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Short communication

The atypical antipsychotic quetiapine increases both noradrenaline and dopamine release in the rat prefrontal cortex

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Abstract

Quetiapine is a novel atypical antipsychotic drug with multi-receptorial affinity. Using in vivo microdialysis, we investigated if quetiapine modulates extracellular noradrenaline and dopamine in brain areas generally believed to be involved in the pathophysiology of schizophrenia and in the action of antipsychotic drugs. Quetiapine (5, 10 and 20 mg/kg, i.p.) increased levels of noradrenaline in both the prefrontal cortex and the caudate nucleus, while it increased dopamine levels mainly in the prefrontal cortex. It is argued that the marked increase of dopaminergic transmission in the prefrontal cortex induced by quetiapine might be relevant to its therapeutical action.

Keywords: α_2-Adrenoceptor antagonist; Atypical antipsychotic drug; Microdialysis; Catecholamine; Caudate nucleus

1. Introduction

Hypofunctionality of the prefrontal cortex has been proposed as an underlying dysfunction in schizophrenia, especially in relation with negative and cognitive symptoms. Furthermore, the ability of atypical antipsychotic drugs, such as clozapine, to increase catecholamine levels in the prefrontal cortex might play a role in their clinical effectiveness (Svensson, 2003).

The prefrontal cortex contains dense and widespread noradrenergic projections and α_2-adrenoceptors, whereas dopaminergic afferents and dopamine D2 receptor mRNAs are more densely present in the medial region of the prefrontal cortex (Gaspar et al., 1995; Young and Kuhar, 1980; Lindvall et al., 1978; Devoto et al., 2001). Devoto et al. (2003) proposed that clozapine (a potent α_2-adrenoceptor, but weak dopamine D2 receptor, antagonist) might induce co-release of noradrenaline and dopamine from noradrenergic terminals in the prefrontal cortex via the blockade of α_2-adrenoceptors. On the other hand, clozapine does not induce a major increase of dopamine levels in the caudate nucleus, an area that receives dense dopaminergic fibers, but only few noradrenergic fibers (Kobayashi et al., 1974; Pehek and Yamamoto, 1994). Clozapine has the advantage of not inducing extrapyramidal side effects and this has been attributed to its low affinity for dopamine D2 receptors in the caudate nucleus (Meltzer, 2004). Unfortunately, the clinical use of clozapine is restricted by its relatively high risk of inducing agranulocytosis (Lieberman and Safferman, 1992). This has motivated the development of new atypical antipsychotic drugs with less secondary effects.

Quetiapine has recently been introduced as a clozapine-derived antipsychotic drug that does not induce agranulocytosis and extrapyramidal symptoms (Arvanitis and Miller, 1997). Quetiapine shows a binding profile similar to clozapine for receptors thought to be involved in the treatment of schizophrenia, but with a lower affinity for these receptors (Ichikawa et al., 2002; Bymaster et al., 1996). Furthermore, quetiapine blocks with moderate affinity α_2-adrenoceptors and, with less affinity, dopamine D2 receptors. Moreover, quetiapine, like clozapine, has

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affinity for serotonin 5-HT_{2A} and 5-HT_{1A} receptors, which are involved in the modulation of dopamine release mainly in the prefrontal cortex (Millan, 2000). Considering that clozapine and quetiapine have similar pharmacological properties, it would be reasonable to think that they exert similar effects on catecholaminergic transmission. There were no available data about the effect of quetiapine on noradrenaline release. However, previous studies reported that quetiapine, except at high doses, had no effect on dopamine levels in the prefrontal cortex (Volonte et al., 1997; Ichikawa et al., 2002). Thus, in order to clarify whether quetiapine alters catecholamines in the brain, we have measured both noradrenaline and dopamine extracellular concentrations in the prefrontal cortex and the caudate nucleus after acute administration of this drug.

2. Methods

2.1. Animals

Male Sprague–Dawley albino rats (Harlan, Italy) weighing 250–280 g were housed in groups of five per cage, at standard conditions of temperature and humidity and were kept on a 12:12-h light/dark cycle with food and water available *ad libitum*. Experimental protocols were approved by a local ethical committee and performed according to the UE guidelines (EEC Council 86/609; D.L. 27/01/1992, no. 116) for the care and the use of experimental animals.

2.2. Microdialysis

Animals were anaesthetized with Equithesin (5 ml/kg, i.p.) and stereotaxically implanted with a transcerebral dialysis probe in the prefrontal cortex (AP: +3.0, V: −2.6) or in the caudate nucleus (AP: +1.1, V: −5.0; Paxinos and Watson, 1997). Microdialysis was performed 20–24 h after surgery, as previously described (Devoto et al., 2001). Perfusate samples (40 μl/20 min) were collected, for at least 60 min prior to any treatment to establish basal neurotransmitter concentrations, and were directly injected into the high-performance liquid chromatography (HPLC) equipment coupled with an electrochemical detector. At the end of the experiments, animals were killed and the placement of the probe was verified histologically. Rats not having the probe properly inserted into the prefrontal cortex or the caudate nucleus were discarded.

2.3. Drugs and treatments

Quetiapine fumarate was dissolved in 10 μl of 0.1 N HCl diluted in 0.9% saline and the pH was adjusted to 6–6.5 with 0.1 N NaOH. The drug was administered i.p. immediately after baseline stabilization.

2.4. Statistics

Means of the three stable baseline values obtained before treatment were fixed as 100% and data were expressed as percentage of baseline±S.E.M. Statistical differences between baseline values and the following time points were evaluated by a repeated-measures analysis of variance (ANOVA) followed by a Dunnett post hoc test. A two-way ANOVA was used to asses the effect of treatments. The Kruskal–Wallis one-way ANOVA on ranks was used to evaluate statistical differences between the basal values of dopamine and noradrenaline concentrations.

3. Results

Basal levels of noradrenaline were significantly higher in the prefrontal cortex (7.2±0.8 pg/40 μl, n=15) than in the caudate nucleus (3.4±0.5 pg/40 μl, n=15; P<0.001). On the other hand, dopamine basal levels were much lower in the prefrontal cortex (2.3±0.2 pg/40 μl, n=15) than in the caudate nucleus (63.5±7.1 pg/40 μl, n=15; P<0.001). Note that basal concentrations of noradrenaline were found to be higher than those of dopamine in the prefrontal cortex (P<0.001), while dopamine levels were higher than noradrenaline levels in the caudate nucleus (P<0.001).

The administration of 5, 10 and 20 mg/kg of quetiapine markedly increased extracellular levels of both noradrenaline (up to 58%, 62% and 84%, respectively) and dopamine (up to 57%, 141% and 191%, respectively) in the prefrontal cortex (Fig. 1A and B). As expected from its poor dopamine D2 receptor antagonist activity, quetiapine exerted a weak effect on dopamine levels in the caudate nucleus; 10 and 20 mg/kg induced only a small increase of dopamine release (up to 39% and 61%, respectively; Fig. 1C). Despite the scarce density of noradrenergic fibers in the caudate nucleus, quetiapine increased in that region extracellular noradrenaline release as expected from its α_2-adrenoceptor antagonist profile. However, a significant effect was observed only at 20 mg/kg (up to 87%; Fig. 1D). The effect of quetiapine (10 and 20 mg/kg) was much lower on noradrenaline than on dopamine levels in the prefrontal cortex, but not in the caudate nucleus (Fig. 1).

4. Discussion

The antipsychotic drug quetiapine induced a marked increase of dopamine release in the prefrontal cortex. This might be important to restore the impaired activity of the prefrontal cortex associated with the negative and the cognitive symptoms of schizophrenia. Indeed, schizophrenia has been linked to hypofrontality and to reduced neuronal activity in the prefrontal cortex. Prefrontal cortex neurons modulate through excitatory glutamatergic projections, ventral tegmental area dopaminergic neurons inner-

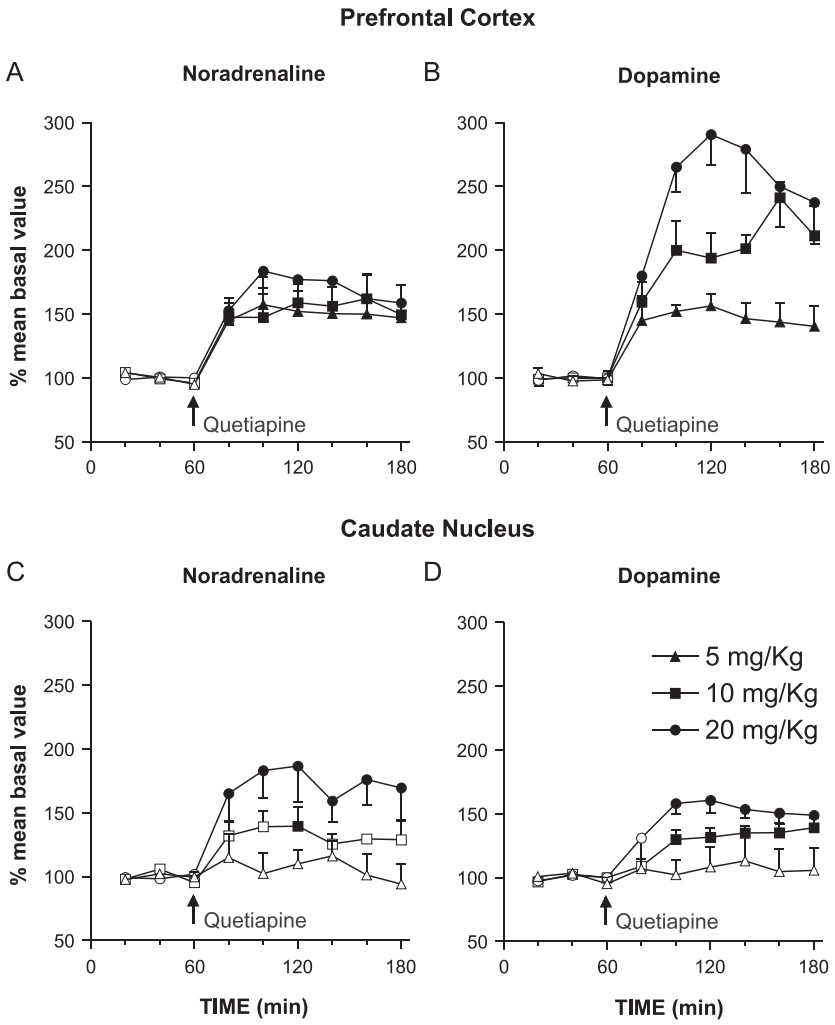

Fig. 1. Effect of quetiapine (5, 10 and 20 mg/kg i.p.) on extracellular noradrenaline and dopamine concentrations in the prefrontal cortex (A and B) and in the caudate nucleus (C and D). Data represents the mean values ± S.E.M. of four to six rats. Statistical significance was calculated with a repeated-measures ANOVA followed by a Dunnett test. Closed symbols indicate $P<0.05$ with respect to basal values.

vating the prefrontal cortex (Sesack et al., 2003). Dopaminergic output from the ventral tegmental area maintains, in turn, prefrontal cortex neurons into a depolarized state facilitating assemblies of neurons in an "enabled" state (Lewis and O'Donnell, 2000). Therefore, enhancing dopaminergic transmission after treatment with quetiapine most likely enhances the function of the prefrontal cortex.

Concomitantly with the increase in dopamine levels, we observed an increased release of noradrenaline following acute treatment with quetiapine. Synaptic levels of noradrenaline are modulated by inhibitory α_2-adrenoceptors located on noradrenergic terminals and cell bodies (Starke, 2001). In addition, it was recently shown that dopamine could be co-released with noradrenaline from cortical noradrenergic terminals following selective blockade of α_2-adrenoceptors with idazoxan (Devoto et al., 2001). Quetiapine, similarly to clozapine, has a high affinity for α_2-adrenoceptors, and therefore the increases of noradrenaline as well as dopamine levels observed in the prefrontal cortex following treatment with these atypical antipsychotic drugs, most likely results from α_2-adrenoceptors blockade. Nevertheless, 5-HT_{1A} receptor activation and $5HT_{2A}$ receptor blockade have both been suggested to mediate the increased release of dopamine produced by atypical antipsychotic drugs in the medial prefrontal cortex (Ichikawa et al., 2001). Considering that at least part of effect of the quetiapine on dopamine release in the medial prefrontal cortex is due to its 5-HT_{1A} receptor partial agonist property (Ichikawa et al., 2002), it is also possible that serotonergic receptors contributed to quetiapine-induced catecholamine release.

It is noteworthy that quetiapine induced a greater increase of dopamine than noradrenaline release in the cortex. This preferential effect on dopamine levels was also reported for clozapine and idazoxan in the rat cortex (Devoto et al., 2003), and is consistent with the major role of α_2-adrenoceptors in controlling cortical dopamine release. To explain this preferential dopaminergic action of quetiapine, it is important to consider that both noradrenaline and dopamine compete for the same transporter. Dopamine in the prefrontal cortex is preferentially cleared by noradrenaline transporters located

on noradrenergic terminals. Therefore, as the noradrenaline transporter becomes saturated from high levels of noradrenaline, less dopamine is recaptured, thus allowing higher dopamine extracellular concentrations (Gresch et al., 1995).

In contrast to the prefrontal cortex, the caudate nucleus contains dense dopaminergic fibers, but only few noradrenergic fibers. It was thus not surprising to find higher basal levels of dopamine in the caudate nucleus than in the prefrontal cortex. Dopamine release in the caudate nucleus is most likely controlled by dopamine D2 receptors on dopaminergic terminals rather than α_2-adrenoceptors on noradrenergic terminals. As a matter of fact, potent dopamine D2 antagonists, like haloperidol, usually produce large increases of dopamine levels in the caudate nucleus, but not in the prefrontal cortex (Volonte et al., 1997). Similarly to clozapine, quetiapine markedly increased dopamine levels in the prefrontal cortex, but weakly affected dopamine in the caudate nucleus. This is probably explained by the low affinity of quetiapine for striatal dopamine D2 receptors.

Our results contrast with those of previous studies which found no or little effect of quetiapine on dopamine levels in the medial portion of the prefrontal cortex (Volonte et al., 1997; Ichikawa et al., 2002). This is probably due to the different microdialysis probe placement, which in our case covered the whole prefrontal cortex area rather than only the medial prefrontal cortex. Dopamine vs. noradrenaline basal levels are lower in the prefrontal cortex (in this study) than in the medial prefrontal cortex (Devoto et al., 2003). Furthermore, the prefrontal cortex, including its medial portion, contains dense and widespread noradrenergic projections and α_2-adrenoceptors, while dopaminergic afferents and dopamine D2 receptor mRNAs are mainly concentrated in the medial prefrontal cortex. Therefore, the ratio of dopamine D2 receptors vs. α_2-adrenoceptors controlling dopamine release is greater in the medial prefrontal cortex than in the prefrontal cortex.

In summary, our findings suggest that quetiapine enhances noradrenergic transmission in both the prefrontal cortex and the caudate nucleus, while it increases dopaminergic transmission much more in the prefrontal cortex than in the caudate nucleus. These effects might be related to the therapeutic action of quetiapine in schizophrenia and its low risk of inducing extrapyramidal side effects.

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References

Arvanitis, L.A., Miller, B.G., 1997. Multiple fixed doses of “Seroquel” (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. Biol. Psychiatry 42, 233–246.

Bymaster, F.P., Calligaro, D.O., Falcone, J.F., Marsh, R.D., Moore, N.A., Tye, N.C., Seeman, P., Wong, D.T., 1996. Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology 14, 87–96.

Devoto, P., Flore, G., Pani, L., Gessa, G.L., 2001. Evidence for co-release of noradrenaline and dopamine from noradrenergic neurons in the cerebral cortex. Mol. Psychiatry 6, 657–664.

Devoto, P., Flore, G., Vacca, G., Pira, L., Arca, A., Casu, M.A., Pani, L., Gessa, G.L., 2003. Co-release of noradrenaline and dopamine from noradrenergic neurons in the cerebral cortex induced by clozapine, the prototype atypical antipsychotic. Psychopharmacology (Berl.) 167, 79–84.

Gaspar, P., Bloch, B., Le Moine, C., 1995. D1 and D2 receptor gene expression in the rat frontal cortex: cellular localization in different classes of efferent neurons. Eur. J. Neurosci. 7, 1050–1063.

Gresch, P.J., Sved, A.F., Zigmond, M.J., Finlay, J.M., 1995. Local influence of endogenous norepinephrine on extracellular dopamine in rat medial prefrontal cortex. J. Neurochem. 65, 111–116.

Ichikawa, J., Ishii, H., Bonaccorso, S., Fowler, W.L., O’Laughlin, I.A., Meltzer, H.Y., 2001. 5-HT(2A) and D(2) receptor blockade increases cortical DA release via 5-HT(1A) receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. J. Neurochem. 76, 1521–1531.

Ichikawa, J., Li, Z., Dai, J., Meltzer, H.Y., 2002. Atypical antipsychotic drugs, quetiapine, iloperidone, and melperone, preferentially increase dopamine and acetylcholine release in rat medial prefrontal cortex: role of 5-HT1A receptor agonism. Brain Res. 956, 349–357.

Kobayashi, R.M., Palkovits, M., Kopin, I.J., Jacobowitz, D.M., 1974. Biochemical mapping of noradrenergic nerves arising from the rat locus coeruleus. Brain Res. 77, 269–279.

Lewis, B.L., O’Donnell, P., 2000. Ventral tegmental area afferents to the prefrontal cortex maintain membrane potential ‘up’ states in pyramidal neurons via D(1) dopamine receptors. Cereb. Cortex 10, 1168–1175.

Lieberman, J.A., Safferman, A.Z., 1992. Clinical profile of clozapine: adverse reactions and agranulocytosis. Psychiatr. Q. 63, 51–70.

Lindvall, O., Bjorklund, A., Divac, I., 1978. Organization of catecholamine neurons projecting to the frontal cortex in the rat. Brain Res. 142, 1–24.

Meltzer, H.Y., 2004. What’s atypical about atypical antipsychotic drugs? Curr. Opin. Pharmacol. 4, 53–57.

Millan, M.J., 2000. Improving the treatment of schizophrenia: focus on serotonin (5-HT)(1A) receptors. J. Pharmacol. Exp. Ther. 295, 853–861.

Paxinos, G., Watson, C., 1997. The Rat Brain in Stereotaxic Coordinates.

Pehek, E.A., Yamamoto, B.K., 1994. Differential effects of locally administered clozapine and haloperidol on dopamine efflux in the rat prefrontal cortex and caudate-putamen. J. Neurochem. 63, 2118–2124.

Sesack, S.R., Carr, D.B., Omelchenko, N., Pinto, A., 2003. Anatomical substrates for glutamate–dopamine interactions: evidence for specificity of connections and extrasynaptic actions. Ann. N.Y. Acad. Sci. 1003, 36–52.

Starke, K., 2001. Presynaptic autoreceptors in the third decade: focus on alpha2-adrenoceptors. J. Neurochem. 78, 685–693.

Svensson, T.H., 2003. Alpha-adrenoceptor modulation hypothesis of antipsychotic atypicality. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 27, 1145–1158.

Volonte, M., Monferini, E., Cerutti, M., Fodritto, F., Borsini, F., 1997. BIMG 80, a novel potential antipsychotic drug: evidence for multireceptor actions and preferential release of dopamine in prefrontal cortex. J. Neurochem. 69, 182–190.

Young, W.S., Kuhar, M.J., 1980. Noradrenergic alpha 1 and alpha 2 receptors: light microscopic autoradiographic localization. Proc. Natl. Acad. Sci. U. S. A. 77, 1696–1700.