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Clozapine increases dopamine release in prefrontal cortex by 5-HT_{1A} receptor activation

Hans Rollema *, Yi Lu, Anne W. Schmidt, Stevin H. Zorn

Pfizer Inc., Central Research Division, Department of Neuroscience, 550 Eastern Point Road, Groton, CT 06340, USA

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Abstract

Clozapine (1–10 mg/kg s.c.) produces a selective increase in dopamine release in rat prefrontal cortex which is, in large part (~ 50%), mediated via activation of 5-HT_{1A} receptors. Clozapine is a moderately potent, partial 5-HT_{1A} receptor agonist and activation of 5-HT_{1A} receptors may contribute to its efficacy against negative symptoms and reduced extrapyramidal side effect liability. Agonist affinity for 5-HT_{1A} receptors could thus be a desirable feature in the design of new antipsychotics. © 1997 Elsevier Science B.V.

Keywords: Clozapine; Cortical DA release; Serotonin 5-HT_{1A} receptor

Clozapine is an efficacious antipsychotic drug with minimal liability to produce extrapyramidal side effects (EPS) and tardive dyskinesia, but it can cause a potentially fatal blood dyscrasia limiting its use to patients refractory to other medication. The greater enhancement of dopamine (DA) release in prefrontal cortex vs. striatum (Moghaddam and Bunney, 1990) may underlie its beneficial effects on negative symptoms, which are thought to arise from a functional impairment of dopaminergic transmission in the prefrontal cortex (Weinberger and Lipska, 1995). Clozapine is a moderately potent 5-HT_{1A} receptor agonist and since 5-HT_{1A} receptor agonists produce a pronounced increase in cortical DA release (Wedzony et al., 1996), we investigated the role of 5-HT_{1A} receptor activation on clozapine's effects on DA release in rat prefrontal cortex and striatum.

Microdialysis in awake male Sprague–Dawley rats was performed by perfusing probes implanted in the prefrontal cortex or striatum with artificial cerbrospinal fluid (1.5 μl/min) and measuring DA and metabolites in 30 μl samples every 25 min by reversed phase chromatography and electrochemical detection. Clozapine and WAY-100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazineyl]ethyl]-*N*-(pyridinyl)-cyclohexanecarboxamide · 3HCl) were administered s.c. and effects on DA release were monitored for 5 h and expressed as percentage of basal levels or as area under the curve ($AUC_{0\text{-}5\ h}$). Functional activity and ligand binding were measured as described previously (Seeger et al., 1995).

Clozapine produced a significantly greater increase in DA release in prefrontal cortex than in striatum at all doses tested (Fig. 1). Pretreatment with the selective 5-HT_{1A} receptor antagonist WAY-100635 (0.1 mg/kg, 30 min before clozapine), which by itself did not affect DA release but completely blocked the effects of the prototypical 5-HT_{1A} agonist 8-OH-DPAT (8-hydroxy-2-(di-*N*-propylamino)tetraline, 0.5 mg/kg; data not shown), markedly attenuated the increases in cortical DA release produced by 1–10 mg/kg clozapine. Dose- and time-response curves showed that WAY-100635 reduced the effects of clozapine on cortical DA by 50% and that this effect reached significance 2–5 h following clozapine administration (Fig. 1). A higher dose (1 mg/kg) of WAY-100635 did not further reduce the effects of clozapine. Pretreatment with WAY-100635 had no effect on the clozapine-induced increase in striatal DA release.

These data show that clozapine increases DA release in rat prefrontal cortex in large part via activation of 5-HT_{1A} receptors. This is consistent with the moderate in vitro affinity of clozapine for 5-HT_{1A} receptors in rat cortex ($K_i = 116$ nM) and with the fact that 8-OH-DPAT and partial 5-HT_{1A} receptor agonists produce cortical DA increases of comparable magnitude which are blocked by selective 5-HT_{1A} receptor antagonists (unpublished observations; Wedzony et al., 1996). The remaining, 5-HT_{1A}-independent increase in cortical DA release could result

* Corresponding author. Tel.: (1-860) 441-6374; Fax: (1-860) 441-1773; e-mail: hans_rollema@groton.pfizer.com

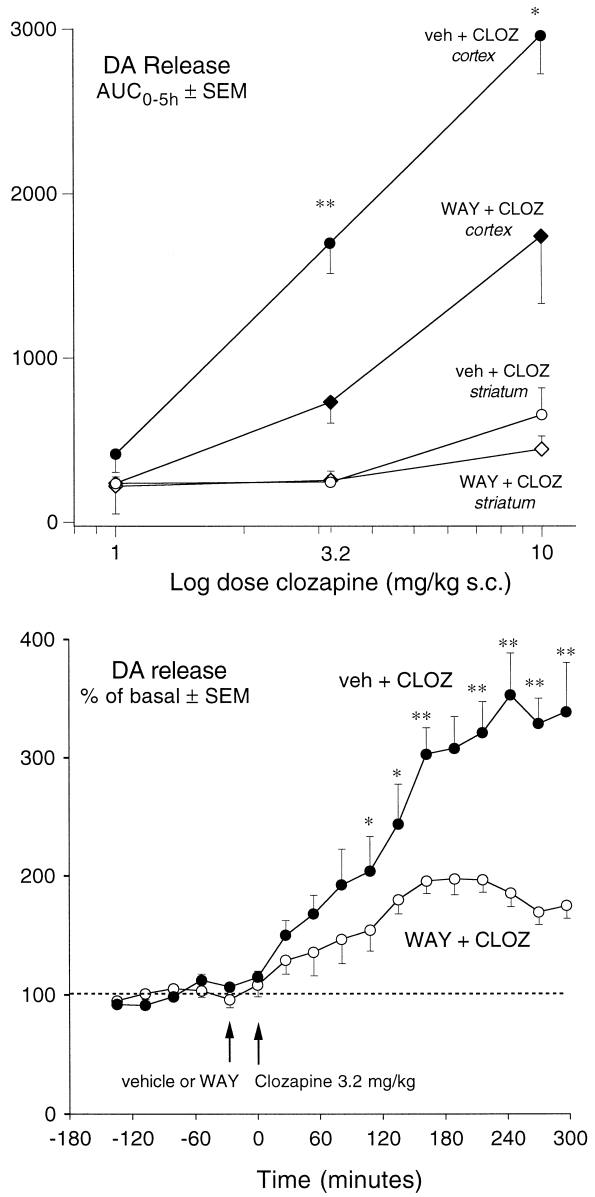

Fig. 1. Upper panel: Dose-response curves showing the effects of clozapine alone on DA release in rat prefrontal cortex (●) and striatum (♦) and after pretreatment with 0.1 mg/kg WAY-100,635 (○,◇). The percentage increase above basal DA release at each dose is expressed as the $AUC_{0-5h} \pm SEM$ ($n = 3–6$). Lower panel: Time–response curve showing the effect of 3.2 mg/kg clozapine, alone (●) and after pretreatment with 0.1 mg/kg WAY-100635 (○), on DA release in rat prefrontal cortex. The increases in DA release at each time point are expressed as mean percentages of basal levels ± SEM ($n = 4–5$). Statistical significance (vehicle + clozapine vs. WAY + clozapine; $^{*}\ p < 0.05$; $^{**}\ p < 0.01$) was tested by ANOVA and post hoc Dunnett test.

from an interaction with other neurotransmitter receptors for which clozapine has moderate to high affinity (5-$HT_{2A,2C,6,7}$, D_{1-4}, α_{1-2}, m_{1-5}). However, it is unlikely that dopaminergic D_2/D_1, adrenergic or muscarinic receptors mediate this DA increase. First, as a dopamine D_2 ($K_i = 83$ nM) and dopamine D_1 receptor antagonist ($K_i = 330$ nM), clozapine would be expected to have a much smaller effect on cortical DA release than on striatal DA release (Moghaddam and Bunney, 1990; Santiago et al., 1993). Secondly, clozapine's adrenergic antagonist pharmacology ($K_i\,\alpha_1 = 5.6$ nM, $\alpha_2 = 32$ nM) is probably not involved since potent α_1- and α_2-adrenoceptor antagonists (prazosin and 1-(2-pyrimidinyl)piperazine) lack effects on cortical DA release (unpublished observations; Wedzony et al., 1996). Finally, although clozapine is a potent m_4 receptor agonist (Zorn et al., 1994), scopolamine blocks the clozapine-induced DA increase in striatum, but not that in prefrontal cortex (Meltzer et al., 1994). The residual cortical DA increase could therefore be mediated by interaction with other receptors (e.g. 5-HT_{2A}, 5-$HT_{6,7}$, D_4).

The selective enhancement of cortical DA release may be a desirable feature for antipsychotics, since it could elevate the reduced cortical dopaminergic transmission purportedly underlying negative symptoms associated with schizophrenia (Weinberger and Lipska, 1995). Using a GTPγ^{35}S binding assay clozapine was found to be a partial agonist at human 5-HT_{1A} receptors with an efficacy of 49% compared to 5-HT (Newman-Tancredi et al., 1996). These data suggest that a direct interaction of clozapine with 5-HT_{1A} receptors may underlie in part clozapine's unique clinical efficacy and 'atypical' antipsychotic profile. It is of interest that the novel antipsychotic, ziprasidone (Seeger et al., 1995), is a potent 5-HT_{1A} agonist which may contribute to its effectiveness against negative and positive symptoms and its low propensity to produce EPS (Tandon et al., 1997).

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