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Quetiapine increases the firing rate of rat substantia nigra and ventral tegmental area dopamine neurons in vitro

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Abstract

The antipsychotic drug quetiapine increases the firing rate of dopamine neurons in the substantia nigra and the ventral tegmental area of the rat. In the present study we used an in vitro midbrain slice preparation and found that 3 μM quetiapine increases the firing rate of dopamine neuron in both structures by ~30%. The magnitude of the increase was not correlated with the basal firing rate of the dopamine neurons. In addition, quetiapine was not able to antagonize the inhibition of the firing evoked by the dopamine D2 receptor agonist quinpirole. Only with a very high concentration (30 μM), quetiapine was able to counteract the amphetamine-induced inhibition of the firing of the ventral tegmental area neurons; this effect was less pronounced in substantia nigra neurons. These findings indicate that the increase in firing rate induced by quetiapine cannot solely be mediated through an interaction with the dopamine D2-like autoreceptor present on the dopamine neurons.

Keywords: Antipsychotic drug; Seroquel; Dopamine D2 autoreceptor; Extracellular recording; In vitro slice preparation

1. Introduction

Quetiapine (Seroquel) is a relatively new atypical antipsychotic drug that is well tolerated by patients (Dev and Raniwalla, 2000). An important feature of the pharmacological profile of quetiapine is that it combines a weak dopamine D2 receptor antagonism with a relatively strong 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptor antagonism, although the affinity for the 5-HT$_{2A}$ receptor is not as high as that of other atypical antipsychotic drugs like clozapine and olanzapine (Meltzer et al., 1989; Saller and Salama, 1993; Schotte et al., 1996; Seeman, 2002). In addition, quetiapine has significant affinity for the histamine H$_1$ receptor and the α_1-adrenoceptor (Richelson, 1999). Especially the combination of dopamine D2 and 5-HT$_{2A}$ receptor antagonism is thought to play an important role in its atypical antipsychotic drug efficacy, i.e. no or minimal extrapyramidal side effects, but the precise mechanism of action is not yet understood (Belmaker and Bersudsky, 2003). Alternatively, it has been suggested that a fast dissociation from the receptor underlies the relatively low affinity for the dopamine D2 receptor of atypical antipsychotic drugs (like quetiapine) and that this property is responsible for the (almost completely) absence of extrapyramidal side effects (Kapur and Seeman, 2001).

Most information regarding the pharmacological profile of quetiapine originates from receptor binding and biochemical assays (Richelson, 1999). Here we examined the effects of quetiapine in an in vitro slice preparation (Werkman et al., 2001) at a more functional level and we determined how it affects the firing rate of midbrain dopamine neurons in the substantia nigra and in the ventral tegmental area. Hyperactivity of a part of the ventral tegmental area dopamine system is thought to play a role in some forms of psychosis (Goldstein and Deutch, 1992) and is has been indicated that the ventral tegmental area

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system is an important target for antipsychotic drugs (White, 1996). Furthermore, it is generally accepted that extrapyramidal side effects occur through antipsychotic drug-mediated blockade of dopamine D2 receptors in the nigrostriatal pathway (Pickar, 1995; Richelson, 1999). In addition to direct effects of quetiapine on dopamine midbrain neurons, we also determined whether an interaction of quetiapine with the inhibitory D2-like autoreceptor present on the dopamine neurons is involved in the effects of quetiapine on the activity of dopamine neurons.

2. Materials and methods

2.1. Brain slices

Male Wistar rats (80–150 g, age 5–7 weeks; Harlan, Zeist, the Netherlands) were used for the experiments. After decapitation, the brain was quickly removed and placed in ice-cold artificial cerebrospinal fluid (ACSF) (gassed with a mixture of 95% O_2 and 5% CO_2), of the following composition (in mM): NaCl 120, KCl 3.5, $MgSO_4$ 1.2, NaH_2PO_4 1.25, $CaCl_2$ 2.5, D-glucose 10, $NaHCO_3$ 25, ascorbic acid 1. From a midbrain tissue block containing both the substantia nigra and the ventral tegmental area, 350-μm-thick coronal slices were cut in ice-cold ACSF with a Leica VT1000S vibratome. From one animal, three slices containing both substantia nigra and ventral tegmental area could be prepared. Immediately after cutting, the slice was transferred to ACSF (35 °C) and incubated for 20 min to permit quick recovery, after which it was kept at room temperature until the recordings were started. Then a slice was placed in the recording chamber (volume ~1 ml) which was continuously perfused with ACSF (~2 ml/min) at 35 °C. After approximately 30 min of equilibration, simultaneous extracellular recordings of neurons in the substantia nigra and ventral tegmental area were started.

2.2. Extracellular recordings

Electrodes pulled from thin-wall borosilicate glass pipettes (1.5 mm outer diameter, Science Products, Hofheim, Germany) with a Brown/Flaming Micropipette puller (Model P-87; Sutter Instruments, CA, USA) and filled with ACSF (electrode resistances 5–10 MΩ) were used for extracellular recordings. One electrode was placed in each brain region, substantia nigra (pars compacta) and ventral tegmental area, and extracellular recordings were made from putative dopamine neurons. A neuron was considered dopaminergic when it had: (1) a regular spontaneous firing pattern (0.5–8 Hz), (2) a broad (>2 ms), triphasic extracellular action potential and (3) quinpirole sensitivity at concentrations below 0.3 μM (reduction of the firing rate by activation of D2-like autoreceptors) (Werkman et al., 2001). Previously, it was demonstrated that in vitro (neurochemically identified) dopamine-containing neurons in the substantia nigra and the ventral tegmental area display the electrophysiological properties listed above (Grace and Onn, 1989). The extracellular signals were high-pass filtered at 300 Hz, stored on videotape and simultaneously digitized at 4 kHz with an ADC converter under control of a PC and stored for off-line analysis.

2.3. Drugs

A stock solution (10 mM) of quetiapine was made in dimethylsulphoxide (DMSO) (final DMSO concentration was≤0.3%). Stock solutions of quinpirole (10 mM; RBI) and amphetamine (1 mM; Duchefa Farma, Haarlem) were made in H_2O. Shortly before the experiment, the stock solutions were diluted to the final concentrations in ACSF and applied to the slices by superfusion.

2.4. Data analyses

With an analysis program running on the PC, extracellular action potentials ("spikes") were detected by template matching that emphasized the characteristic shape of the spikes of dopamine neurons and that allowed quantification of the neuronal activity even when they gradually varied in amplitude. The times of occurrence of action potentials during control periods and during drug applications were determined and they were used to calculate the mean firing rate during periods of five s. The mean firing rate of each neuron in control condition was determined over a time period (usually 2–3 min) during which cell firing was stable. Data are expressed as mean±standard error of the mean (S.E.M.). The quinpirole effect was determined by fitting the relative firing rate RF to a logistic equation:

$$RF = \frac{100}{1 + (C/IC_{50})^h}$$

with RF=$F(C)/F_0 \times 100$, where $F(C)$ is the firing rate in the presence of quinpirole of concentration C, F_0 is the initial firing rate, IC_{50} is the quinpirole concentration that gives 50% reduction in firing rate and h is a slope factor analogous to the Hill coefficient.

A repeated-measures analysis of variance (ANOVA; followed by Dunnett's post hoc test) was used to analyze the effects of quetiapine on the firing rate. $P<0.05$ was assumed to indicate a significant difference. The Pearson correlation was used to determine correlations.

3. Results

3.1. Firing rate of substantia nigra and ventral tegmental area dopamine neurons

Extracellular recordings were made from substantia nigra and ventral tegmental area dopamine neurons. In most

cases, it involved simultaneous recordings, i.e. in one midbrain slice a substantia nigra and a ventral tegmental area dopamine neuron were recorded at the same time. Only neurons that displayed the characteristic electrophysiological properties for midbrain dopamine neurons (Werkman et al., 2001) were analyzed. The mean baseline firing rate in the substantia nigra (2.2±0.1 spikes/s, n=18) was slightly higher than the one observed in the ventral tegmental area (1.7±0.2 spikes/s, n=14, P<0.05), a difference that we have previously reported in this preparation (Werkman et al., 2001).

3.2. Quetiapine increases the firing rate of substantia nigra and ventral tegmental area dopamine neurons

To determine the direct effect of quetiapine on the activity of midbrain dopamine neurons, it was cumulatively bath applied in two concentrations (0.1 and 3 μM for 10 min per concentration) (Fig. 1). Quetiapine induced a concentration-dependent increase in the firing rate of substantia nigra and ventral tegmental area dopamine neurons and this effect was not different for both neuron types.

The increase in firing rate for both neuron types reached significance only at a concentration of 3 μM quetiapine (P<0.01). After a wash period of 10 min, the mean firing rate of both dopamine neuron types returned to baseline levels; in a few ventral tegmental area neurons full recovery could take a longer time (e.g. Fig. 1B).

3.3. Increase in firing rate by quetiapine is independent of initial firing rate

Blocking the dopamine D2-like autoreceptors of midbrain dopamine neurons with the selective D2 receptor antagonist (−)-sulpiride increases the firing rate of these neurons (Werkman et al., 2001). We demonstrated that the level of increase in firing rate was negatively correlated with the initial firing rate of the neurons (i.e. neurons with a low firing rate showed a relatively large increase in firing rate upon application of (−)-sulpiride), which indicated that in vitro dopamine neuron activity is dependent on dopamine D2 receptor activity. To see whether quetiapine has a similar mechanism of action, we here also investigated if the magnitude of the increased firing rate by quetiapine was correlated with the initial firing rate of the neurons. Fig. 2 illustrates the lack of such a correlation for both neuron types. This could imply that the effect of quetiapine on the dopamine neuron firing rate is different from the previously observed direct interaction of antipsychotic drugs with the dopamine D2-like autoreceptor.

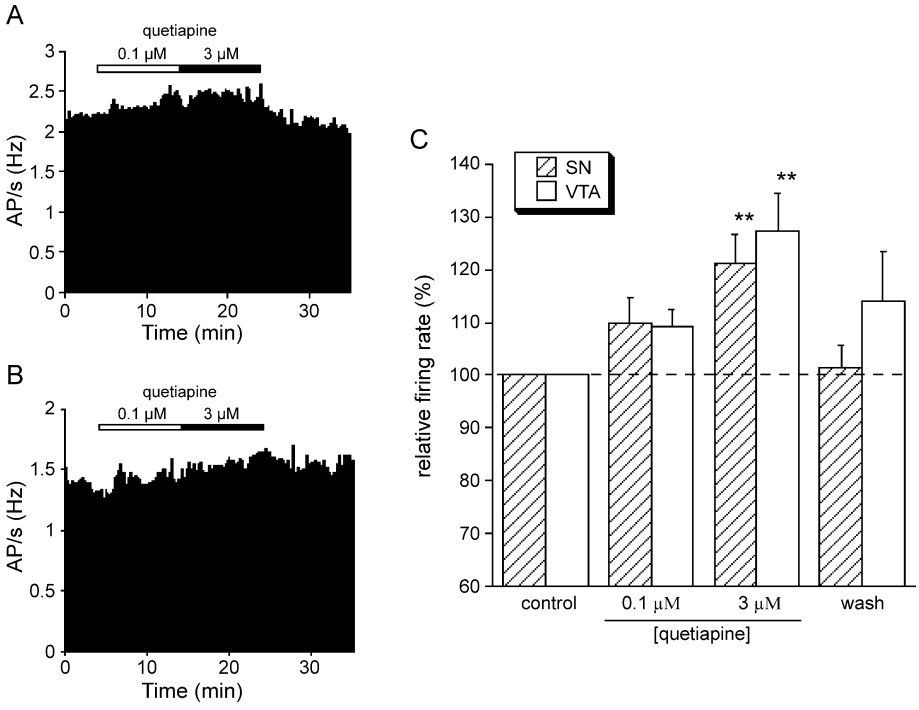

Fig. 1. Quetiapine-induced increase in firing rate of substantia nigra and ventral tegmental area dopamine neurons. Left panels show simultaneously recorded firing rates (expressed as number of action potentials per second (AP/s; bin width 5 s)) of a substantia nigra (A) and a ventral tegmental area (B) dopamine neuron. Quetiapine was cumulatively applied (10 min per concentration) followed by a 10-min washout period. Right panel (C) shows the effect of the two quetiapine concentrations on the normalized mean firing rate of substantia nigra (SN; n=10) and ventral tegmental area (VTA; n=8) dopamine neurons; bars indicate S.E.M. Statistical significance was determined with a repeated-measures ANOVA, followed by the post hoc Dunnett's test (**P<0.01, compared to control).

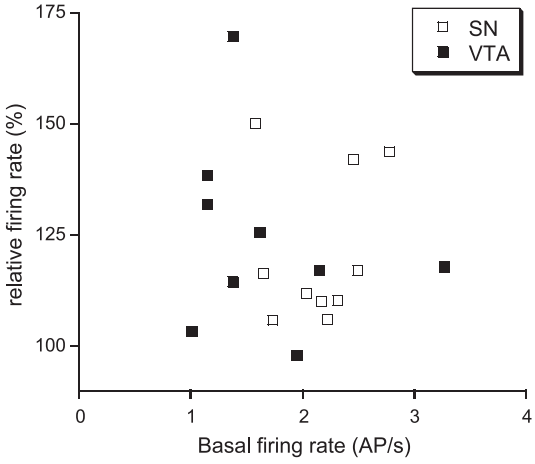

Fig. 2. The relative firing rate of the substantia nigra (SN; open symbols) and ventral tegmental area (VTA; closed symbols) dopamine neurons in the presence of 3 μM quetiapine does not correlate with the basal firing rate (Pearson correlation test). 100% indicates normal firing rate.

3.4. Quetiapine does not affect inhibition induced by the selective D2-like receptor agonist quinpirole

The selective D2 receptor agonist quinpirole inhibits the firing rate of the dopamine neurons in a concentration-dependent way and we have previously demonstrated that the sensitivity to quinpirole of substantia nigra and ventral tegmental area dopamine neurons is not different (Werkman et al., 2001). The previous paragraph suggests that quetiapine exerts its effect on the firing rate of midbrain dopamine neurons through a mechanism that is different from the dopamine D2-like autoreceptor used by quinpirole and other antipsychotic drugs. To corroborate this, we investigated the interaction between quetiapine and quinpirole in modulating the firing rate by testing the inhibition of quinpirole in the presence and absence of 3 μM quetiapine. Quinpirole was cumulatively applied to the slice in increasing concentrations (1, 10, 30, 100 and 300 nM; 4 min per concentration) and at each concentration the firing rate was determined. Subsequently quinpirole was washed out and we waited at least 30 min to ensure recovery. Then quetiapine (3 μM) was applied and 5 min later the same series of quinpirole concentrations was applied now in the presence of quetiapine. When fitting the mean data points from the concentration–response relationship with a logistic equation, we found that the IC_{50} values of quinpirole were not different in the absence or presence of quetiapine (substantia nigra: 31±2 and 25±2 nM, respectively; ventral tegmental area: 27±1 and 26±1 nM, respectively) (Fig. 3). Also, the slope factor *h* was not different in the absence or presence of quetiapine (substantia nigra: 1.9±0.2 and 1.6±0.2, respectively; ventral tegmental area: 1.7±0.1 and 1.5±0.1, respectively). These results show that 3 μM

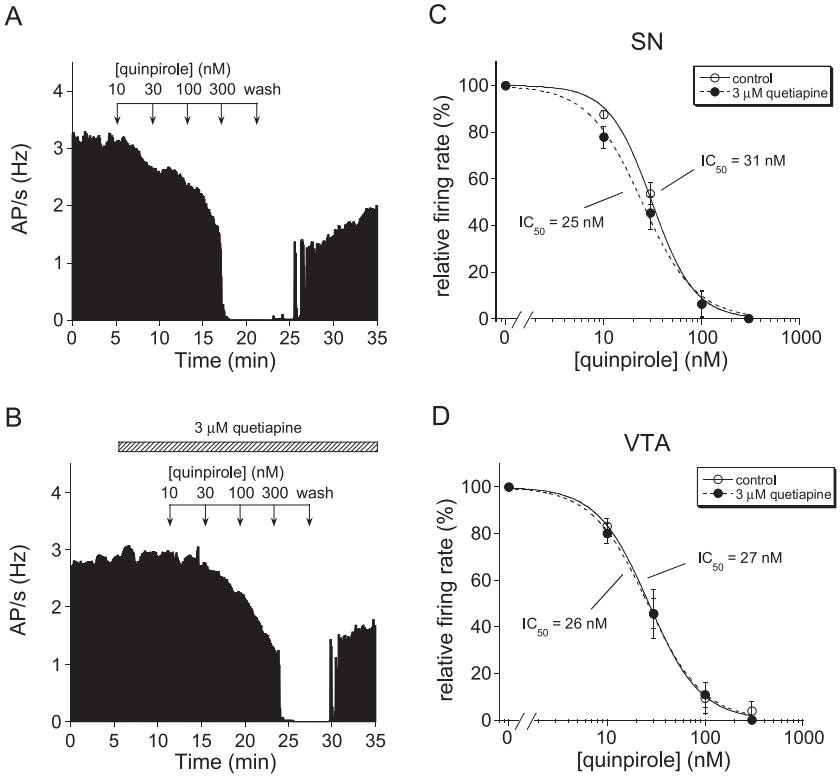

Fig. 3. The quinpirole-induced inhibition of the firing rate is not affected by 3 μM quetiapine. Left panels show the effect of four quinpirole concentrations (4 min per concentration) on the firing rate of a substantia nigra dopamine neuron in the absence (A) and presence (B) of 3 μM quetiapine. Right panels give the relative firing rate in substantia nigra (SN; C) and ventral tegmental area (VTA; D) dopamine neurons as a function of the quinpirole concentration in the absence (open symbols) or presence (closed symbols) of 3 μM quetiapine. Points represent mean, bars the S.E.M. (substantia nigra, *n*=7; ventral tegmental area, *n*=6). The smooth curves are the fits to the logistic equation.

quetiapine did not antagonize the quinpirole-induced inhibition of the firing rate.

3.5. Quetiapine hardly affects amphetamine-induced inhibition

Quinpirole, used in the previous paragraph, has a relatively high affinity for the dopamine D2 receptor compared to the endogenous ligand dopamine (Levant et al., 1993). Therefore we also investigated whether quetiapine could interfere with endogenous dopamine. Amphetamine can enhance the extracellular dopamine level by inducing dopamine release and/or blocking dopamine reuptake (Seiden et al., 1993). Consequently, it decreases the dopamine neuron firing rate, without direct interfering with the dopamine D2 autoreceptors. We investigated whether quetiapine was able to reverse this inhibition. Amphetamine was applied continuously in a concentration of 10 μM at which it induced a reduction in firing of the substantia nigra and ventral tegmental area dopamine neurons to 5±5% (n=8) respectively 11±10% (n=5) of baseline firing rate. Six minutes after the start of the amphetamine perfusion, quetiapine was applied in two concentrations of 3 and 30 μM (6 min per concentration). Quetiapine (3 μM) did not reverse the amphetamine-mediated inhibition in the substantia nigra or ventral tegmental area dopamine neurons (Fig. 4). A high concentration quetiapine (30 μM) could at least partially reverse the inhibition in the ventral tegmental area (P<0.01). The enhancement of firing rate in substantia nigra dopamine neurons did not reach significance (Fig. 4), reflecting the same small difference in sensitivity as observed for the modulation of quetiapine alone. Our results show that the dopamine-mediated auto-inhibition of ventral tegmental area dopamine neurons is only weakly affected by quetiapine, which suggests that at the concentrations used in Section 3.2 quetiapine cannot replace dopamine from its binding site.

4. Discussion

In the present study, we demonstrate that quetiapine in the concentration range (0.1–3 μM) increases the firing rate of dopamine neurons in substantia nigra and in ventral tegmental area, when tested in a midbrain slice preparation that allows simultaneous recording from both regions. This confirms observations made on quetiapine in vivo (Goldstein et al., 1993), although in our study, the difference between the increase in firing rate in ventral tegmental area and substantia nigra dopamine neurons to the application of quetiapine alone did not reach significance. The slice preparation allows good pharmacological access and thus made it possible to investigate whether the quetiapine-evoked change in firing rate in substantia nigra and ventral tegmental area dopamine neurons is mediated through the same pathway as the one that is observed in response to the application of antipsychotic drugs like (−)-sulpiride, clozapine, olanzapine and risperidone (Werkman et al., 2001). The latter antipsychotic drugs are all dopamine D2 receptor antagonists (Kapur and Mamo, 2003). Blocking the dopamine D2-like autoreceptor present on the midbrain dopamine neurons results in depolarization of the neurons and in an increase in firing rate as has been demonstrated in vivo as well as in vitro (Pucak and Grace, 1996; Werkman et al., 2001; White and Wang, 1984). Quetiapine, however, lacks appreciable affinity for dopamine D2 receptors but it does possess affinities for 5-HT receptors (5-HT_{1A} and 5-HT_{2A}), for the α_1-adrenoceptor and for the histamine H_1 receptor (Meltzer et al., 2003; Newman-Tancredi et al., 1998; Saller and Salama, 1993; Schotte et al., 1996), all of which could contribute to the modulation of the firing rate observed here.

In the present study, we first investigated whether we could find indications for a direct interaction of quetiapine with the dopamine D2 receptor. Firstly, we found that the increase in firing induced by quetiapine in the dopamine

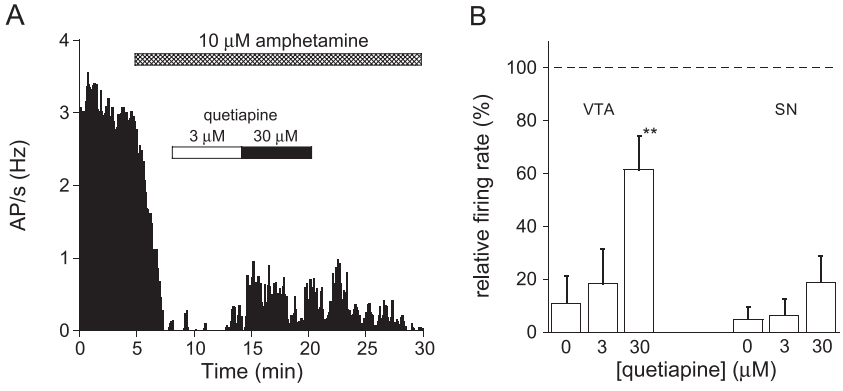

Fig. 4. Partial reversal of amphetamine-induced inhibition of substantia nigra and ventral tegmental area dopamine neuron firing activity by quetiapine. (A) Recording of a substantia nigra dopamine neuron, showing the effect of quetiapine on amphetamine-induced inhibition. During amphetamine perfusion (10 μM) quetiapine was applied in two concentrations (3 and 30 μM; 6 min per concentration). (B) Relative firing rate of dopamine neurons in substantia nigra (SN) and ventral tegmental area (VTA) (mean and S.E.M). With 30 μM quetiapine, the (partial) reversal of amphetamine-induced inhibition reached significance in ventral tegmental area neurons (substantia nigra, n=8; ventral tegmental area, n=5). Asterisks indicate comparison with amphetamine-induced inhibition level (at 0 μM quetiapine) (**P<0.01).

neurons did not correlate with baseline firing rate. Apparently auto-inhibition by endogenous dopamine on neurons with many active (inhibitory) dopamine D2-like autoreceptors on cell bodies and dendrites is responsible for their low firing rate (Pucak and Grace, 1996; Werkman et al., 2001; White and Wang, 1984). Drugs with dopamine D2 receptor antagonist activity (such as most antipsychotic drugs) relieve this auto-inhibition and increase the firing rate. The lack of correlation between basal firing rate and the magnitude of the increase in firing induced by quetiapine suggests that dopamine D2 receptor antagonism is not the major cause of quetiapine firing rate modulation. This is in contrast with previous observations on (−)-sulpiride (Pucak and Grace, 1994; Werkman et al., 2001). Secondly, we investigated whether quetiapine affected the inhibition induced by the highly selective dopamine D2 receptor agonist quinpirole. We found that the presence of 3 μM quetiapine, which was sufficient to induce the 30% increase in firing rate, did not interfere in any way with the concentration–response relationship of quinpirole-induced inhibition (i.e. the IC_{50} values in the absence and presence of quetiapine were not different) and we conclude that it is unlikely that quetiapine is an effective dopamine D2 receptor antagonist.

However, because the affinity of quinpirole for the dopamine D2 receptor is much higher than the one for dopamine itself (Levant et al., 1993), the above-mentioned experiment does not completely rule out a weak antagonistic effect of quetiapine which might interfere with the endogenous ligand. Therefore we also tested in our midbrain slice preparation the capability of quetiapine to antagonize auto-inhibition directly induced by dopamine. The psychotomimetic drug amphetamine increases extracellular dopamine levels by inducing release of dopamine and/or blocking re-uptake of dopamine (Seiden et al., 1993). The increased dopamine level activates dopamine D2(-like) autoreceptors and decreases the firing rate. Only a very high concentration of quetiapine (30 μM) could (partially) counteract the amphetamine-induced inhibition, and the effect was more pronounced in ventral tegmental area neurons than in neurons in the substantia nigra. This is in agreement with observations in vivo where high quetiapine concentrations were needed to reverse amphetamine-mediated inhibition and where the effect was also most potent in ventral tegmental area neurons (Goldstein et al., 1993). This again corroborates the findings from receptor binding and biochemical studies that quetiapine has a low affinity for the dopamine D2 receptor (K_i~300 nM) (Saller and Salama, 1993; Schotte et al., 1996).

Besides a weak affinity for the dopamine D2 receptor, quetiapine has a moderate affinity for 5-HT_{2A} receptors, resulting in a relatively high ratio of 5-HT_2/dopamine D2 receptor blockade. This is a property shared by many atypical antipsychotic drugs (Goren and Levin, 1998; Meltzer et al., 1989; Schotte et al., 1996) and it implies the possibility that quetiapine's selectivity towards the ventral tegmental area dopamine system is due to a blockade of 5-HT_2 receptors (resulting in an attenuation of auto-inhibition), leading to a higher propensity of depolarization block in this brain area (Grace et al., 1997; Olijslagers et al., 2004). However, in our recent study regarding 5-HT_2 receptor-mediated attenuation of auto-inhibition in ventral tegmental area dopamine neurons, we observed that 5-HT_2 receptor agonists and antagonists by themselves do not have a *direct* effect on dopamine neuronal firing rates (Olijslagers et al., 2004), suggesting that the 5-HT_{2A} receptor activity of quetiapine cannot be solely responsible for the observed modulation of the firing rate.

As it seems unlikely that the interaction of quetiapine with the dopamine D2-like autoreceptors and the 5-$HT_{2A/C}$ receptors is sufficient to explain all observations, additional activity of quetiapine at other neurotransmitter receptor types may exist. For example, the reported (partial) 5-HT_{1A} receptor agonist activity of quetiapine (Meltzer et al., 2003; Newman-Tancredi et al., 1998) and/or its antagonistic action at the histamine receptor H_1 (Richelson, 1999) could contribute to the increase in firing rate. Although the α_1-adrenoceptor antagonist activity of quetiapine (Saller and Salama, 1993; Schotte et al., 1996) could also play a role, such a mechanism seems less likely, because activation of this receptor results in enhanced activity of the midbrain dopamine neurons (Grenhoff et al., 1995).

In conclusion, we have demonstrated in vitro that the atypical antipsychotic drug quetiapine increases the firing rate of substantia nigra and ventral tegmental area dopamine neurons. The result strikingly mimics the effects of other antipsychotic drugs, but in the case of quetiapine it is highly unlikely that the mechanism of action only consists of an interaction with the inhibitory dopamine D2(-like) autoreceptors present on the dopamine neurons or solely relates to the relative dopamine D2/5-HT_2 receptor selectivity.

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