

Clozapine Normalizes Prefrontal Cortex Dopamine Transmission in Monkeys Subchronically Exposed to Phencyclidine

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The mechanism responsible for the therapeutic effects of the prototypical atypical antipsychotic drug, clozapine, is still not understood; however, there is persuasive evidence from *in vivo* studies in normal rodents and primates that the ability to elevate dopamine neurotransmission preferentially in the prefrontal cortex is a key component to the beneficial effects of clozapine in schizophrenia. Theoretically, such an effect of clozapine would counteract the deficient dopaminergic innervation of the prefrontal cortex that appears to be part of the pathophysiology of schizophrenia. We have previously shown that following repeated, intermittent administrations of phencyclidine to monkeys there is lowered prefrontal cortical dopamine transmission and impairment of cognitive performance that is dependent on the prefrontal cortex; these biochemical and behavioral changes therefore model certain aspects of schizophrenia. We now investigate the effects of clozapine on the dopamine projections to prefrontal cortex, nucleus accumbens, and striatum in control monkeys and in those withdrawn from repeated phencyclidine treatment, using a dose regimen of clozapine that ameliorates the cognitive deficits described in the primate phencyclidine (PCP) model. In normal monkeys, clozapine elevated dopamine turnover in all prefrontal cortical, but not subcortical, regions analyzed. In the primate PCP model, clozapine normalized dopamine (DA) turnover in the dorsolateral prefrontal cortex, prelimbic cortex, and cingulate cortex. Thus, the present data support the hypothesis that the therapeutic effects of clozapine in this primate model and perhaps in schizophrenia may be related at least in part to the restoration of DA tone in the prefrontal cortex.

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INTRODUCTION

Atypical antipsychotic drugs have been traditionally distinguished from typical ones by their decreased proclivity to induce extrapyramidal side effects and an absence of sustained prolactin elevation. Clozapine was the original atypical antipsychotic drug used in the treatment of schizophrenia, and in contrast to typical agents, it improves the positive symptoms, negative symptoms, and cognitive dysfunction of schizophrenia (Kane *et al*, 1988; Lee *et al*, 1994; Meltzer and McGurk, 1999). Typical antipsychotics have rarely been reported to produce significant improvement in negative symptoms or cognitive function in

schizophrenia, yet these symptoms are considered the most difficult problem in schizophrenia. The cognitive problems consist of poor memory and attention, impaired executive and verbal functions, and deficits of psychomotor and sensory capabilities, and these features combine to impair psychosocial function dramatically and powerfully in schizophrenia (Elvevag and Goldberg, 2000). Thus, the cognitive symptoms of schizophrenia are a target of intensive research, both to uncover the relevant pathophysiological determinants and to highlight potential pharmacotherapeutic strategies.

Despite much research, the unique mechanism(s) responsible for the superior effects of clozapine are still not fully understood. However, there is strong evidence that clozapine preferentially elevates dopamine (DA) neurotransmission in the prefrontal cortex, and that this might be an important ingredient of its therapeutic effects (Moghaddam and Bunney, 1990; Karoum and Egan, 1992; Youngren *et al*, 1994; Broderick and Piercey, 1998; Kuroki *et al*, 1999; Melis *et al*, 1999; Youngren *et al*, 1999; Westerink *et al*, 2001). This hypothesis is compelling because reduced

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dopaminergic innervation to the prefrontal cortex occurs in schizophrenia (Akil *et al*, 1999; Egan *et al*, 2001; Guo *et al*, 2003), and dysfunction of the prefrontal DA system is thought to contribute to the cognitive deficits of the disorder (Davis *et al*, 1991; Knable and Weinberger, 1997; Goldman-Rakic *et al*, 2004).

The success of efforts to enhance cognition in schizophrenia depends, to some extent, on the availability of pre-clinical models that represent the relevant symptomatic features sufficiently to permit invasive and/or exploratory research not possible in humans (Green and Braff, 2001; Jentsch, 2003; Castner *et al*, 2004; Floresco *et al*, 2005; Hagan and Jones, 2005; Robbins, 2005). Non-human primate models are of particular impact, in as much as they can be assessed for cognitive functioning using tasks with both face and construct validity with relative ease.

Our previous work has shown that repeated treatment of monkeys with phencyclidine (PCP) results in a marked and persistent reduction in DA, but not serotonin or norepinephrine, turnover in the prefrontal cortex (Jentsch *et al*, 1997b, 1999a). As a change in DA turnover does not occur in striatal regions following repeated PCP administration, the effect induced in the primate PCP model on the prefrontal DA system is anatomically and neurochemically specific. Furthermore, the extent of impact of drug on DA innervation to the dorsolateral prefrontal cortex correlates significantly with the degree of cognitive impairment when performing an object retrieval with a detour (ORD) task, which is dependent on prefrontal cortex function (Jentsch *et al*, 1999a). Thus, the primate PCP model and its associated PFC DA deficit and cognitive dysfunction is well suited for a biochemical investigation of clozapine's action relevant to its therapeutic ability to reverse the cognitive dysfunction observed in this model and in schizophrenia.

We have previously shown that clozapine (1 mg/kg daily for 3 days) improves performance of the ORD task in the primate PCP model (Jentsch *et al*, 1997c). Thus, we decided to test the hypotheses that this dosing regimen of clozapine elevates DA turnover in the dorsolateral prefrontal cortex of control monkeys and those previously exposed to PCP and that in PCP-treated monkeys this increase is sufficient to normalize DA turnover. Until recently it was widely believed that antipsychotic drugs have a delayed onset of action. Based on recent specific new studies and meta-analysis of previous studies, there is now appreciation that therapeutic action occurs early on, even within the first 24 h of treatment (Agid *et al*, 2003, 2006; Kapur *et al*, 2005; Leucht *et al*, 2005). These data support the relevance of the clozapine treatment paradigm employed in the current study.

MATERIALS AND METHODS

Young adult male or female St Kitts green (vervet) monkeys (*Chlorocebus aethiops sabaeus*) at the St Kitts Biomedical Research Foundation (St Kitts, West Indies) were used. As the subjects were feral monkeys, their exact age was not known. These studies were approved by the relevant institutional animal care and use committee. Monkeys, housed individually in squeeze-cages, were injected with 0.3 mg/kg PCP hydrochloride (Sigma-Aldrich, St Louis,

MO) or saline twice daily for 14 days, as described before (Jentsch *et al*, 1997c). Clozapine (1 mg/kg daily for 3 days) or clozapine vehicle was injected for 3 days, following our previous regimen (Jentsch *et al*, 1997b), starting 7 or 8 days after completion of PCP or saline treatment. Some monkeys that did not receive clozapine were not injected with clozapine vehicle, and received no injections between the termination of 14 days of PCP or saline treatment and sacrifice; the biochemical values for these monkeys were pooled with those that received clozapine vehicle, as no significant difference between them existed. Animals were rapidly euthanized 90 min after the final clozapine dose by an injection of sodium pentobarbital, as before (Jentsch *et al*, 1997b, 1999a). Brains were perfused with cold saline by cardiac perfusion until the fluid exiting fell below 10°C. After transferring the brain in ice-cold saline to the dissection area, it was cut into 4 mm coronal slices using a custom brain mold. The following brain regions were rapidly dissected from slices on a thermostatically controlled refrigerated surface maintained at 1–2°C (Jentsch *et al*, 1997a, b; Elsworth *et al*, 2000): dorsolateral prefrontal cortex (Walker's Area 46), prelimbic cortex (Area 32), cingulate cortex (Area 24), supplementary motor area (Area 6M), dorsolateral caudate nucleus, and nucleus accumbens (enriched in the core sub-region). The caudate nucleus sample was taken from a coronal slice through the 'head' of the region. Tissue samples were assayed for concentrations of DA and its major metabolite in primate brain, homovanillic acid (HVA), by HPLC as described elsewhere (Elsworth *et al*, 1996, 2000). The ratio of HVA/DA in each tissue was used as an index of DA turnover. Mean values of the dependent variable were compared between groups using two-factor ANOVA (PCP/saline pretreatment, and clozapine/vehicle treatment), followed by Contrasts analysis (SuperANOVA, Abacus Concepts, Berkeley, CA), declaring significance at the 0.05 level.

RESULTS

As shown in Figure 1, withdrawal from repeated treatment with PCP resulted in a significant decrease in DA turnover, as measured by HVA/DA ratio, in the dorsolateral prefrontal cortex, prelimbic cortex, and cingulate cortex. No significant change in this ratio occurred in supplementary motor area, nucleus accumbens or caudate nucleus.

Clozapine treatment elevated the index of DA turnover in all analyzed prefrontal cortical regions of normal and PCP-exposed monkeys. However, in neither examined subcortical region did clozapine raise DA turnover. Inspection of the raw data indicated that for the prelimbic, cingulate, and supplementary motor area the raised ratio was mainly due to changes in HVA level. For the dorsolateral prefrontal cortex, a decrease in DA level contributed significantly to the increase in HVA/DA ratio.

Table 1 shows the control levels of DA for the different regions analyzed, derived from monkeys that received only saline and/or vehicle injections. There was no significant difference in basal DA concentration between any of the cortical regions. As expected, the control level in the caudate nucleus was greater than in the nucleus accumbens, and both these subcortical regions contained substantially

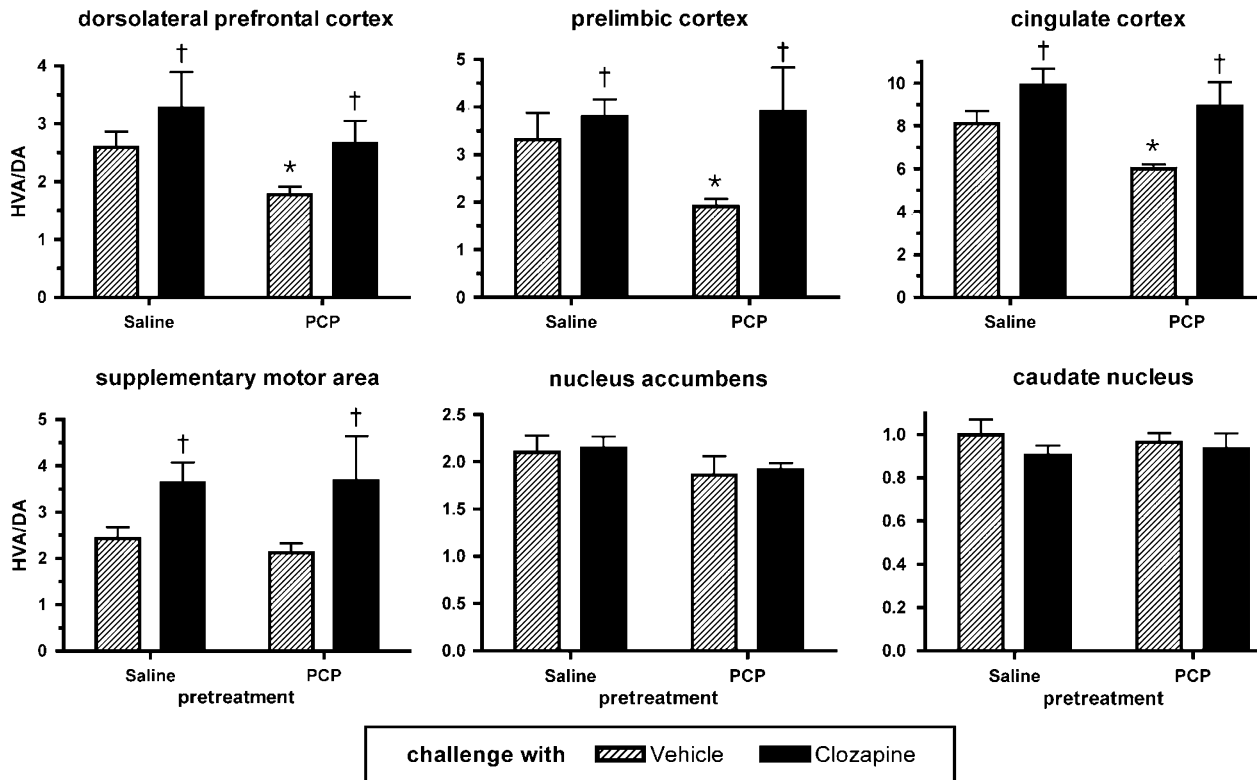


Figure 1 Clozapine causes a preferential increase in dopamine turnover in cortical regions compared with subcortical brain regions in normal and PCP-pretreated monkeys. †Clozapine significantly different from vehicle challenge (main effect for the four cortical regions, $F = 13.1-4.8$, $P < 0.001-0.05$). * PCP pretreatment-vehicle challenge significantly different from saline pretreatment-vehicle challenge (contrast analysis for three significant cortical regions, $F = 6.3-4.9$, $P < 0.02-0.05$). HVA and DA values (mean% control \pm SEM) for the clozapine-treated animals were as follows: dorsolateral prefrontal cortex; saline-clozapine 93 ± 9 [HVA]/ 78 ± 12 [DA], PCP-clozapine $99 \pm 19/90 \pm 9$; prelimbic cortex; saline-clozapine $135 \pm 10/109 \pm 15$, PCP-clozapine $135 \pm 35/103 \pm 13$; cingulate cortex; saline-clozapine $150 \pm 8/121 \pm 10$, PCP-clozapine $127 \pm 15/112 \pm 9$; supplementary motor area; saline-clozapine $133 \pm 6/89 \pm 9$, PCP-clozapine $128 \pm 28/80 \pm 3$; nucleus accumbens; saline-clozapine $126 \pm 4/116 \pm 8$, PCP-clozapine $89 \pm 2/91 \pm 5$; caudate nucleus; saline-clozapine $99 \pm 5/107 \pm 6$, PCP-clozapine $90 \pm 9/93 \pm 3$. Numbers of monkeys in each group: saline-vehicle, 10-14; PCP-vehicle, 7-13; saline-clozapine, 3-6; PCP-clozapine, 3-4.

Table 1 Control Values (\pm SE) for DA and HVA/DA in Different Monkey Brain Regions

Region (n)	Dopamine (ng/mg protein)	HVA/dopamine
Dorsolateral prefrontal cortex (13)	0.92 ± 0.09	2.60 ± 0.26
Prelimbic cortex (10)	1.27 ± 0.16	3.31 ± 0.57
Cingulate cortex (11)	1.19 ± 0.08	8.11 ± 0.59^a
Supplementary motor area (14)	1.04 ± 0.09	2.43 ± 0.24
Nucleus accumbens (14)	75.7 ± 6.0^b	2.10 ± 0.18
Caudate nucleus (14)	127.0 ± 6.6^c	1.00 ± 0.07^d

Values were compared between regions by one-way ANOVA followed by Student-Newman-Keuls test (significance at $P < 0.05$).

^aHVA/DA ratio significantly greater than all other examined regions.

^bDA value significantly greater than the value in all cortical regions.

^cDA value significantly greater than the value in all cortical regions and nucleus accumbens.

^dHVA/DA ratio significantly lower than all other examined regions, n is the number of monkeys in each group.

higher levels of DA than cortical regions. However, the HVA/DA ratio in control animals did not correlate with the DA concentration in each region, reflecting differences in

intrinsic and extrinsic regulation between the DA projections (Elsworth and Roth, 2004), and possibly the relative density of norepinephrine innervation (Carboni and Silvagni, 2004). Notably, the HVA/DA ratio was higher in the cingulate cortex than any other regions measured, and the ratio in nucleus accumbens was not significantly different from most cortical regions despite having a far greater DA content.

DISCUSSION

Previous studies have examined biochemical indices of the effect of clozapine on DA neurons in normal and PCP-treated rodents (Jentsch and Roth, 2000), and the present data extend these investigations to the primate brain. Studies of the central actions of clozapine in a higher species are important because of primate-rodent differences in the anatomy and biochemistry of brain DA systems (Elsworth and Roth, 2004). The results from this study showed that clozapine elevated DA turnover in cortical, but not striatal, regions in monkeys. In addition, when administered at a dose that is effective at reversing the cognitive deficits associated with repeated PCP treatment in the monkey, clozapine normalized the PCP-induced reduc-

tion in DA turnover in the dorsolateral prefrontal cortex, prelimbic cortex, and cingulate cortex.

We have previously shown using the microdialysis technique that clozapine administration preferentially increases extracellular DA levels in the dorsolateral prefrontal cortex compared with the caudate nucleus of normal monkeys (Youngren *et al*, 1999). Consistent with this finding, in the present study, we demonstrate that clozapine increased the HVA/DA ratio, an index of DA turnover, in post-mortem tissue from the prefrontal cortical regions examined, but not in tissue from nucleus accumbens or caudate nucleus. In the dorsolateral prefrontal cortex a decrease in DA level contributed significantly to the increase in HVA/DA ratio elicited by clozapine. In the mesoprefrontal DA system, where the recapture mechanism is inefficient (Ciliax *et al*, 1995; Sesack *et al*, 1998; Lewis *et al*, 2001) and transmitter homeostasis is more dependent on synthesis (Galloway *et al*, 1986), increases in functional activity can be reflected by a decrease in transmitter as well as an increase in metabolite level (Bean and Roth, 1991). It is not entirely clear why clozapine, but not typical antipsychotic drugs such as haloperidol, has a preferential action on cortical DA systems compared to the striatal DA systems. Although one feature that obviously distinguishes these areas is the density of DA innervation (Table 1), this does not in itself provide an explanation of the preferential action of clozapine on DA neurons projecting to the cortex. However, one of the early suggestions was that a selective action of clozapine on A10 DA neurons innervating the cortex, relative to A9 DA neurons projecting to the striatum may play a part in its observed preferential effects (eg Hand *et al*, 1987). While there have been several other theories over the years to explain the relative impact of clozapine on different DA systems, recent rodent data favor an explanation based on a difference in the local interaction of clozapine with receptors or uptake sites in the terminal regions (Gessa *et al*, 2000). The effect of a typical antipsychotic such as haloperidol could not be directly compared with the response to clozapine in the present study. This was because even a low dose of haloperidol (0.025 mg/kg i.m.) impairs cognitive performance in the monkey PCP model (Jentsch *et al*, 1999b), whereas 20–50 times this dose is required to elevate DA release in the dorsolateral prefrontal cortex (Youngren *et al*, 1999).

Repeated, intermittent exposure of monkeys to PCP produces a behavioral syndrome and neurochemical changes that may be relevant to the frontal cortical dysfunction characteristic of schizophrenia. The strong homology between the cognitive effects produced by PCP treatment and the frontal lobe impairment of schizophrenia support the notion that this model has face validity for the cognitive subsyndrome of the idiopathic disorder (Jentsch *et al*, 2000). Moreover, the striking similarities between neurochemical changes in the frontal cortex produced by long-term PCP administration and those evident in schizophrenia suggest that there may be construct validity for this model. Finally, our new neurochemical evidence together with behavioral data (Jentsch *et al*, 1999a) suggest that this model may have some predictive validity for the frontal cortical dysfunction of schizophrenia.

As we have shown before, DA turnover is reduced in some, but not all, prefrontal cortical regions following

repeated PCP treatment in the monkey, a model that results in cognitive deficits on a task dependent on prefrontal cortical DA function (Jentsch *et al*, 1997b, c, 1998). In the present study, DA turnover was reduced by PCP in the dorsolateral prefrontal cortex, prelimbic cortex, and cingulate cortex, but not in supplementary motor area (Figure 1). In addition, no effect of repeated PCP on DA turnover in the caudate nucleus or nucleus accumbens was observed (Figure 1), as we have found before in the monkey and rat (Jentsch *et al*, 1997b, c). These changes implicate reduced dopaminergic transmission selectively in subregions of the prefrontal cortex of the monkey after repeated exposures to PCP.

In the present study, we were particularly interested to see whether clozapine, at a dose that reversed the cognitive deficits induced by repeated PCP in the monkey, would also normalize the reduced DA turnover produced in the primate PCP model. The present data show that in the dorsolateral prefrontal cortex, prelimbic cortex, and cingulate cortex, clozapine treatment returned the depressed PCP-induced DA turnover to the control level (Figure 1). Previously, we had shown that clozapine treatment in PCP-pretreated rats raised extracellular DA levels significantly above that of normal rats (Jentsch and Roth, 2000). In another proposed animal model of aspects of schizophrenia, it has been found that rats raised in social isolation have an exaggerated dopaminergic response to acute clozapine in the prefrontal cortex (Heidbreder *et al*, 2001). This potentiation was not detected in the present primate study, and this may be important, as both deficient and excessive prefrontal cortex DA activation in primates result in working memory deficits (Arnsten *et al*, 1994; Murphy *et al*, 1996).

The data in Figure 1 are consistent with the conclusion that the ability of clozapine to alleviate preferentially the dopaminergic hypofunction induced by PCP in the dorsolateral prefrontal cortex, prelimbic cortex, and cingulate cortex is related to its ability to reduce cognitive impairment in PCP-treated monkeys. A critical test of this hypothesis will be to examine the comparative changes in the DA system and cognition in the primate PCP model produced by treatment with other atypical antipsychotic drugs. The present data also open up the possibility of investigating the receptor profile of clozapine that is responsible for its effect on the primate DA system and on cognition. Dopamine D4 receptors are highly enriched in the primate prefrontal cortex (Mrzljak *et al*, 1996) and as clozapine is a potent D4 antagonist, it has been suggested that this property might subserve some of its therapeutic effects in schizophrenia. It is noteworthy that our previous studies have demonstrated that a D4-selective antagonist, NGD-94-1, is able to reverse the cognitive deficits in the primate PCP model at a dose that has no significant effect on cognitive behavior in control monkeys (Jentsch *et al*, 1999b). In this study, an increase in CSF HVA was noted in the PCP monkeys, but not in control monkeys treated with NGD-94-1. The brain regions responsible for this change are unknown although previous studies have demonstrated a correlation between CSF and cortical levels of HVA in the monkey (Elsworth *et al*, 1987). Further studies will be required to determine if the behavioral reversal of the cognitive deficits in PCP-treated monkeys by NGD-94-1 or

other selective D4 antagonists is associated with a restoration of DA tone in the PFC before one can implicate D4 receptors in the clozapine-induced changes observed in the current study.

The present data showing preferential augmentation of DA neurotransmission by clozapine in the dorsolateral prefrontal cortex and prelimbic cortex in the PCP primate model supports the idea that its therapeutic antipsychotic effects in schizophrenia may be related at least in part to the normalization of reduced DA innervation of the prefrontal cortex and sparing of striatal DA systems.

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DISCLOSURE/CONFLICT OF INTEREST

None of the authors has any conflict of interest.

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