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In vivo characterization of novel full and partial 2-(4-aminophenyl)-*N*,*N*-dipropylethylamine dopamine D_2 receptor agonists [1]

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Abstract

Behavioral and biochemical techniques were used to compare the in vivo intrinsic efficacy of two new 2-(4-aminophenyl)-*N*,*N*-dipropylethylamine dopamine D_2 receptor agonists, 2-(4-amino-3-trifluoromethylphenyl)-*N*-*N*-dipropyl-ethylamine (NBF-203) and 2-(4-amino-3-bromo-5-trifluoromethylphenyl)-*N*-*N*-dipropylethylamine (NBF-234). Adult male Sprague–Dawley rats were used as experimental animals. NBF-203 was characterized as a full dopamine D_2 receptor agonist, whereas NBF-234 displayed properties of a partial agonist, or antagonist, at dopamine D_2 receptors. Thus, NBF-203 produced effects similar to those of apomorphine in models for dopamine synthesis, release and turnover. As a strong indication of markedly less intrinsic efficacy, the administration of NBF-234 did not result in antagonism of reserpine-induced suppression of locomotor activity in the presence of (±)-1-phenyl-2,3,4,5,-tetrahydro-(1*H*)-3-benzazepine-7,8-diol HCl (SKF-38393)-induced dopamine D_1 receptor activation. The present series of compounds offer the possibility of adjusting intrinsic efficacy at dopamine D_2 receptors, and such fine-tuning could be an important strategy in the search for optimal antipsychotic or antiparkinson drugs within the partial dopamine D_2 receptor agonist concept. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Dopamine D_2 receptor; Partial agonist; Dopamine synthesis; Locomotor activity; (Rat)

1. Introduction

A number of partial dopamine receptor agonists have been developed for use as antipsychotics (see e.g. Benkert et al., 1995). The rationale for this approach has been an apparent selectivity of such agents for the dopamine autoreceptor, resulting in inhibition of impulse flow in dopaminergic neurons, as well as dopamine synthesis (see Andén, 1980; Bunney et al., 1987). There is laboratory evidence suggesting that this strategy, inhibition of dopaminergic neurotransmission pre-synaptically, rather than post-synaptically, would result in agents with less endocrine and extrapyramidal side-effects (see e.g. Carlsson, 1987; Roth and Elsworth, 1995). Preclamol, or (−)-3-(3-hydroxypenyl)-*N*-*n*-propyl-piperidine (3-PPP), is the prototypical agent of this group, and its characteristic in vivo pharmacodynamic profile has been used in the search for new agents of this kind, such as talipexole (Andén et al., 1982), 7-[3-(4-(2,3-dimethylphenyl)piperazinyl)propoxy]-2(1*H*)-quinolinone (OPC-4392) (Yasuda et al., 1988), roxindole (Seyfried et al., 1989), terguride (Kehr, 1984) and pramipexole (Mierau and Schingnitz, 1992). Although the particular biochemical and behavioral effects of these agents may vary somewhat, depending on the animal species and experimental models used, the fact that preclamol has been a reference compound, has resulted in agents with a very similar pharmacodynamic profile, and in all probability similar intrinsic efficacies at brain dopamine D_2 receptors.

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[1] Dedicated to Lennart Florvall who died on April the 18th 1999. Without his feel for tailoring molecules in relation to biological effects, this work would not have been possible.

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Preliminary clinical studies have indicated that most of these agents have a propensity to exacerbate the positive symptoms, and only marginally improve the negative symptoms, of schizophrenia (see Benkert et al., 1995). However, some of these agents may be effective in Parkinson's disease (see Hagan et al., 1997). Thus, it is likely that the intrinsic efficacy generally has been too high, and that a useful antipsychotic of this type should have considerably weaker intrinsic efficacy at brain dopamine D_2 receptors than the compounds mentioned above. In this perspective, aripiperazine, a congener of OPC-4392, but with much less intrinsic efficacy, is an interesting recent development (Lawler et al., 1999).

In an earlier communication, we reported the synthesis of a series of 2-(4-aminophenyl)-*N*-*N*-dipropylethylamine dopamine D_2 receptor agonists with different degrees of efficacy as dopamine autoreceptor agonists (Florvall et al., 1996). Thus, variations in the placement of methyl or halogen radicals in the aromatic ring resulted in compounds with different intrinsic efficacy at brain dopamine D_2 receptors. In the present report, we provide in vivo evidence for two compounds in this series, a full dopamine D_2 receptor agonist (NBF-203) and a partial dopamine D_2 receptor agonist (NBF-234). Fine-tuning the intrinsic efficacy at dopamine D_2 receptors holds promise as a way to optimize agents targeted for schizophrenia or Parkinson's disease.

2. Methods

2.1. Animals

Adult male Sprague–Dawley rats (280–320 g) were used (B&K Universal, Sollentuna, Sweden). The animals arrived in the laboratory at least 10 days before being used in experiments, and were housed five per cage (Makrolon IV) under controlled temperature conditions (21.0 ± 0.5°C), relative humidity (55–65%) and light–dark cycle (12:12 h, lights off 0600 h). Food (R36, Ewos, Södertälje) and tap water were available ad libitum in the home cage.

2.2. Drugs

2-(4-Amino-3-trifluoromethylphenyl)-*N*,*N*-dipropylethylamine 2HCl (NBF-203), mol wt 361.3 (Astra); 2-(4-amino-3-bromophenyl)-*N*,*N*-dipropylethylamine 2HCl (NBF-049), mol wt. 372.2 (Astra); 2-(4-amino-3-bromo-5-trifluoromethylphenyl)-*N*,*N*-dipropylethylamine 2HCl (NBF-234), mol wt. 403.8 (Astra); apomorphine HCl, mol wt. 312.8 (Sigma, St Louis, MO); (±)-1-phenyl-2,3,4,5,-tetrahydro-(1*H*)-3-benzazepine-7,8-diol HCl (SKF-38393), mol wt. 291.8 (RBI, Natick, MA); DL-α-methyl-*p*-tyrosine methyl ester HCl, mol wt 245.7 (RBI); D-amphetamine sulphate, mol wt 368.5 (Apoteksbolaget, Stockholm, Sweden); haloperidol, mol wt. 375.9 (generously donated by Janssen Pharmaceutica, Beerse, Belgium); reserpine, mol wt. 608.7 (Fluka, Buchs, Switzerland), 3-hydroxy-benzylhydrazine 2HCl (NSD-1015), mol wt. 211.10 (Sigma); γ-butyrolactone (GBL), mol wt 86.1 (RBI); pargyline HCl, mol wt. 195.7 (Sigma). Reserpine and haloperidol were dissolved in a minimal quantity of glacial acetic acid and made up to volume in 5.5% glucose. All other compounds were dissolved in 0.9% saline. The injection route was subcutaneous, except for NSD-1015, which was administered intraperitoneally. The volume of injection was kept constant at 2 ml kg^{-1}.

2.3. Motor activity observations

Spontaneous motor activity was observed in a square open-field arena ($680 \times 680 \times 450$ mm) equipped with two rows of photocells, sensitive to infrared light, placed 40 and 125 mm above the floor. The photocells were spaced 90 mm apart, and the last photocell in a row was spaced 25 mm from the wall. The open field was enclosed in a ventilated, sound-attenuating box with a Perspex top. Measurements were made in the dark and performed between 0900 and 1600 h.

The number of photocell beam interruptions was recorded on an IBM-compatible computer, and the following variables were calculated: *locomotor activity* (all interruptions of photo beams in the lower rows); *rearing* (all interruptions of photo beams in the upper rows). For further details of the apparatus used, see Ericson et al. (1991).

2.4. Brain dissection and biochemical procedures

Following decapitation of the rat by means of a guillotine, the whole brain (including the olfactory bulb rostrally and the medulla oblongata caudally) was quickly removed and placed in a mould where it could be sliced in 2.5-mm sections with a thin stainless-steel wire ($\phi = 70$ μm). The dorso-lateral neostriatum, and the overlying neocortex were dissected on ice from one of these slices. The rostral edge of this slice was +2.1 mm in relation to bregma. The brain was cut at an angle of approximately 7°, such that ventrally the sections extended slightly rostrally, according to the atlas of Paxinos and Watson (1998). The mean weight (mg) ± S.D. of the D–L neostriatum and the neocortex, as dissected here, was 24.7 ± 4.8 and 98.4 ± 5.8, respectively. For further details on the dissection procedures, see Hillegaart et al. (1990). The brain samples were immediately frozen on dry ice and stored at −70°C until processing. Dihydroxy-phenylalanine (DOPA), 5-hydroxytryptophan (5-HTP), 3-methoxytyramine and dopamine were determined by means of coupled column liquid chromatography with electrochemical detection. The intra-assay precision was 1–2% and the limit of detection was

about 1 pmol sample^{-1} (10–20 pmol g^{-1}). The preparation of the samples and further details are given in Magnusson et al. (1980) and Mohringe et al. (1986).

2.5. Statistical description and analysis

In order to increase the likelihood of homogeneity in variance between samples, the locomotor activity and rearing data were subjected to a square root transformation. Parametric procedures for statistical description and analysis were used throughout. Thus, results are presented as means ± S.D. in the figures. Statistical analysis was performed by means of appropriate one-way or two-way analysis of variance (ANOVA), and post hoc *t*-tests, as described in figure legends (Winer 1971).

3. Results

3.1. Effects of NBF-203 and NBF-234 on forebrain catecholamine synthesis and on spontaneous motor activity in reserpine-treated rats

3.1.1. DOPA accumulation in the neostriatum and the neocortex

NBF-203 produced a marked and dose-dependent decrease in neostriatal dopamine synthesis, as evidenced by a statistically significant decrease in DOPA accumulation after inhibition of cerebral decarboxylase. This was in contrast to the biphasic effects of NBF-234 injections. Thus, the maximal effect, obtained at the 1.9-μmol dose, was about 50% of the maximal effect of NBF-203. Furthermore, with increasing doses (7.5–30.0 μmol kg^{-1}), the effects of NBF-234 gradually returned to reserpine baseline values. This interpretation was supported by the ANOVA analysis, which revealed a statistically significant interaction between dose and drug treatment (Fig. 1, top left).

In the noradrenaline-rich neocortex, both compounds produced a similar modest decrease in DOPA accumulation, suggesting weak activation of α_2-adrenoceptors by both compounds. In agreement with the interpretation of a similar pattern of effects for both compounds, there were no statistically significant interactions between dose and drug treatment in the neocortex (Fig. 1, bottom left).

3.1.2. Effects on spontaneous motor activity

NBF-203 produced a modest, dose-dependent reversal of the reserpine-induced suppression of locomotor activity. In addition, there was antagonism of the reserpine-induced suppression of rearing. This effect was maximal at the 7.5-μmol dose, and not statistically significant at the highest dose, in all probability due to emerging stereotypies (Fig. 1, right panel). There was no antagonism by NBF-234 of the reserpine-induced suppression of locomotion or rearing.

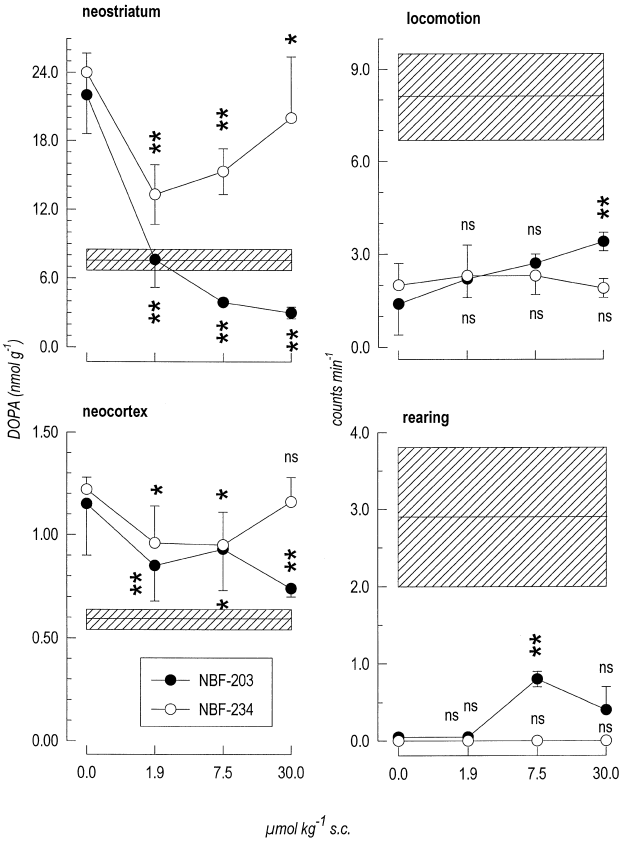

Fig. 1. Effects of NBF-203 and NBF-234 on neostriatal and neocortical monoamine synthesis, and on spontaneous motor activity in reserpine-treated rats. Drug treatments in relation to decapitation were as follows: Reserpine (8.2 μmol kg^{-1} s.c.) — 18 h; NBF-203 and NBF-234 (1.9–7.5 μmol kg^{-1}, s.c.) — 65 min; and NSD-1015 (475 μmol kg^{-1}, i.p.) — 30 min. Motor activity measurements were performed for 30 min, starting 5 min following the NBF-203 or NBF-234 injections. The results are presented as means ± S.D., based on three to four animals per group. Results obtained in vehicle-treated controls are indicated by the hatched area in the figure. Statistical analysis was performed by means of a two-way ANOVA, followed by the appropriate *t*-tests (see Winer, 1971) for comparisons with reserpine-treated controls, as indicated in the figure. Neostriatum: $F(1,29) = 87.02$, $P < 0.001$ (treatment); $F(4,29) = 45.49$, $P < 0.001$ (dose); $F(4,29) = 13.59$, $P < 0.01$ (treatment × dose). Neocortex: $F(1,29) = 6.15$, $P < 0.05$ (treatment); $F(4,29) = 18.14$, $P < 0.001$ (dose); $F(4,29) = 2.78$, n.s. (treatment × dose). Locomotion: $F(1,29) = 0.55$, n.s. (treatment); $F(4,29) = 56.55$, $P < 0.001$ (dose); $F(4,29) = 1.20$, (treatment × dose). Rearing: $F(1,26) = 10.40$, $P < 0.01$ (treatment); $F(4,26) = 76.28$, $P < 0.001$ (dose); $F(4,26) = 2.53$, n.s. (treatment × dose). $^{ns}P > 0.05$; $^{*}P 0.05$; $^{**}P < 0.01$.

3.2. Effects of NBF-203 and NBF-234 on apomorphine-induced suppression of neostriatal dopamine synthesis in GBL-pretreated rats

As expected, the administration of GBL (875 μmol kg^{-1}) resulted in a statistically significant increase in DOPA accumulation to approximately 250% of saline controls ($t_{17} = 16.18$, $P < 0.01$), and this increase was fully antagonized by apomorphine (2.5 μmol kg^{-1}) administration ($t_{17} = 19.69$, $P < 0.01$). As shown in Fig. 2,

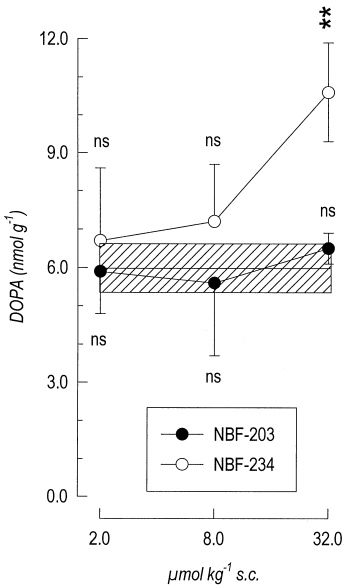

Fig. 2. Effects of NBF-203 and NBF-234 on the reversal of GBL-induced increase in neostriatal DA synthesis by apomorphine. The drugs were administered at the following times in relation to decapitation: apomorphine (2.5 μmol kg^{-1}, i.p.), NBF-203 or NBF-234, — 40 min; GBL (875 μmol kg^{-1}, i.p.) — 35 min; NSD-1015 (475 μmol kg^{-1}, i.p.) — 30 min. The figure shows means ± S.D., based on three to four determinations per group. The mean DOPA accumulation ± S.D. in GBL-treated controls was 21.5 ± 0.7 nmol g^{-1}. In vehicle-treated controls, the corresponding value was 8.8 ± 0.6. Statistical analysis by means of a one-way ANOVA, followed by Dunnett's *t*-test for comparisons with apomorphine-treated controls (shaded area in the figure). $F(5,17) = 114.96$, $P < 0.001$ (NBF-203); $F(5,16) = 79.91$, $P < 0.001$ (NBF-234). $^{ns}P > 0.05$; $^{**}P < 0.01$.

NBF-234 produced a dose-dependent partial antagonism of the apomorphine-induced suppression of DOPA accumulation in this model, whereas NBF-203 was ineffective.

3.3. Antagonism by NBF-203 and NBF-234 of reserpine-induced suppression of locomotor activity in SKF-38393-challenged rats

Combining the two experiments shown in Fig. 3, pretreatment with reserpine (8.2 μmol kg^{-1}) resulted in a suppression of locomotor activity to about 15% of that of saline-treated controls ($t_{14} = 8.60$, $P < 0.01$), and there were no effects of SKF-38,393 (10 μmol kg^{-1}) by itself ($t_{14} = 0.30$, $P > 0.05$). As further shown in this figure, NBF-203 produced a dose-dependent, and complete, reversal of the reserpine-induced suppression of locomotor activity in the presence of SKF-38393. The effects of NBF-203 by itself were weak and not statistically significant in this experiment (cf. Fig. 1, right panels). In contrast to these effects of NBF-203, NBF-234 by itself, and in SKF-38,393-challenged animals, did not antagonize the reserpine-induced suppression of locomotor activity (Fig. 3, bottom).

3.4. Effects of NBF-203 on neostriatal dopamine release and utilization

3.4.1. Accumulation of 3-methoxytyramine following inhibition of monoamine oxidase by pargyline pretreatment

As expected, D-amphetamine (5.5 μmol kg^{-1}) produced a statistically significant increase in 3-methoxytyramine accumulation, whereas treatment with apomorphine (6.5 μmol kg^{-1}) resulted in a statistically significant decrease (Fig. 4, top). In this model, NBF-203 produced a statistically significant decrease in 3-methoxytyramine ac-

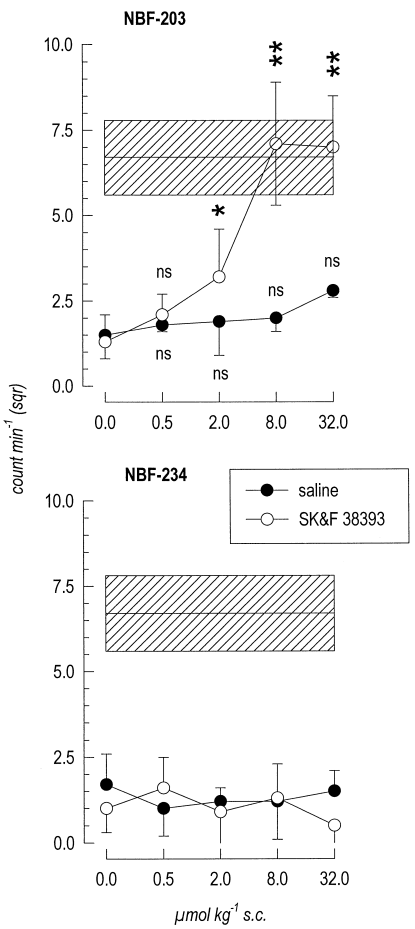

Fig. 3. Effects of NBF-203 and NBF-234 on locomotor activity in rats pretreated with SKF-38393 and reserpine. The animals were pretreated with reserpine (8.2 μmol kg^{-1} s.c.) and SKF-38,393 (10 μmol kg^{-1} s.c.) 18 h and 20 min, respectively, before a 30-min session in the open-field activity cages. NBF-203 and NBF-234 were administered 20 min before locomotor activity measurements. Shown are the means ± S.D., based on three to four determinations per group. The mean locomotor activity ± S.D. for seven pooled controls is shown by the hatched area. Statistical analysis was performed by means of a two-way ANOVA, followed by post hoc *t*-tests as described in Winer (1971) for comparisons with saline-injected controls (''0'' μmol kg^{-1}). NBF-203: $F(1,21) = 37.71$, $p < 0.001$ (pretreatment); $F(4,21) = 16.33$, $p < 0.001$ (dose); $F(4,21) = 9.06$, $P < 0.001$ (pretreatment *x* dose). NBF-234: $F(1,22) = 0.65$, $P > 0.05$ (pretreatment); $F(4,22) = 0.15$, $p > 0.05$ (dose); $F(4,22) = 0.91$, $P > 0.05$ (pretreatment × dose). $^{ns}P > 0.05$; $^{*}P < 0.05$; $^{**}P < 0.01$.

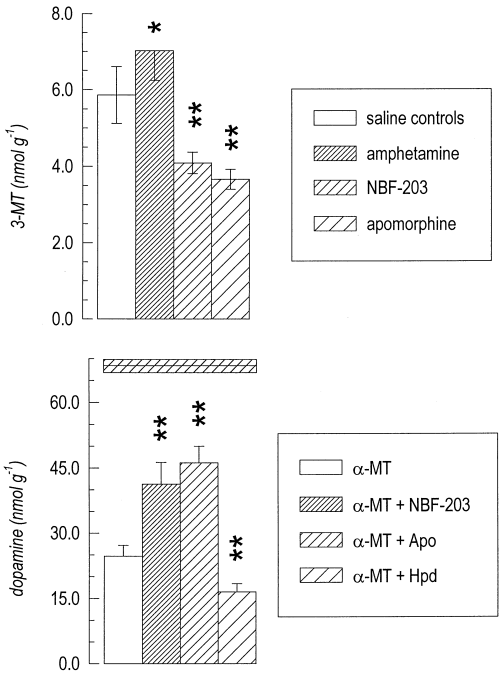

Fig. 4. (A) Effects of NBF-203, D-amphetamine and apomorphine on striatal dopamine release, estimated as the formation of 3-methoxytyramine, following monoamine-oxidase inhibition and (B) effects of NBF-203, apomorphine and haloperidol on the disappearance of neostriatal dopamine and neocortical noradrenaline following inhibition of tyrosine hydroxylase in rats. Pargyline experiments: all the animals were administered pargyline (380 μmol kg^{-1} i.p.) 60 min before decapitation. D-Amphetamine (5.5 μmol kg^{-1} s.c.) apomorphine (6.5 μmol kg^{-1} s.c.) and NBF-203 (13.5 μmol kg^{-1} s.c.) were administered 30 min before decapitation. α-Methyltyrosine experiments: α-methyl-*p*-tyrosine (1000 μmol kg^{-1} s.c.) was administered 4 h before decapitation. NBF-203 (5.5 μmol kg^{-1}) and apomorphine (6.5 μmol kg^{-1}) were administered s.c. twice, 220 and 100 min before decapitation. Haloperidol (2.5 μmol kg^{-1}) was administered s.c., 220 min before decapitation. The results are presented as means ± S.D., based on four to five determinations per group. There was a marked and statistically significant depletion of dopamine and noradrenaline after the α-MT treatment ($t_{15} = 19.30$, $P < 0.01$). Statistical evaluation by means of a one-way ANOVA, followed by Dunnett's *t*-test for comparisons with pargyline-treated controls. Pargyline treatment: $F(3,16) = 37.62$, $P < 0.001$; α-Methyltyrosine experiments: $F(4,15) = 222.50$, $P < 0.001$ $^{ns}P > 0.05$; $^{*}P < 0.05$; $^{**}P < 0.01$.

cumulation, an effect that was not statistically significantly different from the effect of apomorphine ($t_{16} = 1.18$, $P > 0.05$).

3.4.2. Disappearance of dopamine following inhibition of tyrosine hydroxylase by means of α-methyl-p-tyrosine pretreatment

The administration of apomorphine (6.5 μmol kg^{-1}) retarded, and haloperidol (2.5 μmol kg^{-1}) hastened, the disappearance of dopamine in animals pretreated with α-methyl-*p*-tyrosine (1000 μmol kg^{-1}) (Fig. 4, bottom). In this model, the administration of NBF-203 (13.5 μmol kg^{-1}) retarded the disappearance of dopamine to the same extent as that seen after apomorphine treatment ($t_{15} = 2.18$, $P > 0.05$).

4. Discussion

The present results show that two chemical congeners, NBF-203 (''mono-halogen'' substitution) and NBF-234 (''double-halogen'' substitution) (cf. Fig. 5), are full and partial dopamine receptor agonists, respectively. Both compounds have nanomolar affinity for dopamine D_2 receptors (Florvall et al., 1996). NBF-203 has a CF_3 substitution in the R_1 position. The corresponding bromine compound (NBF-049) was also tested (cf. Fig. 5). Although there was a tendency for a somewhat weaker effect of the bromine-substituted compound in the reserpine model (cf. Fig. 1), there were no statistically significant differences between the dose–effect curve (0.0–30.0 μmol kg^{-1}) for these two compounds ($F(1,32) = 2.13$, $P > 0.05$) (NBF-049 data not shown in Section 3). The placement of an additional halogen, however, in the opposite R_2 position markedly decreased the dopamine receptor agonist properties of the resulting NBF-234 compound. This conforms with the general scheme outlined by Florvall et al. (1996), and the results presented in that paper, in fact, suggest a gradient of increasing agonist activity from R_1 substituent CH_3, Cl, Br to CF_3, and of decreasing intrinsic efficacy with additional R_2 substituents within the same series.

From results presented in the present report, NBF-203 behaves like a full dopamine D_2 receptor agonist in behavioral and biochemical models. In the models where apomorphine was included as a reference, the effects of NBF-203 were statistically indistinguishable from those of apomorphine. Thus, NBF-203 decreased dopamine release, estimated by measuring 3-methoxy-tyramine accumulation

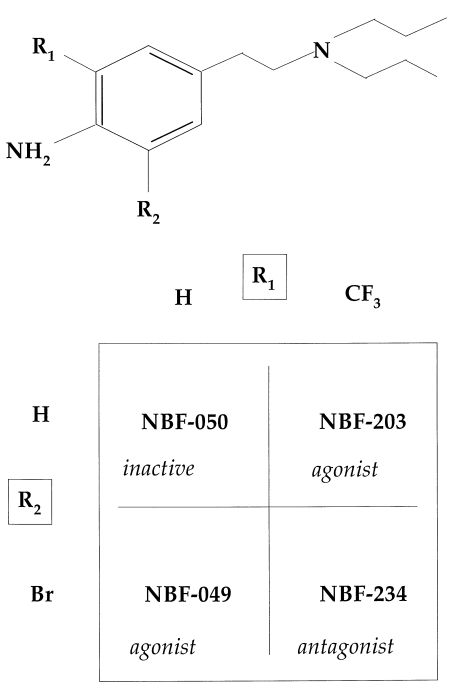

Fig. 5. Schematic presentation of halogen substitutions in the aromatic ring in relation to intrinsic efficacy at brain dopamine $D_{2/3}$ receptors.

in pargyline-treated rats (see Wood and Altar, 1988). Furthermore, the disappearance of dopamine following synthesis inhibition by metyrosine was retarded by NBF-203 treatment (see Andén, 1980).

Direct comparisons between NBF-203 and NBF-234 clearly show an antagonist/partial agonist profile of the latter compound. Firstly, there was no antagonism of reserpine-induced suppression of spontaneous locomotor activity, also in the presence of SKF-38393 (see e.g. Waddington et al., 1995), suggesting that the high-affinity dopamine D_2 receptor ligand NBF-234 displays only weak intrinsic efficacy in vivo. Secondly, there was only weak antagonism of the reserpine-induced increase in the rate of dopamine synthesis. In addition, NBF-234 caused a partial antagonism of apomorphine-induced suppression of dopamine synthesis in GBL-treated rats (see e.g. Roth, 1984). Together, these observations indicate an antagonist-like profile for NBF-234, albeit with some residual intrinsic efficacy at dopamine D_2 receptors. Needless to say, the present in vivo models are not appropriate for obtaining precise estimates of intrinsic efficacy. Nonetheless, the in vivo models used here could be highly relevant for the actual behavior of these compounds as potential antipsychotics or antiparkinson drugs (see Hoyer and Boddeke, 1993).

It is well known that a full dopamine receptor agonist, such as apomorphine, bromocriptine or quinpirole, influences behavior in a biphasic manner, i.e. inhibition or sedation, followed by stimulation (Strömbom, 1976; Pizzolata et al., 1985; Eilam and Szechtmann, 1989). The initial inhibition of behavior produced by these agents is in all probability due to a preferential activation of inhibitory dopaminergic autoreceptors at low doses (see Clark et al., 1985a). The partial dopamine receptor agonist has preferential actions at the autoreceptor and generally display antipsychotic-like effects (see Clark et al., 1985b; Lundström et al., 1992), whereas signs of endocrine and extrapyramidal effects are minor in comparison with classic dopamine D_2 receptor blocking antipsychotics (see Clark et al., 1985b). Taken together, these observations suggest a strategy for the development of new antipsychotic drugs, avoiding endocrine and extrapyramidal side-effects. Indeed, in a recent open clinical study, preclamol displayed antipsychotic properties with a benign side-effect profile (Lahti et al., 1998). However, in this study, as previously reported for *n*-propyl-norapomorphine (Tamminga et al., 1986), there appears to be a very rapid tolerance to the antipsychotic effects, in all probability due to down-regulation of dopaminergic autoreceptors — as also suggested by laboratory studies (e.g. Jackson et al., 1982; Hjorth et al., 1985). Thus, the predominant effect of preclamol upon repeated administration will be post-synaptically mediated, and it appears that the weak intrinsic efficacy of preclamol, and that of other similar compounds tested clinically, is sufficient to cause an unacceptable exacerbation of positive symptoms in schizophrenia (see Benkert et al., 1995). It should be noted that the post-synaptic effect predominated with preclamol, although initially a distinct pre-synaptic contribution can be distinguished in the dose-effect curve (Ahlenius, 1992; Lundström et al., 1992). However, these compounds represent a significant contribution to the treatment of Parkinson's disease with the potential to carry less propensity for dyskinesias and psychotic episodes (see Hagan et al., 1997).

The above considerations stress the importance of qualifying the intrinsic efficacy of partial dopamine D_2 receptor agonists in terms of clinical projections. Thus, it appears that a compound like pramipexole, which is unacceptable as an antipsychotic, has favorable properties as an antiparkinson drug. Conversely, it is probable that the ideal antipsychotic compound within the partial dopamine D_2 receptor concept should have negligible intrinsic efficacy. Thus, it is likely that a compound like NBF-234, which probably exacerbates symptoms of Parkinson's disease, will possess antipsychotic efficacy. In addition, it is also probable that even a very low intrinsic efficacy of such a compound will suffice to markedly diminish the incidence of extrapyramidal and endocrine side-effects (cf. Svensson et al., 1993).

4.1. Conclusion

The present results demonstrate marked differences in the intrinsic efficacy of a new series of 2-(4-aminophenyl)-*N*,*N*-dipropyl-ethylamine dopamine D_2 receptor agonists as a result of minor changes in halogen substitutions in the aromatic ring. Thus, the trifluoromethyl-substituted compound NBF-203 behaved as a full agonist, whereas the bromine-trifluoromethyl-substituted compound NBF-234 displayed a more antagonist-like profile. It is suggested that fine-tuning intrinsic efficacy could be an important strategy for defining optimal antipsychotic or antiparkinson drugs within the partial dopamine D_2 receptor agonist concept.

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