the normal controls and clozapine-treated patients and its presence in schizophrenic patients is most intriguing. It further raises the issue of the role of 5-HT in schizophrenia, since it suggests that the origin of plasma 5-HIAA in schizophrenic patients may be different, in part, from that of normal controls. Previous studies have also found no differences in plasma tryptophan levels between drug-free or neuroleptic-treated schizophrenic patients and normal controls (Potkin et al. 1983). Tryptophan levels in brain are believed to control 5-HT synthesis. Free tryptophan in plasma, i.e., the fraction of total tryptophan not bound to albumin, is believed to determine brain tryptophan levels but large neutral amino acids such as leucine and isoleucine compete with tryptophan for transport into the brain, so that the free tryptophan concentration relative

to that of the large neutral amino acids is relevant to the effect of tryptophan on brain 5-HT synthesis (Fernstrom and Wurtman 1972). It is conceivable that a decrease in the available tryptophan for brain 5-HT synthesis leads to decreased serotonergic activity. This would synergize with the clozapine-induced 5-HT antagonism evident from the MK-212 challenge studies cited above. There are numerous interactions between 5-HT and other neurotransmitters, e.g., DA, norepinephrine, acetylcholine and GABA, which also might contribute to the unique effects of clozapine. It is beyond the scope of this article to discuss these in detail.

Basal plasma cortisol levels

In the course of examining the effect of clozapine and typical neuroleptic drugs on the MK-212-induced increase in plasma cortisol levels, it was noted that there was some evidence for decreased basal plasma cortisol levels in the clozapine-treated patients prior to giving MK-212. For example, the plasma cortisol levels obtained 60 min after catheter placement in ten patients studied first on a typical neuroleptic and then after 4–6 weeks of clozapine treatment were significantly lower during clozapine treatment (12.1 ± 3.1 versus 9.2 ± 1.7 μg/dl, $P = 0.015$). The typical neuroleptic drugs included fluphenazine, chlorpromazine, haloperidol and molindone. When we examined plasma cortisol levels in groups of different schizophrenic patients at 30-min intervals between 10 A.M. and 12 A.M., the area under the curve was lower in the clozapine-treated patients (683.0 ± 251.2, $N = 16$) versus the neuroleptic-treated schizophrenic patients (878.0 ± 315.7, $N = 23$; $P = 0.05$).

The decrease in plasma cortisol levels produced by clozapine could be due to a non-specific reduction of stress-induced activation of the hypothalamic-pituitary-adrenal axis and a reflection of the overall greater improvement produced by clozapine treatment. It could also be related to its antiserotonergic effect, since 5-HT has a tonic stimulatory effect on cortisol secretion. It is not inconceivable that both the anti-serotonergic effect of clozapine (Meltzer 1989a; Meltzer et al. submitted) and the ability of clozapine to diminish cortisol secretion both directly contribute to its superior antipsychotic efficacy. We have discussed how the antiserotonergic effects of clozapine might do this elsewhere (Meltzer et al. submitted). The effect of cortisol in altering dopaminergic activity (Faunt and Crocker 1988), its numerous effects on other neurotransmitter systems (McEwen 1987), and its ability to prevent hippocampal damage (Sapolsky 1985), or in modulating DA neurotransmission in the hippocampus, might also be relevant to its antipsychotic actions. The latter hypothesis is based on recent evidence suggesting hippocampal damage is important in schizophrenia (Bogerts et al. 1985), that DA has a neurotransmitter role in the hippocampus (Bischoff et al. 1979) and that glucocorticoids can modulate DA receptor sensitivity in the hippocampus as well as other brain regions (Bischoff et al. 1983).

Discussion

There is clear evidence, as reviewed previously, that clozapine, in man, acts as a D-2 DA receptor blocker, e.g., its ability to block the apomorphine-induced increase in GH and to block at least partially, the occupancy of D-2 DA receptors in the striatum as revealed by PET studies. However, its D-2 receptor blockade in man is not so potent as to lead to an increase in plasma PRL concentrations. This is in accord with the finding that 18 atypical antipsychotic drugs had significantly lower affinity for the rat striatal D-2 receptor binding site than 20 typical neuroleptic drugs (Meltzer et al. submitted). The failure of clozapine to increase plasma PRL levels in man could also be related to its ability to increase DA release in the TIDA neurons, an effect it appears to exert on a variety of DA neurons as indicated by in vivo dialysis studies. The ability clozapine to decrease plasma HVA levels does not rule out the hypothesis that clozapine is a potent DA releasing agent in at least some regions of the human brain, since the origin of plasma HVA is so varied. Even if clozapine increased DA release in all brain regions, it still might not be reflected in plasma HVA levels, since peripheral sources of HVA may overcome the central increases. CSF HVA studies may also not be meaningful tests of this hypothesis.

A second major effect of clozapine on DA neurons appears to be its ability to occupy D-1 DA receptors. Farde et al. (1989), on the basis of PET clinical studies, suggest that this is critical to its mechanism of action. Others have reached the same conclusion on the basis of preclinical studies (Andersen et al. 1986; Andersen and Braestrup 1986). Indeed, we, too, thought this was highly important at one time (Meltzer 1989a; Gudelsky and Meltzer 1989). However, D-1 receptor affinity is correlated with 5-HT_2 receptor affinity for many atypical and typical antipsychotic drugs (Meltzer et al. submitted; Bischoff et al. 1988; McQuade et al. 1988). Some, perhaps 20%, of the apparent ability of clozapine to occupy ^{11}C-SCH 23390 binding sites in the striatum might be due to 5-HT_2 rather than D-1 binding sites. We have presented evidence elsewhere that D-2 and 5-HT_2 affinities discriminate atypical from typical antipsychotic drugs and that D-1 affinities contribute little to this (Meltzer et al. submitted). Nevertheless, further study of the possibility that D-1 DA receptor blockade is an important component of the action of clozapine and other atypical antipsychotic drugs is clearly indicated.

Just as clozapine appears to be able to block DA receptors and to increase DA release, so it also blocks 5-HT receptors of the 5-HT_2 subtype and increases 5-HT release. The ability of clozapine to block 5-HT_2 receptors in man is clearly demonstrated by its ability to block the cortisol response to an MK-212 challenge. Its ability to increase 5-HT release is not simply a result of a negative feedback effect, since clozapine has been reported to increase 5-HT release in the limbic system by at least two different presynaptic mechanisms (Drescher and Hetey 1988). The lack of effect of clozapine on plasma 5-HIAA levels and the mixed evidence that it may increase CSF 5-HIAA levels does not rule out the hypothesis that it can increase 5-HT release in some brain regions. The decrease in plasma total tryptophan levels produced by clozapine in man and rodents might indicate that it decreases 5-HT synthesis in brain but investigation of the effect of clozapine on total and free tryptophan levels, together with the levels of neutral amino acids which compete with clozapine for entry into the brain, will be needed to study this issue properly.

We have discussed elsehwere (Meltzer 1989b) the evidence that clozapine may be achieving its unique potency

in alleviating positive and negative symptoms, without producing EPS or tardive dyskinesia, and with no effect on plasma PRL concentration by virtue of the effects on dopaminergic and serotonergic neurotransmission which have just been considered. The integrated effect of clozapine on the neural transmission-mediated via D2 and 5-HT_2 receptors could be the "final common pathway" for its multiple clinical benefits.

This does not mean, of course, that an abnormality in D-2 and 5-HT_2-mediated neurotransmission is the core deficit in schizophrenia. There is some evidence of primary abnormalities in the extrapyramidal and neuroendocrine systems in some schizophrenic patients, e.g., abnormal involuntary movements and neuromuscular abnormalities in schizophrenic patients never treated with neuroleptic drugs (Kraepelin 1919; Meltzer 1976; Crow et al. 1982) as well as neuroendocrine abnormalities (Meltzer et al. 1984a). We have recently found that plasma PRL levels in some unmedicated schizophrenic patients may be elevated (Meltzer et al. in preparation). Abnormalities in the neuromuscular system may be relatively common in schizophrenia (Meltzer 1976) but abnormal involuntary movements (not due to neuroleptic administration) and plasma PRL increases are rare. It is possible that some of these abnormalities could be due to abnormalities in D-2 or 5-HT_2 receptor mediated neurotransmission. It is, of course, also possible that abnormalities in D-2 and 5-HT_2 receptors are causally related to the psychopathology of schizophrenia.

It is beyond the scope of this article to review the evidence for the role of DA (Meltzer and Stahl 1976; Carlsson 1977, 1988) and 5-HT (Stahl and Wets 1987; Bleich et al. 1988) in the etiology of schizophrenia. However, some key points will be considered. There have been some studies indicating increased density of D-2 receptors in the striatum and nucleus accumbens (Lee et al. 1978; Owen et al. 1978; Seeman et al. 1987) and two studies reporting decreased 5-HT_2 receptors in the frontal cortex of schizophrenic patients (Bennett et al. 1979; Mita et al. 1986). Other studies have not replicated these findings or attributed them to the effects of neuroleptic treatment (MacKay et al. 1978; Whitaker et al. 1981; Reynolds et al. 1983). If there were decreased 5-HT_2 and increased D-2 receptors in some schizophrenics, this could contribute to a low ratio of 5-HT_2 to D-2-mediated neurotransmission. This would be true even if the increased D-2 density was an artifact due only to neuroleptic treatment, since diminished 5-HT_2 density could alone lower the ratio. Indeed, the density of both 5-HT_2 and D-2 receptors might be within normal limits but the ratio might still be low in schizophrenic patients if the 5-HT_2 density was at the lower end of normal and the D-2 at the higher end, and if D-2 and 5-HT_2 densities in normal subjects were inversely correlated. Atypical neuroleptic drugs, compared to typical neuroleptics, have a high ratio of ability to antagonize 5-HT_2, relative to D-2, receptors (Altar et al. 1986; Meltzer et al., in preparation). Thus, atypical antipsychotic drugs such as clozapine would be expected to produce a greater reduction in 5-HT_2-mediated relative to D-2-mediated neorotransmission compared to the effect of treatment with typical neuroleptic drugs. Further, clozapine has a particular potency to downregulate cortical 5-HT_2 receptors (Lee and Tang 1984; Matsubara et al., in press). Thus, clozapine may produce changes in serotonergic neurotransmission that parallel changes already present in the brain of chronic schizophrenic patients. The interpretation of this parallelism must await definitive clarification of whether the decreased 5-HT_2 receptor density reported in schizophrenia is drug induced or not. If not, it could be an adaptive change, rather than etiologic, i.e. an attempt to reduce serotonergic neurotransmission. These effects might be beneficial if there is, in fact, a decrease in dopamine release in some brain regions in schizophrenia and decreasing serotonergic activity enhances dopaminergic activity. We and others have suggested that the negative symptoms of schizophrenia may be related to decreased dopaminergic activity while the positive symptoms may be related to increased dopaminergic activity (MacKay 1980; Bannon and Roth 1983; Meltzer 1985).

We have discussed elsewhere the possibility of mutual influences of dorsal and median raphé serotonergic activity on frontal cortical, mesolimbic and mesostriatal dopaminertic systems which could lead to decreased dopaminergic activity in the frontal cortex and increased dopaminergic activity in the mesolimbic and mesostriatal system (Meltzer et al. submitted; Meltzer 1989b). If there is any validity to this hypothesis, it would suggest that the primary abnormality in schizophrenia could be in dopaminergic-serotonergic interactions rather than in either transmitter alone. An abnormality in either neurotransmitter alone could be at least partially compensated for by appropriate changes in the other. Dysfunction might result only from an imbalance between the two. Clozapine and other atypical antipsychotic drugs because of their unique effects on the relationship between 5-HT_2- and D-2-mediated neurotransmission may be uniquely able to correct this abnormality. It is possible that if the ratio of serotonergic to dopaminergic activity is high, negative symptoms predominate while in the opposite case, positive symptoms predominate.

The ability of clozapine to rapidly if partially ameliorate both positive and negative symptoms in many treatment-resistant schizophrenics would appear to limit the population to whom Crow's hypothesis of type I and II schizophrenia (Crow 1980) might apply. This theory proposed that treatment-resistant schizophrenia was due to structural brain damage, unrelated to abnormalities in DA, and that negative symptoms did not respond to antipsychotic drug treatment. None of these predictions have been supported in clozapine-responsive treatment-resistant patients.

In conclusion, clozapine treatment produces a number of significant effects on dopaminergic and serotonergic mechanisms in man. These may be related to its unique clinical effects, since they usually parallel effects in laboratory animals that are also produced by other atypical antipsychotic drugs. Dopamine and 5-HT_2 receptor antagonism as well as increased DA and 5-HT release appear to be critical elements in clozapine's action. This may be related to a parallel change in 5-HT_2- and D-2-mediated neurotransmission in schizophrenia. Further study is needed to evaluate the importance of the effects of clozapine on D-1, cholinergic, adrenergic, GABAergic or peptidergic mechanisms at this time.

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