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Biochemical and behavioural properties of clozapine

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Abstract. The selection and early development of clozapine was based upon its gross behavioural, arousal-inhibiting, sleep-promoting, and caudate spindle-prolonging properties. Compared to classical neuroleptics, clozapine causes only a short-lasting elevation of plasma prolactin levels, elevates both striatal homovanillic acid and dopamine content, is devoid of marked apomorphine-inhibitory or cataleptogenic activity and fails to induce supersensitivity of striatal dopaminergic systems after chronic administration. Clozapine's intrinsic anticholinergic activity, while stronger than that of other neuroleptic agents, does not appear to underlie either its failure to induce tardive dyskinesias or its superior antipsychotic activity. Furthermore, the overlap between clozapine and several classical neuroleptics with regard to alpha-adrenergic-, serotonin- and histamine-blocking activity makes it unlikely that one or more of these properties is the key to its atypical characteristics. More recent findings show that clozapine and classical neuroleptics differ with regard to their indirect effects on nigral GABA-ergic mechanisms implicated in the induction of tardive dyskinesias and, possibly in keeping with this, that clozapine and similar agents exhibit preferential blockade of D-1 dopamine receptors in the whole animal. Such an action of clozapine in man could well explain both its low EPS liability and, in some subjects, its superior antipsychotic activity.

Key words: Clozapine – D-1 Blockade – Behavioural effects

Clozapine (Fig. 1), a dibenzazepine derivative exhibiting atypical, neuroleptic-like properties in both animals and man, has been the subject of investigation for almost 30 years. While many findings and hypotheses have been put forward during this time to explain its non-classical profile, a widely accepted, cohesive explanation has proved elusive. The purpose of this article is to briefly review some of the animal data which led to the clinical testing of clozapine in schizophrenia, compare its behavioural and biochemical actions to those of conventional antischizophrenic agents and, finally, focus upon recent findings which may throw more light on both the actions of clozapine and the biochemical disturbances occurring in schizophrenia.

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Atypical neuroleptic properties in animal studies

Although the synthesis and early pharmacological testing of clozapine occurred in the early 1960s, prior to the identification of dopamine as a CNS transmitter, its gross behavioural effects in various animal species, in analogy to those of chlorpromazine, identified it as a likely major tranquilizer (Stille et al. 1971). Subsequent studies in the rat confirmed this early impression, with clozapine being shown to inhibit conditioned avoidance responding, prolong the duration of caudate spindles and cause a shift in the sleep-waking pattern towards dozing (Table 1). The increased dozing seen in rats treated with clozapine, as with chlorpromazine or haloperidol, is furthermore atypical, being characterised by a basic 8–10 Hz rhythm punctuated by 8–12 Hz spindles. In the rabbit, clozapine strongly inhibits EEG-arousal reactions induced by either electrical stimulation of the reticular formation or IV administration of the cholinergic agonist arecoline, being more potent than other antischizophrenic agents in this regard.

While subsequent studies revealed further similarities between clozapine's actions and those of conventional neuroleptics, a number of major differences emerged. In particular, clozapine was found to be a relatively strong anticholinergic agent (Stille et al. 1971; Snyder et al. 1974), cause only a short-lasting increase in serum prolactin levels (Meltzer et al. 1975; Meltzer et al. 1986), be virtually devoid of cataleptogenic activity and to only weakly antagonise apomorphine- or amphetamine-induced stereotypies in the rat (Stille et al. 1971). Chronic administration of clozapine, moreover, does not induce dopaminergic supersensitivity, fails to result in tolerance to the drug's striatal HVA-elevating action and, in keeping with this, does not cause cross-tolerance to the HVA-elevating action of the classical neuroleptic haloperidol (Sayers et al. 1975; Bowers and Rozitis 1976).

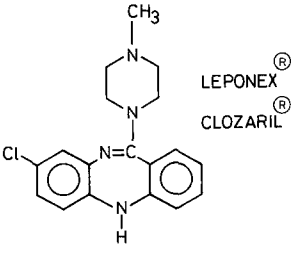

Fig. 1. Chemical structure of clozapine

Table 1. Similarities between the actions of clozapine and chlorpromazine in preclinical tests indicative of likely antischizophrenic activity in man. Studies were performed on groups of four or more rats or rabbits (arousal studies). SWS = slow wave sleep, PS = paradoxical sleep

Test	Drug	
	Chlorpromazine	Clozapine
Conditioned avoidance	ED_{50} 4.1 mg/kg PO (3.28–5.12)	ED_{50} 20.0 mg/kg PO (11.67–27.71)
Arousal		
Electrical	ED150% 5.8 mg/kg IV	ED150% 1.5 mg/kg IV
Cholinergic	ED_{Block} >10.0 mg/kg IV	ED_{Block} 1.2 mg/kg IV
Sleep		
Change at 20.0 mg/kg PO	Waking: − 43% Dozing: +112%[a] SWS: − 71% PS: −100%	Waking: 0 Dozing: +91%[a] SWS: −54% PS: −81%
Caudate spindle		
Duration at 20.0 mg/kg PO	+	+++

[a] Atropical

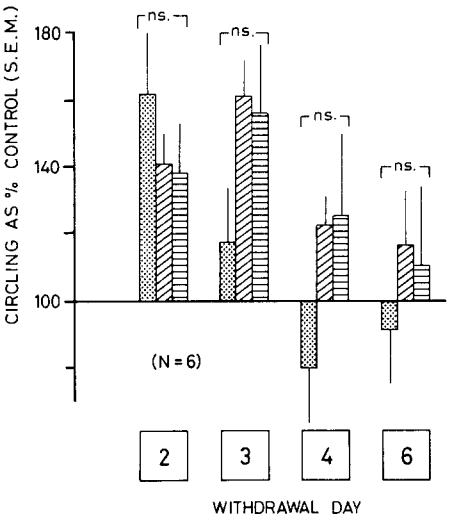

Fig. 2. Failure of co-administration of atropine or clozapine to prevent the induction of supersensitivity towards the circling-inducing action of 0.4 mg/kg SC apomorphine in unilaterally caudate-lesioned rats withdrawn from 6 days treatment with haloperidol. Neither atropine nor clozapine alone affect the baseline sensitivity to apomorphine after chronic administration. ▩ Haloperidol, 3 p.o.; ▨ Haloperidol + Atropine, 10 s.c.; ▤ Haloperidol + Clozapine, 20 p.o.

Neurotransmitter interactions

The prediction that clozapine should be an effective antipsychotic agent while failing to induce extrapyramidal disturbances of the dystonic or parkinsonian type was soon borne out by clinical feedback (Gross and Langer 1966; Angst et al. 1971). These observations emerged at a time when attempts were first made to correlate the antischizophrenic potency of neuroleptics to their blocking activity at dopamine D-2 receptors and, on this basis, it began to appear as though clinically-active doses of clozapine were producing a similar degree of D-2 receptor blockade to that seen with classical neuroleptics (Creese et al. 1976; Seeman et al. 1976). If this is indeed the case, why does clozapine not give rise to classical extrapyramidal side-effects?

The most obvious explanation for the lack of acute dystonias or parkinsonism after clozapine treatment, assuming that the drug does indeed block D-2 receptors at clinically effective doses, is that such effects are prevented by a concomitant interaction of the drug with other neurotransmitter systems. Thus, clozapine interacts with most if not all conventional neurotransmitters, and its anticholinergic action in particular would be expected to prevent cataleptogenic activity in the rat and protect against dystonias and parkinsonism in man. However, several findings speak against this simplistic explanation for clozapine's atypical neurological properties. Thus, animal studies show that combining haloperidol with atropine only partly mimics the atypical pharmacological properties of clozapine (Sayers et al. 1976). Amongst others, for example, haloperidol still inhibits apomorphine-induced circling behaviour in caudate-lesioned rats when combined with atropine, whereas clozapine is ineffective. Furthermore, co-administration of atropine or clozapine does not prevent the induction of supersensitivity in caudate-lesioned rats withdrawn from chronic treatment with haloperidol (Fig. 2). These findings are supported by the clinical observation that while combining classical neuroleptics with anticholinergic agents reduces the incidence of acute extrapyramidal side effects, it does not appear to reduce the risk of tardive dyskinesia development after long-term neuroleptic exposure (Klawans 1973; Gerlach 1977).

Amongst its other neurotransmitter interactions, clozapine's serotonin-blocking properties have received considerable attention in relation to its extrapyramidal profile, stemming from the observation that serotoninergic mechanisms appear to play a major role in opiate-induced catatonia (Balsara et al. 1979a; Broekkamp et al. 1984). However, neuroleptic-induced catalepsy bears only a limited resemblance to the catatonia produced by opiates, and the evidence for a major role of serotoninergic mechanisms in this condition is equivocal. While some workers have obtained evidence supporting a role of serotonin in neuroleptic catalepsy, for example (Carter and Pycock 1977; Balsara et al. 1979b), others have been unable to influence it with either *para*-chlorophenylalanine (Sarnek and Baran 1975), metergoline (Vidali and Fregnan 1979) or the selective 5-HT-2 antagonist ketanserine (Arnt et al. 1986). More recently, Broekkamp and colleagues have performed a detailed study of the relative role of serotoninergic mechanisms in catatonia and catalepsy, concluding that while they are of major importance for the former condition they appear to be of limited relevance for the latter (Broekkamp et al. 1988).

One area where the effects of clozapine clearly differ from those of classical neuroleptics, and which may be of paramount importance to its long-term neurological properties, concerns its indirect effects on central GABA-ergic function. GABA is a major neurotransmitter in many of

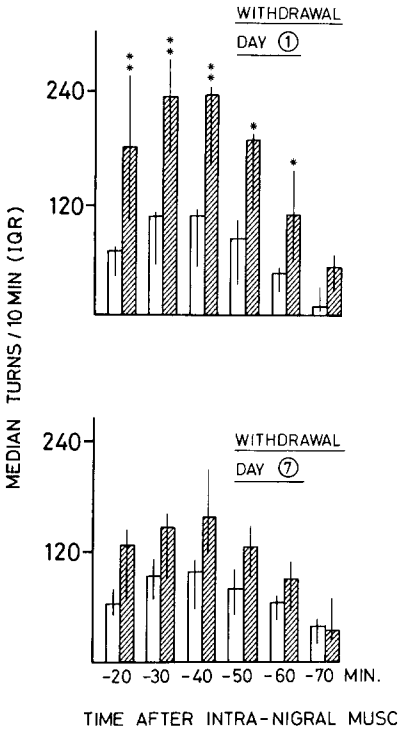

Fig. 3. Supersensitivity towards the circling-inducing action of intra-nigral muscimol (5.0 ng) in rats withdrawn 1 but not 7 days from 10 days treatment with haloperidol, 1.0 mg/kg PO. * $P<0.05$, ** $P<0.01$, $N=8$. □ Vehicle; ▨ Haloperidol

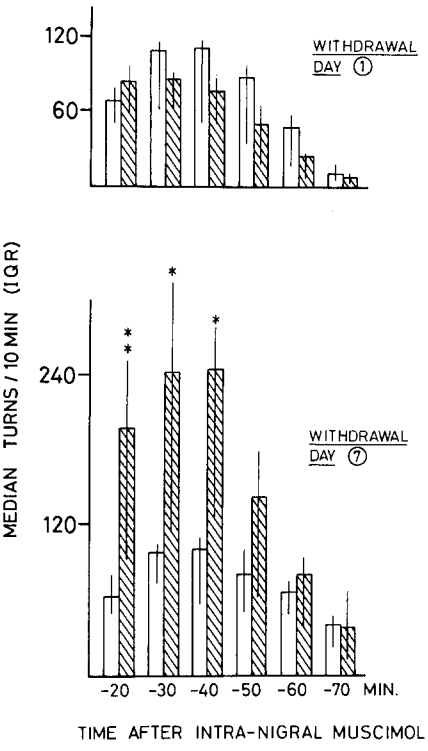

Fig. 4. Supersensitivity towards intra-nigral muscimol in rats withdrawn 7 days from 10 days treatment with clozapine, 20.0 mg/kg PO. Short-term withdrawal, in contrast, shows a non-significant, subsensitivity towards muscimol. * $P<0.05$, ** $P<0.01$, $N=8$. □ Vehicle; ▧ Clozapine

the efferent pathways from dopamine-innervated areas such as the nucleus accumbens and corpus striatum, and also plays a central role within nigro-thalamic and nigro-tectal pathways (Nauta et al. 1978; Redgrave et al. 1980). In addition, most of the behavioural effects produced by dopamine agonists and antagonists in the rat can be mimicked by modifying GABA-ergic activity within the substantia nigra (Olianas et al. 1978; Scheel-Krüger et al. 1981), and intra-nigral injections of GABA antagonists produce oral dyskinesias reminiscent of those seen after classical neuroleptic exposure in man (Arnt and Scheel-Krüger 1980). Chronic administration of classical neuroleptics reduces GABA turnover within the substantia nigra of the rat (Mao et al. 1977) and, probably as a result of this, induces GABA-ergic supersensitivity within this region (Gale 1980; Coward 1982; Frey et al. 1987; Fig. 3). In contrast, nigral GABA sensitivity is slightly reduced after short-term withdrawal from chronic clozapine exposure, but is increased after one week (Fig. 4). This increased sensitivity of nigral GABA-ergic systems then declines, with no difference being observed between placebo-, haloperidol- and clozapine-exposed animals after 14 days withdrawal from treatment (Coward 1982). The relevance of this temporal difference between the actions of clozapine and those of classical neuroleptics on nigral GABA-ergic sensitivity to the possible induction of neurological side effects in the clinic is suggested by chronic studies in both the rat (Gunne and Haggstrom 1983) and monkey (Gunne et al. 1984), where an association has been established between altered nigral GABA function and the appearance of tardive dyskinesia – like phenomena.

Striatal versus mesolimbic actions of clozapine

Since schizophrenia appears to reflect a primary disturbance of the limbic system as opposed to basal ganglia function, and vice versa with regard to motor defects, many studies have addressed the question of whether clozapine's atypical properties might be attributable to a preferential action of the drug within the mesolimbic system, especially the nucleus accumbens. This region receives a major dopaminergic input from the ventral tegmental area and functions as a critical interface between limbic and motor structures (Stevens 1973; Stevens et al. 1974; Nauta et al. 1978).

While early biochemical studies produced conflicting findings, recent investigations support the contention that clozapine produces proportionally greater suppression of mesolimbic as opposed to striatal dopamine function, particularly after chronic administration (Table 2). Thus, electrophysiological studies show that while clozapine increases the firing rate of both nigro-striatal and mesolimbic dopamine neurones after acute administration, only the mesolimbic population exhibit chronic depolarisation blockade after repeated exposure to the drug (Chiodo and Bunney 1983; White and Wang 1983). Classical neuroleptic treatment, in contrast, results in depolarisation blockade of both groups of neurones after chronic treatment. These findings are consistent with the earlier observation that tolerance fails to develop to clozapine's elevation of striatal HVA levels in the rat (Bowers and Rozitis 1976) and, to some extent, with recent voltammetric studies examining the effects of chronic neuroleptic administration on striatal and accumbal DOPAC release (Maidment and Marsden 1987).

Table 2. Similarities and differences between the effects of acutely- and chronically-administered clozapine (CLOZ) and haloperidol (HALO) on neuronal firing rate and voltammetrically-determined DOPAC concentrations within the nigro-striatal (A9) and meso-limbic (A10) dopamine systems of the rat. TOL = tolerance, ? = effect unknown

	Parameter			
	Firing rate		[DOPAC]	
Region	Acute	Chronic	Acute	Chronic
HALO				
A9	↗	↙	↗	TOL
A10	↗	↙	↗	?
CLOZ				
A9	↗	↗	↗	↗
A10	↗	↙	↗	↗

Table 3. Comparison of the affinity of various typical and atypical neuroleptics for dopamine D-1 (SCH 23390) and D-2 (spiperone) binding sites in vitro. IC_{50}s represent the means from two or more separate determinations

	IC_{50} (nmol/l)		D-1:D-2
Drug	D-1	D-2	Ratio
Typical			
Sulpiride	>10000	233	–
Fluphenazine	17	0.2	77
Haloperidol	365	10	37
Chlorpromazine	110	17	7
Thioridazine	93	31	3
Atypical			
Tilozepine	94	273	0.34
Clozapine	279	834	0.33
RMI 81582	19	160	0.12
Fluperlapine	96	1565	0.06

The clinical relevance of the above findings is indicated by the fact that the onset of depolarisation blockade within the two systems correlates with the emergence of both antipsychotic efficacy and extrapyramidal side effects. Furthermore, co-administration of an anticholinergic agent can prevent the induction of depolarisation blockade within the nigro-striatal system produced by haloperidol (Chiodo and Bunney 1985), suggesting that clozapine's intrinsic anticholinergic activity may underlie its failure to cause depolarisation blockade within the nigro-striatal system. What these findings do not resolve, however, is the relevance of such changes (or lack of them) to clozapine's failure to induce tardive dyskinesias, or its apparently superior antipsychotic activity in some subjects (Kane et al. 1988). Thus, co-administration of anticholinergic agents fails to prevent the increase in striatal D-2 receptor density produced by classical neuroleptics such as fluphenazine (Boyson et al. 1988) or haloperidol (Carvey et al. 1988) in animal studies, and clinical findings show that combining classical neuroleptics with anticholinergic agents neither prevents the induction of tardive dyskinesia (Tarsy and Baldessarini 1977), nor improves their antischizophrenic activity (Kane et al. 1988). These observations, together with those discussed earlier, suggest that an unknown or perhaps previously ignored factor may be playing a fundamental role in relation to clozapine's novel clinical profile.

New insights into clozapine's actions

Since the identification of the selective D-1 receptor antagonist SCH 23390 and the demonstration of its ability to influence many behavioural phenomena previously ascribed to D-2 receptor blockade (see Waddington 1986), attention has focussed upon the possible clinical relevance of neuroleptic drug interactions with D-1 receptors. While clozapine has long been recognised as a moderate inhibitor of D-1 – linked adenylate cyclase activity, the possibility of this action contributing to its unique clinical profile has formerly been dismissed since classical neuroleptics such as fluphenazine and *cis*-flupenthixol are much stronger inhibitors of adenylate cyclase activity in vitro than is clozapine. However, recent findings (Andersen et al. 1986; Table 3) indicate that clozapine and drugs having similar preclinical profiles may produce preferential blockade of D-1 receptors, whereas the blockade of D-1 receptors by *cis*-flupenthixol (Hess et al. 1988) and fluphenazine (Andersen 1988) in vivo appears to be much weaker than indicated by their in vitro activity. On the basis of binding data alone, however, it would be premature to conclude that clozapine and similar agents produce preferential blockade of D-1 receptors in the whole animal. Thus, assay conditions employed in vitro cannot completely mimic the in vivo environment, and even binding data obtained in vivo say nothing about the *functional* consequences, if any, of drug interactions with particular receptors. This issue has recently been addressed by employing the technique of trans-striatal dialysis in the conscious rat to see whether a functional "D-1 bias" of clozapine-like compounds can be demonstrated in the whole animal.

When using this approach to measure changes in dopamine function in the conscious rat, low doses of clozapine are seen to cause a marked, long-lasting increase of striatal dopamine release and a smaller increase of HVA and DOPAC levels (Imperato and Angelucci 1988; Fig. 5). These actions of clozapine are blocked by pretreating the animals with the selective D-1 agonists CY 208–243 (Fig. 5) or SKF 38393, which by themselves have no effect on the basal release of dopamine or its metabolites. This picture changes, however, when high doses of clozapine are employed. Thus, at 20–40 mg/kg SC clozapine induces a (haloperidol-like) greater increase of HVA and DOPAC release than of dopamine release, and these effects are only partially reversed by even high doses of selective D-1 agonists (Imperato and Angelucci 1988). In the "reverse situation", intra-striatal infusion of the selective D-2 agonist LY 171555 retains its normal ability to suppress striatal dopamine release in the presence of low doses of clozapine, but this action is blocked in the presence of high doses of clozapine (Fig. 6). Taken together, the findings of these functional studies confirm the predictions based upon the binding data in Table 3, showing that clozapine induces preferential blockade of D-1 receptors in vivo.

In the clinical situation, this would mean that at the average daily doses previously correlated to inhibition of haloperidol binding at D-2 receptors (Creese et al. 1976; Seeman et al. 1976), clozapine should be producing propor-

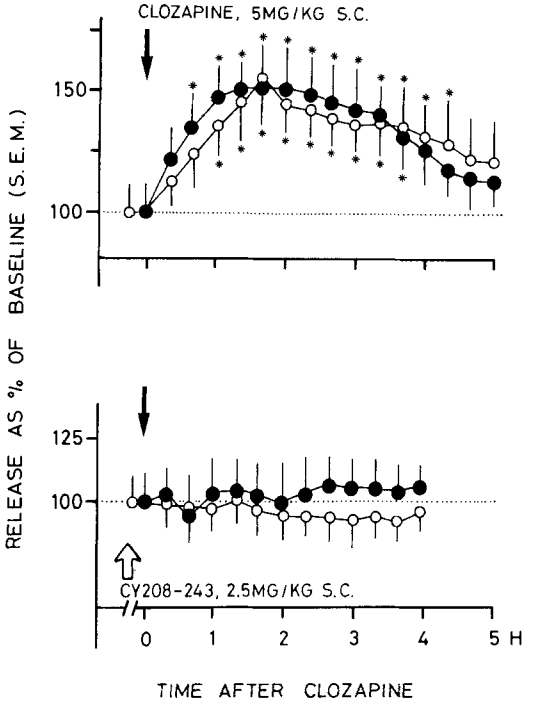

Fig. 5. Increase of striatal dopamine and DOPAC release in the conscious rat by a low dose of clozapine and its prevention by the selective D-1 agonist CY 208–243 given 20 min beforehand. * $P<0.05$ compared to baseline values, $N=4$. • Dopamine; o DOPAC

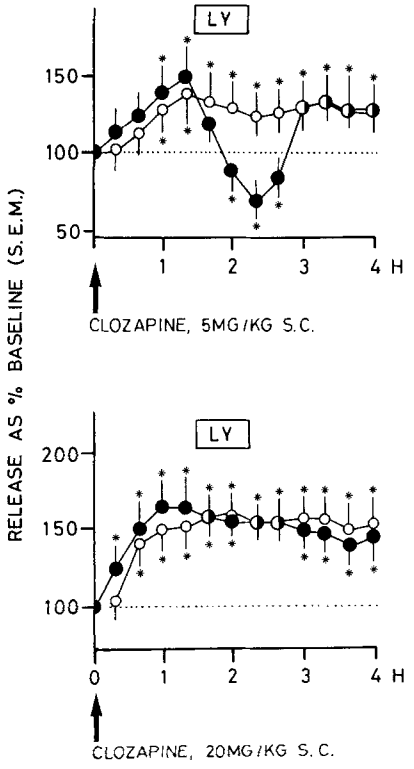

Fig. 6. Inhibition of the D-2 agonist LY 171555's ability to suppress striatal dopamine release after high, but not after low doses of clozapine. LY 171555 was applied directly into the striatum via the dialysis tubing, * $P<0.05$, $N=4$. • Dopamine; o DOPAC

tionally greater inhibition of D-1 – associated activity than is the case with classical neuroleptics. Alternatively, if D-1 blockade is in fact of relevance for antipsychotic activity, it could be argued that clozapine might be effective at doses causing less D-2 blockade than occurs with classical neuroleptics. In fact, preliminary feedback from PET-scan studies of relative D-1 and D-2 receptor occupancy in schizophrenics responding to neuroleptic treatment is consistent with this notion (Farde et al. 1988a, b). Whereas therapeutic responses to classical neuroleptics appear to be associated with D-2 receptor occupancy rates of 70–85%, for example, one subject responding to treatment with 600 mg/day of clozapine showed 65% D-2 receptor occupancy and a second patient responding to 300 mg/day only 40% occupancy. This second subject, however, showed a D-1 occupancy rate of 40%, greater than that so far observed with any other drug.

The hypothesis that clozapine's interaction with D-1 receptors might be a critical factor in relation to its clinical profile is supported by a number of additional observations. Within the extrapyramidal system, for example, D-1 receptors are closely associated with those striato-nigral GABAergic pathways implicated in the development of nigral GABA supersensitivity and, after long-term exposure, the emergence of tardive dyskinesia-like phenomena (see earlier). Furthermore, whereas some striatal D-2 receptors are linked in an inhibitory fashion to D-1 receptor systems, this type of interaction does not appear to occur within the mesolimbic system (Stoof and Verheijden 1986). This latter finding might be particularly relevant to clozapine's differential effects within the nigro-striatal and mesolimbic systems, since it would explain why combining classical neuroleptics with anticholinergic agents, which reverse drug-induced depolarisation blockade of A9 neurones, still fails to mimic the long-term neurological profile of clozapine. In addition to being of possible relevance to its neurological profile, however, preferential D-1 receptor blockade might also contribute towards or explain the superior antipsychotic activity of clozapine in some subjects (Kane et al. 1988). While the distribution of D-1 and D-2 receptors within the CNS is similar, for example, the density of D-1 receptors is higher in almost all brain regions examined (Boyson et al. 1986), particularly in the human cortex (De Keyser et al. 1988). Furthermore, there is evidence for increased coupling of D-1 receptors with adenylate cyclase in postmortem tissue from schizophrenic subjects (Memo et al. 1983), and recent animal studies have provided evidence that D-1 (but not D-2) – linked mechanisms play a critical role in the expression of both reinforcing and aversive motivational processes (Shippenberg and Herz 1988). This latter finding could contribute towards the beneficial effects of clozapine on negative symptoms, with the failure of even high doses of drugs such as flupenthixol and chlorpromazine to achieve clozapine's clinical efficacy being explained by detrimental effects arising from excessive D-2 antagonism, and/or their failing to achieve the necessary degree of D-1 blockade.

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