Bioorganic & Medicinal Chemistry Letters 24 (2014) 2429–2432

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Vascular effects of diphenylmethoxypiperidine-derived dopamine uptake inhibitors

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ARTICLE INFO

Article history:
Received 29 January 2014
Revised 8 April 2014
Accepted 9 April 2014
Available online 18 April 2014

Keywords:
Piperidinol-4
Arterial contraction
Dopamine transporter

ABSTRACT

Vascular effects of 4-aryl methoxypiperidinol compounds previously shown to share with cocaine the ability to inhibit the dopamine transporter are described. All the compounds tested inhibit KCl-induced and noradrenaline-dependent contractions in mesenteric arteries ex vivo. Thus, diphenylpyraline and its analogs may have a role as therapeutic options for the treatment of some of the cardiotoxic effects of cocaine intoxications.

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As a powerful sympathomimetic agent, cocaine exerts its rewarding activity by blocking the dopamine transporter (DAT) with the subsequent increase in dopamine (DA) concentrations in the synapse. The search for cocaine antagonists has been the focus of researchers and several compounds with DAT inhibiting activity have been described.[1] For example, benzotropine (BZT) analogs possess a diphenylmethoxy moiety and a piperidyl ring; these compounds were previously studied as potential pharmacotherapies for cocaine addiction.[2] Similar to cocaine, the well-known histamine H1 receptor antagonist diphenylpyraline (DPP) increases brain dopamine, possesses psychostimulant properties in mice[3] and also shares the same BZT structural features. The fact that DPP functions as a potent dopamine reuptake inhibitor without producing significant rewarding effects suggests that DPP and its analogs merit further study as potential candidates for pharmacotherapies for cocaine addiction. These observations prompted the synthesis of a series of DPP analogs and it was shown that they share with DPP the ability to inhibit the DAT.[4] In these DPP analogs, symmetrical *para* substituents of the benzene ring were found to be important for high potency in binding to the DAT.[4] In addition, several piperidine derivatives have been shown to block an array of dopaminergic, serotoninergic and adrenergic monoamine transporters,[5] reinforcing the physiological relevance of the interactions between the piperidine structure and monoamine transporters.

Besides the well-established alterations in behavior, cocaine exerts powerful effects on the cardiovascular system with chest pain being one of the most common complaints with acute cocaine use.[6] Several studies have shown that cocaine increases contraction in isolated arteries and hearts,[7–9] supporting the notion that this increased contraction of coronary arteries caused by cocaine may be related to the myocardial infarction associated with acute cocaine intoxication.[10,11]

Since DPP and its analogs share with cocaine the inhibition of the DAT, we investigated whether these compounds share vascular properties with cocaine. In this study, the effects of equimolar doses of cocaine, DPP and its analogs were tested on KCl- and noradrenaline (NA)-induced contractions of the rat mesenteric resistance artery (MRA).

The DPP analogs were synthesized as previously described[4] utilizing methods used for the synthesis of the tropane series of compounds[12–14] (see Fig. 1). Final mixtures were purified by flash chromatography with mass and ^{1}H NMR spectra used for further analyses.[15]

Vascular contraction was tested in isolated mesenteric resistance arteries mounted in a wire myograph as previously described.[16] Arterial segments were normalized to 0.9· L_{100}, with L_{100} being the internal circumference the vessels would have if

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http://dx.doi.org/10.1016/j.bmcl.2014.04.040
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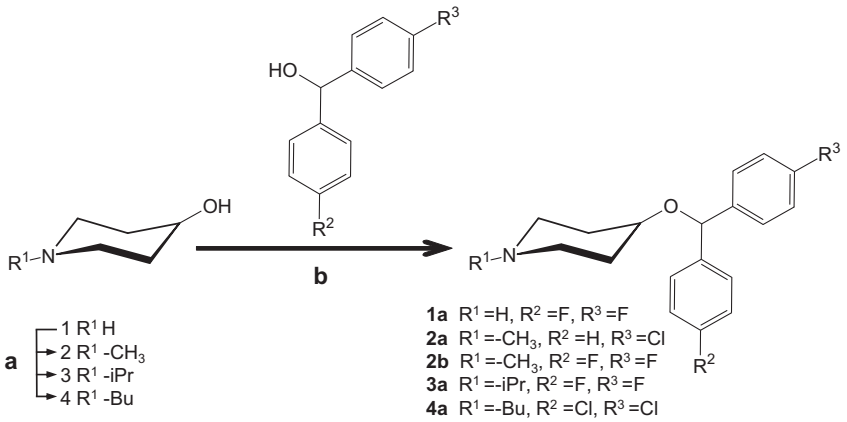

Figure 1. Synthesis of substituted diphenylmetoxypiperidines. Reagents and conditions: (a) Hal-R, K_2CO_3, DMF, 40 °C; (b) *p*-TSA, benzene/DMF (25:1), reflux. For details see Refs. 3,4.

they were exposed to a transmural pressure of 100 mmHg.[17] Optimal diameters (OD) were calculated as $OD = 0.9\ L_{100}/\pi$. Arteries with an OD of 278 ± 10 μm were used.[18]

The contraction to 75 mM KCl was used to evaluate receptor-independent responses, whereas receptor-dependent responses were evaluated as the contraction to a dose–response curve to NA. Maximal contraction to KCl was unaffected by pre-incubation with cocaine (3×10^{-6} M), however DPP (3×10^{-6} M) and all the diphenylmethoxypiperidines (each one at a concentration of 3×10^{-6} M) tested blocked KCl contraction (Fig. 2, $p < 0.05$). The diphenylmethoxypiperidines studied blocked KCl-induced contraction with varying efficacy. Compounds **3a** and **4a** were the most effective whereas **1a**, **2a** and **2b** share with DPP approximately a 70% of inhibition of KCl-induced contraction.

Dose response curves to noradrenaline (NA) in the presence of cocaine, DPP and diphenylmethoxypiperidine compounds are shown in Figure 3. Maximal responses to NA were not affected by pre-incubation with cocaine (Fig. 3A, Table 1), whereas **4a** was the only diphenylmethoxypiperidine compound that decreased NA maximal contraction (Fig. 3B, Table 1, $p < 0.05$). Sensitivity to NA was increased by cocaine and decreased by DPP and all diphenylmethoxypiperidines tested. The greatest inhibitory effect was observed with compounds **3a** and **4a** (Fig. 4, Table 1, $p < 0.05$). In the presence of cocaine the inhibitory effect of the diphenylmethoxypiperidine compounds on NA contraction remained unaffected (data not shown).

Parameters of the 'Rule of 5'[19] were calculated for the compounds tested using the online software Molinspiration.[20]

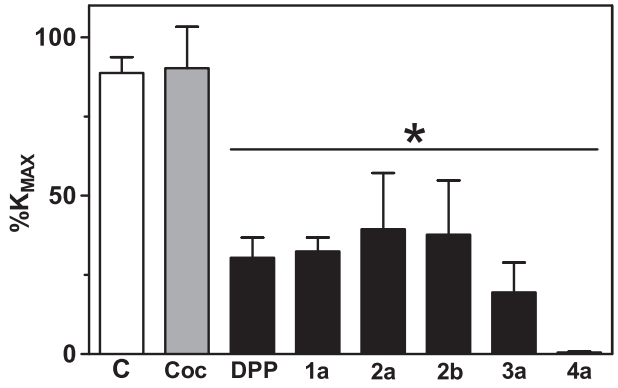

Figure 2. Effects of cocaine, DPP and diphenylmetoxypiperidines on KCl-induced contraction. MRA ($n = 6$) were exposed to 75 mM KCl during 5 min in the presence of cocaine (3×10^{-6} M), DPP (3×10^{-6} M) and DPP analogs (all at 3×10^{-6} M) as indicated. *$p < 0.05$ versus control arteries.

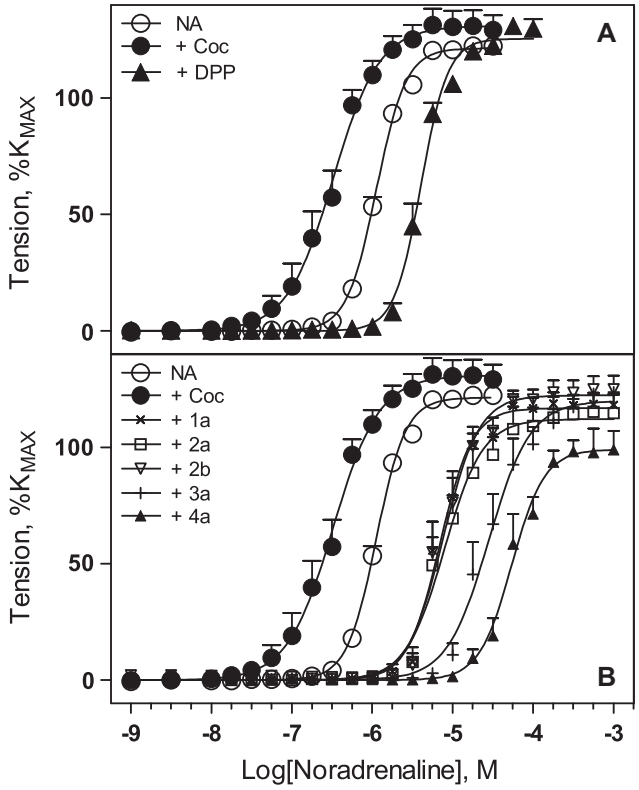

Figure 3. Effects of cocaine, DPP and diphenylmetoxypiperidines on NA-induced contraction. MRA were exposed to increasing concentrations of NA in the presence of cocaine (Coc, $n = 6$, 3×10^{-6} M) or DPP ($n = 6$, A, 3×10^{-6} M) and DPP analogs **1a**, **2a**, **2b**, **3a** and **4a**, ($n = 5$, B, all at 3×10^{-6} M) as indicated.

The relationship between the calculated octanol/water partition coefficient (Log*P*) and the observed effects on NA contraction were fitted to a linear regression. Compounds **3a** and **4a** with the greatest inhibitory effect on NA contraction display the largest Log*P* values (Table 1). Figure 5 shows the linear relationship between Log*P* and ΔpD_2 ($\Delta pD_2 = -0.3499 \cdot \text{Log}P + 0.3383$) suggesting that more effective inhibitors should possess increased lipophilicity.

Our results show for the first time that DPP and the DPP analogs tested inhibit receptor-dependent as well as receptor-independent contractions in MRA. Compared to cocaine, DPP and its analogs displayed opposite effects on vascular contraction; whereas cocaine treatment increases sensitivity to NA, all diphenylmethoxypiperidines compounds tested diminished sensitivity to NA.

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