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The preferential dopamine D_3 receptor ligand, (+)-UH 232, is a partial agonist

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Abstract

In a NG 108 15 hybrid cell line stably expressing a recombinant dopamine D_3 receptor, (+)-UH 232 (*cis*-(+)-1*S*,2*R*)-5-methoxy-1-methyl-2-(di-*n*-propylamino)tetralin), a partially selective D_3 receptor ligand, stimulates mitogenesis, as measured by incorporation of [^{3}H]thymidine, with an EC_{50} of 7.6 nM and a maximal increase corresponding to 23% of the response elicited by quinpirole, a full agonist. This effect was antagonised by nafadotride, a D_3 receptor-selective antagonist. (+)-UH 232 also antagonised quinpirole-induced mitogenesis with a K_i value of 9.4 nM. (+)-UH 232 (1 μM) inhibited by 22% the forskolin-induced accumulation of cAMP, whilst the inhibition by quinpirole (100 nM) was 53%. These results indicate that (+)-UH 232 is a partial agonist at the D_3 receptor with an intrinsic activity of 0.2–0.4.

Keywords: Mitogenesis; cAMP formation; Intrinsic activity

The dopamine receptor antagonist, (+)-UH 232 (*cis*-(+)-1*S*,2*R*)-5-methoxy-1-methyl-2-(di-*n*-propylamino)-tetralin), was reported to stimulate locomotor activity in rats, a paradoxical effect (since it resembles that elicited by dopamine agonists) which was attributed to preferential blockade of dopamine autoreceptors (Svensson et al., 1986). However, after cloning of the dopamine D_3 receptor, (+)-UH 232 was identified in binding studies as one of the very few alleged dopamine antagonists displaying higher affinity at this receptor than at the D_2 receptor (Sokoloff et al., 1990). Together with other observations, this suggested that D_2 and D_3 receptors may exert opposite influences on the control of locomotion (Griffon et al., 1995). In view of these functional extrapolations, it was of importance to assess whether (+)-UH 232 behaves as a pure D_3 receptor antagonist.

D_3 receptor activation in cell lines transfected with a recombinant human D_3 receptor stimulates mitogenesis, c-fos expression, and inhibits cAMP formation (Pilon et al., 1994; Chio et al., 1994). These responses are dependent on the activation of a Pertussis toxin-sensitive G protein. We used a subclone of a NG 108 15 neuroblastoma × glioma hybrid cell line stably expressing the human D_3 receptor to measure the mitogenic response, assessed by incorporation of [^{3}H]thymidine, and the inhibition of cAMP accumulation induced by forskolin. Obtaining the cell line and the methods used for this have already been described (Pilon et al., 1994; Sautel et al., 1995a).

(+)-UH 232 dose dependently increased mitogenesis, with an EC_{50} of 7.6 ± 0.9 nM (mean ± S.E.M. of three experiments) and a maximal response of +33 ± 4% over basal values (Fig. 1, upper panel). In four additional experiments, 1 μM (+)-UH 232 enhanced mitogenesis by +40 ± 5% in comparison with +8 ± 2% in control cells not transfected with the D_3 receptor cDNA. Quinpirole, a full agonist (Sautel et al., 1995a), produced at 100 nM a maximal response of +143 ± 8% (not shown). The concentration-response curve of (+)-UH 232 was shifted to the right in the presence of nafadotride (Fig. 1, upper panel), leading to the expected nM K_i value of this full D_3 receptor-preferring antagonist (Sautel et al., 1995b). These results show that (+)-UH 232 is a partial agonist in the mitogenic response, with an intrinsic activity of 0.23. Unlike other agonists with a high intrinsic activity (Sautel et al., 1995a), the EC_{50} value of (+)-UH 232 for the mitogenesis response is close to its apparent K_i of 9 nM measured in binding studies (Sokoloff et al., 1990),

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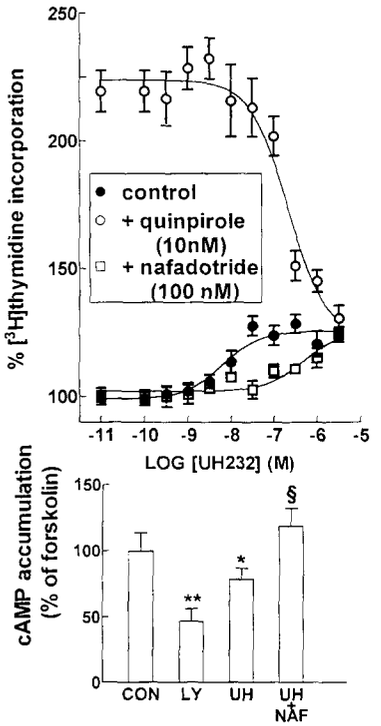

Fig. 1. Effects of (+)-UH 232 on D_3 receptor-mediated responses in transfected NG 10815. Upper panel: Concentration-dependent increase of [^{3}H]thymidine incorporation by (+)-UH 232 in the absence (●) or presence of 100 nM nafadotride (□). (+)-UH 232 antagonised the increase of [^{3}H]thymidine incorporation induced by 1 nM quinpirole (○). Values are expressed as percents of basal values (3860 ± 269 cpm, $n = 3$). Lower panel: Accumulation of cAMP with forskolin (1 μM) alone (CON) or forskolin plus quinpirole (100 nM, LY), (+)-UH 232 (1 μM, UH) or (+)-UH 232 in the presence of 1 μM nafadotride (UH+NAF). Values are expressed as percents of control values measured in the presence of forskolin (550 ± 100 pmol of cAMP per 10^5 cells). $^*P < 0.05$; $^{**}P < 0.01$ vs. forskolin alone; $^§P < 0.01$ vs. (+)-UH 232 alone by Student's t-test.

which is consistent with its lower intrinsic activity. (+)-UH 232 antagonised the quinpirole response, with an IC_{50} of 188 ± 20 nM, up to a plateau corresponding to the maximal response induced by (+)-UH 232 alone (Fig. 1, upper panel). This indicates that (+)-UH 232 also behaves as an antagonist for the mitogenic response.

In the NG 108 15 clone used in the present experiments, quinpirole and (+)-UH 232 were also found to inhibit the forskolin-induced cAMP accumulation by 53% and 22%, respectively. The effect of (+)-UH 232 was completely prevented in the presence of 1 μM nafadotride (Fig. 1, lower panel). These results indicate that (+)-UH 232 is also a partial agonist for inhibiting cAMP formation, with an intrinsic activity of 0.4.

The present study showed that (+)-UH 232, a compound formerly considered as a pure antagonist, is in fact a partial agonist at the dopamine D_3 receptor, regarding two different responses. Although its intrinsic activity is low, it may produce significant D_3 receptor activation in models involving high receptor reserve. However, its paradoxical locomotor stimulating properties in rodents do not seem to result from this partial agonism, also being produced by pure D_3 receptor antagonists such as nafadotride (Sautel et al., 1995b). Interestingly, a partial agonist such as (+)-UH 232 may act as a regulator of dopamine transmission through the D_3 receptor, behaving as activator when the level of dopamine is low and as inhibitor in the reverse situation. This ability to regenerate normal transmission might imply a therapeutic potential.

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