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Pharmacological studies of 8-OH-DPAT-induced pupillary dilation in anesthetized rats

Yongxin Yu[a,*], Andrew G. Ramage[b], Michael C. Koss[a]

[a] Department of Cell Biology, University of Oklahoma College of Medicine, Oklahoma City, OK 73190, USA
[b] Department of Pharmacology, University College London, Royal Free Campus, Rowland Hill Street, Hampstead, London NW3 2PF, UK

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Abstract

Serotonin (5-HT)$_{1A}$ receptor agonists have been reported to produce mydriasis in mice, and miosis in rabbits and humans. However, the underlying mechanisms for this action are unclear. This study was undertaken in an attempt to explore the mechanism by which 5-HT$_{1A}$ receptors are involved in the modulation of pupillary size in pentobarbital-anesthetized rats. Intravenous administration of the 5-HT$_{1A}$ receptor agonist, (2*R*)-(+)-8-hydroxy-2-(di-*n*-propylamino)tetralin hydrobromide (8-OH-DPAT; 0.003–3 mg/kg), elicited dose-dependent pupillary dilation, which was not affected by section of the preganglionic cervical sympathetic nerve. 8-OH-DPAT-elicited mydriatic responses were attenuated by the selective 5-HT$_{1A}$ receptor antagonist, *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamide maleate (WAY 100635; 0.3–1 mg/kg, i.v.), as well as by the selective α_2-adrenoceptor antagonist, (8*aR*,12*aS*,13*aS*)-5,8,8*a*,9,10,11,12,12*a*,13,13*a*-dechydro-3-methoxy-12-(ethylsulfonyl)-6*H*-isoquino[2,1-*g*][1,6]naphthyridine hydrochloride (RS 79948; 0.3 mg/kg, i.v.), but not by the selective α_1-adrenoceptor antagonist, prazosin (0.3 mg/kg, i.v.). Mydriatic responses elicited by the α_2-adrenoceptor agonist, guanabenz (0.003–0.3 mg/kg, i.v.), were not antagonized by WAY 100635 (0.3–1 mg/kg, i.v.). To determine whether central nervous system (CNS) 5-HT$_{1A}$ receptors, like α_2-adrenoceptors, are involved in reflex mydriasis, voltage response curves of pupillary dilation were constructed by stimulation of the sciatic nerve in anesthetized rats. WAY 100635 (1 mg/kg, i.v.) did not antagonize the evoked reflex mydriasis, which, however, was blocked by RS 79948 (0.3 mg/kg, i.v.). Taken together, these results suggest that 8-OH-DPAT produces pupillary dilation in anesthetized rats by stimulating CNS 5-HT$_{1A}$ receptors, which in turn trigger the release of norepinephrine, presumably from the locus coeruleus. The latter reduces parasympathetic neuronal tone to the iris sphincter muscle by stimulation of postsynaptic α_2-adrenoceptors within the Edinger-Westphal nucleus. Unlike α_2-adrenoceptors, 5-HT$_{1A}$ receptors in the CNS do not mediate reflex mydriasis evoked by sciatic nerve stimulation.

Keywords: Serotonin; 5-HT$_{1A}$ receptor; α_2-Adrenoceptor; Mydriasis; Miosis; Pupil

1. Introduction

Central nervous system (CNS) serotonin pathways utilizing 5-HT$_{1A}$ receptors are involved in the reflex activation of parasympathetic outflow to the heart, airways and bladder (Ramage, 2001). The data suggests that this occurs at least at the level of central parasympathetic nuclei (Wang and Ramage, 2001) although other areas have not been completely ruled out. The mechanism appears to involve activation of 5-HT$_{1A}$ receptors, which, in turn, inhibit a tonic γ-aminobutyric acid (GABA)-mediated inhibition of parasympathetic preganglionic neurons (Wang and Ramage, 2001).

In the case of parasympathetic control of the pupil, there is evidence to imply that 5-HT$_{1A}$ receptors also may be involved. For example, 5-HT$_{1A}$ receptor agonists produce miosis in humans and rabbits (Fanciullacci et al., 1995; Chidlow et al., 1999; Phillips et al., 1999). However, as seen with α_2-adrenoceptor agonists (Allen and Langham, 1976; Koss and San, 1976; Gherezghiher and Koss, 1979; Clifford et al., 1982; Sharpe and Pickworth, 1985; Heal et al., 1989), there appears to be a species difference with regard to pupillary responses to 5-HT$_{1A}$ receptor agonists. In mice, the 5-HT$_{1A}$ receptor agonist, (2*R*)-(+)-8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), induces dose-related mydriasis, but not miosis (Prow et al., 1996). In humans,

* Corresponding author. Tel.: +1-405-271-2107; fax: +1-405-271-3415.
E-mail address: yongxin-yu@ouhsc.edu (Y. Yu).

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it has been reported that the 5-HT_{1A} receptor agonist, buspirone, produces miosis solely by inhibiting sympathetic mechanisms (Fanciullacci et al., 1995). However, more recent studies suggest that the parasympathetic nerve also is involved (Phillips et al., 1999). The mechanisms by which 5-HT_{1A} receptor ligands modulate pupillary size is thus unclear.

The present series of experiments in anesthetized rats were designed to determine (1) the neural (sympathetic or parasympathetic) mechanisms that mediate mydriasis elicited by 8-OH-DPAT, (2) the relationship between 5-HT_{1A} receptors and α_2-adrenoceptors in regulating pupillary size, and (3) whether the 5-HT_{1A} receptor mediates reflex mydriasis evoked by afferent sciatic nerve stimulation.

Our results indicate that 8-OH-DPAT-elicited pupillary dilation is exclusively mediated by a parasympathetic inhibition. Evoked dilator responses are antagonized by both 5-HT_{1A} receptor and α_2-adrenoceptor antagonists, suggesting that both receptors are involved. Unlike α_2-adrenoceptors, however, 5-HT_{1A} receptors are not within the CNS pathway that mediates reflex mydriasis evoked by sciatic nerve stimulation.

2. Materials and methods

2.1. General preparation

Adult male Sprague–Dawley rats (350–550 g) were anesthetized with pentobarbital (60 mg/kg i.p. + 5 mg i.v. as needed). A femoral artery and vein were cannulated for monitoring blood pressure (Statham P23 pressure transducer; Statham, Murray Hill, NJ) and for i.v. drug administration, respectively. Heart rate was derived from the pressure wave using a Grass tachograph (7P4D; Grass Instruments, Quincy, MA). The trachea was intubated. Rectal temperature was maintained at approximately 37 °C with a Deltaphase isothermal pad (Braintree Scientific, Braintree, MA). The preganglionic cervical sympathetic nerve was sectioned unilaterally. Pupillary diameter was measured using a 0.1-mm ruler and a surgical microscope (Olympus, Tokyo, Japan). General ambient lighting conditions were maintained constant throughout the experiment. Studies were approved by the Institutional Animal Care and Use Committee of University of Oklahoma Health Sciences Center and were undertaken in accordance with the "NIH Guide to the Care and Use of the Laboratory Animals".

2.2. Agonist dose–response curves

Cumulative dose–response curves to 8-OH-DPAT and guanabenz were constructed utilizing increasing doses administered intravenously at 10-min intervals. The pupillary dilation produced by both drugs was rapid in onset with the maximum response reached at approximately 5 min. This was sustained for at least a 10-min observation period. The pupillary dilation, as compared with the basal level, was recorded 10 min after each drug administration to establish dose–response relationships. Antagonist drugs were administered intravenously 10 min before starting the agonist dose–response curve. In all experiments, each animal received only one agonist and only one dose of antagonist or vehicle.

2.3. Sciatic nerve stimulation

In anesthetized rats, one sciatic nerve was separated and sectioned. A bipolar electrode was placed under the proximal portion of the sciatic nerve and covered with mineral oil. The electrical stimulation was generated with a Grass S88 stimulator. The 10-s trains consisted of pulses of 2-ms duration at 4 Hz with the voltage varied between 1 and 64 V. Each pupillary dilator response was allowed to recover to the basal level before the next higher voltage of stimulation was applied. Voltage–responses were generated before and approximately 10 min after intravenous drug or vehicle administration.

2.4. Drugs and data analysis

Guanabenz acetate, prazosin hydrochloride and *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamide maleate salt (WAY 100635) were purchased from Sigma (St. Louis, MO). 8-OH-DPAT and (8*aR*,12*aS*,13*aS*)-5,8,8*a*,9,10,11,12,12*a*,13,13*a*-dechydro-3-methoxy-12-(ethylsulfonyl)-6*H*-isoquino[2,1-*g*][1,6]naphthyridine hydrochloride (RS 79948) were from Tocris Cookson (Ballwin, MO). Solutions of drugs were prepared in sterile physiological saline. Doses administered represent the respective salts.

Values are reported as means ± S.E.M. Statistical significance was determined using Student's *t*-test or one-way analysis of variance followed by Dunnett's *t*-test. *P*-values of less than 0.05 are considered significant.

3. Results

3.1. Inhibition of 8-OH-DPAT-elicited pupillary dilation by both 5-HT_{1A} and α_2-adrenoceptor antagonists

Cumulative injections of 8-OH-DPAT (0.003–3 mg/kg) produced dose-dependent increases in pupillary diameter in anesthetized rats (Fig. 1). The ED_{50} for this response was approximately 1 mg/kg. Section of the preganglionic cervical sympathetic nerve did not significantly reduce the mydriatic response. To determine whether 8-OH-DPAT-elicited pupillary dilation was mediated by 5-HT_{1A} receptors, the selective 5-HT_{1A} receptor antagonist, WAY 100635 (0.3–1 mg/kg, i.v.), was administered 10 min before the dose–response curve was generated. WAY 100635 did not significantly alter the resting pupillary size in these prepa-

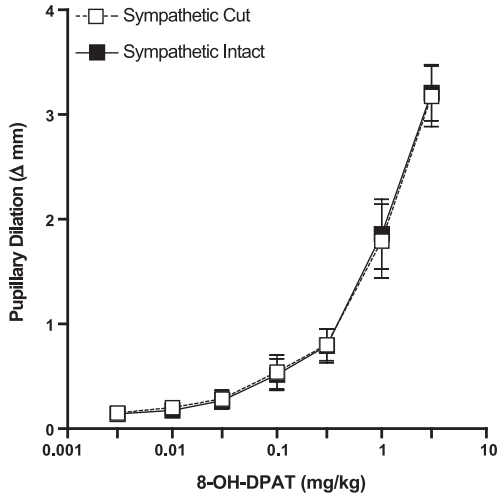

Fig. 1. Pupillary dilation in response to cumulative administration of the 5-HT_{1A} receptor agonist, 8-OH-DPAT (0.003-3 mg/kg, i.v.), given at 10-min intervals in six pentobarbital-anesthetized rats. Values represent means ± S.E.M. In this group of animals, one preganglionic cervical sympathetic nerve was sectioned. Dose–response curves of pupillary dilation were compared on both eyes. Note that section of the sympathetic nerve did not significantly alter the mydriatic response.

rations. Pupillary diameter was 0.49 ± 0.05 mm 10 min after 0.3 mg/kg of WAY 100635, as compared to control values of 0.48 ± 0.04 mm ($n = 9$, $P > 0.05$) and 0.53 ± 0.05 mm 10 min after 1 mg/kg of WAY 100635, as compared to control values of 0.43 ± 0.04 mm ($n = 13$, $P > 0.05$). As shown in Fig. 2, mydriasis produced by 8-OH-DPAT was significantly attenuated by WAY 100635.

To further determine if α_2-adrenoceptors also mediate the pupillary dilation produced by 8-OH-DPAT, the selective α_2-adrenoceptor antagonist, RS 79948 (0.3 mg/kg, i.v.), was utilized. As shown in Fig. 3, mydriasis produced by 8-OH-DPAT was almost totally blocked by α_2-adrenoceptor antagonism. However, the α_1-adrenoceptor antagonist, prazosin (0.3 mg/kg, i.v.), did not attenuate the evoked mydriasis (Fig. 3).

3.2. Guanabenz-elicited pupillary dilation is not inhibited by 5-HT_{1A} receptor antagonism

As 8-OH-DPAT-elicited mydriasis was blocked by the α_2-adrenoceptor antagonist, RS 79948, experiments were conducted to examine whether the mydriasis elicited by an α_2-adrenoceptor agonist would also be blocked by the 5-

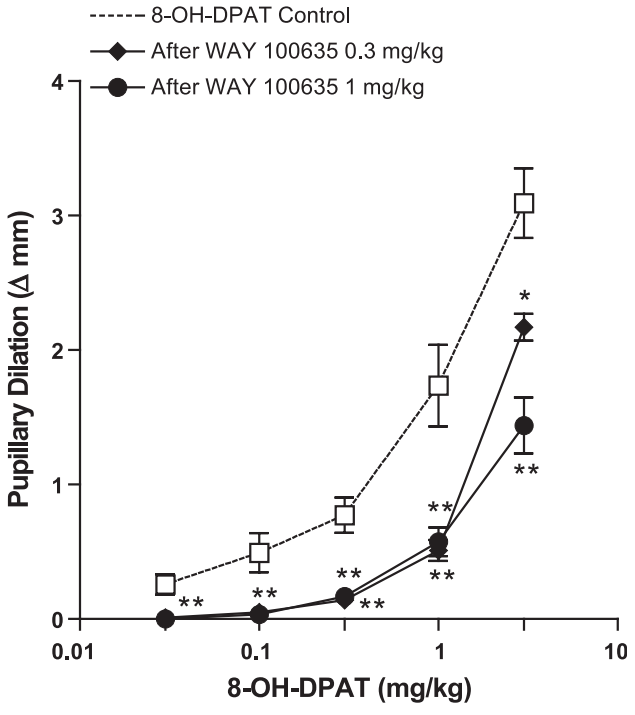

Fig. 2. Effects of the selective 5-HT_{1A} receptor antagonist, WAY 100635, on pupillary dilation elicited by 8-OH-DPAT in anesthetized rats. The preganglionic cervical sympathetic nerve was sectioned. 8-OH-DPAT (0.03–3 mg/kg, i.v.) was administered cumulatively at 10-min intervals. WAY 100635 was given intravenously 10 min before starting the agonist dose–response curve. Each animal received only one dose of antagonist or vehicle. Values represent means ± S.E.M. for five to seven animals. Asterisks indicate levels of significance, as compared with control values. *$P < 0.05$, **$P < 0.01$. Note that 8-OH-DPAT elicited pupillary dilation was significantly attenuated by WAY 100635 (0.3–1 mg/kg).

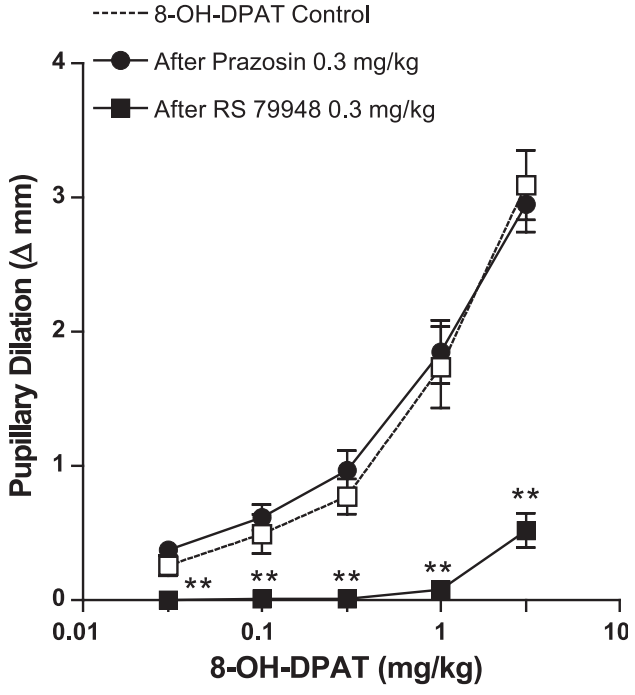

Fig. 3. Effects of the selective α_1-adrenoceptor antagonist, prazosin and the selective α_2-adrenoceptor antagonist, RS 79948, on pupillary dilation elicited by 8-OH-DPAT in anesthetized rats. The preganglionic cervical sympathetic nerve was sectioned. 8-OH-DPAT (0.03–3 mg/kg, i.v.) was administered cumulatively at 10-min intervals. Antagonist drugs were given intravenously 10 min before starting the agonist dose–response curve. Each animal received only one dose of antagonist or vehicle. Values represent means ± S.E.M. for five to seven animals. Asterisks indicate levels of significance, as compared with control values. *$P < 0.05$, **$P < 0.01$. Note that 8-OH-DPAT elicited pupillary dilation was not attenuated by prazosin (0.3 mg/kg), but significantly inhibited by RS 79948 (0.3 mg/kg).

HT_{1A} receptor antagonist, WAY 100635. Dose–response curves of pupillary dilation were constructed by intravenous cumulative administration of the selective α_2-adrenoceptor agonist, guanabenz (0.003–0.3 mg/kg). As shown in Fig. 4, WAY 100635 (0.3–1 mg/kg, i.v.) did not inhibit the pupillary dilation elicited by guanabenz. However, guanabenz-induced mydriasis was readily antagonized by RS 79948 (0.3 mg/kg, i.v.).

3.3. Pupillary dilation elicited by sciatic nerve stimulation is not inhibited by 5-HT_{1A} receptor antagonism

To assess whether the 5-HT_{1A} receptor, like the α_2-adrenoceptor, also mediates reflex-induced mydriasis, voltage-dependent mydriatic responses were generated by stimulation of an afferent sciatic nerve. Intravenous administration of WAY 100635 (1 mg/kg) did not inhibit the elicited reflex mydriasis (Fig. 5A). WAY 100635 has been reported to have α_1-adrenoceptor antagonistic activities (Villalobos-Molina et al., 2002), which may potentiate reflex mydriasis in rats (Hey and Koss, 1988). Therefore, in additional experiments, the selective α_1-adrenoceptor antagonist, prazosin (0.3 mg/kg, i.v.), was administered to block CNS and peripheral α_1-adrenoceptors. As shown in Fig. 5B, prazosin potentiated the mydriasis evoked by sciatic nerve stimulation. Reflex-induced mydriasis was not inhibited by WAY 100635 (1 mg/kg, i.v.), but was almost totally blocked by RS 79948 (0.3 mg/kg, i.v.).

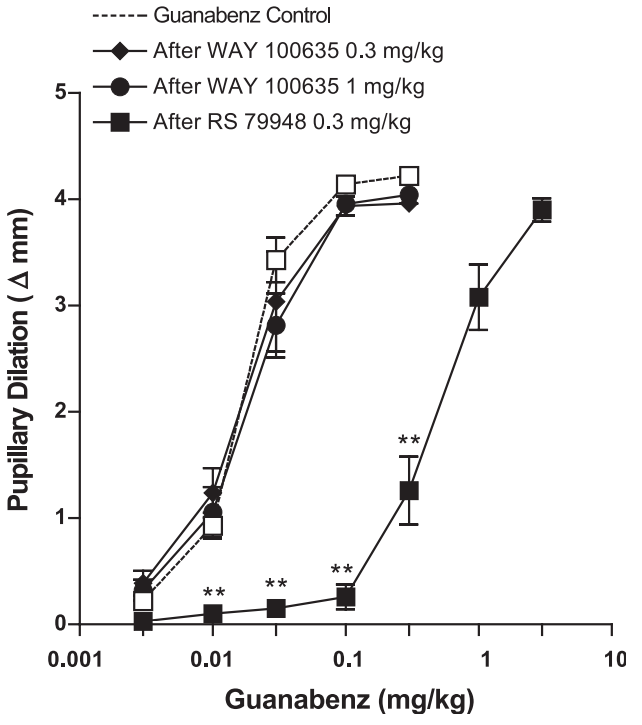

Fig. 4. Effects of the selective 5-HT_{1A} receptor antagonist, WAY 100635, and the selective α_2-adrenoceptor antagonist, RS 79948, on pupillary dilation elicited by the α_2-adrenoceptor agonist, guanabenz, in anesthetized rats. The preganglionic cervical sympathetic nerve was sectioned. Guanabenz (0.003–0.3 mg/kg, i.v.) was administered cumulatively at 10-min intervals. Antagonist drugs were given intravenously 10 min before starting the agonist dose–response curve. Each animal received only one dose of antagonist or vehicle. Values represent means ± S.E.M. for 4–10 animals. Asterisks indicate levels of significance, as compared with control values. $^{**}P<0.01$. Note that guanabenz elicited pupillary dilation was significantly attenuated by RS 79948 (0.3 mg/kg), but not by WAY 100635 (0.3–1 mg/kg).

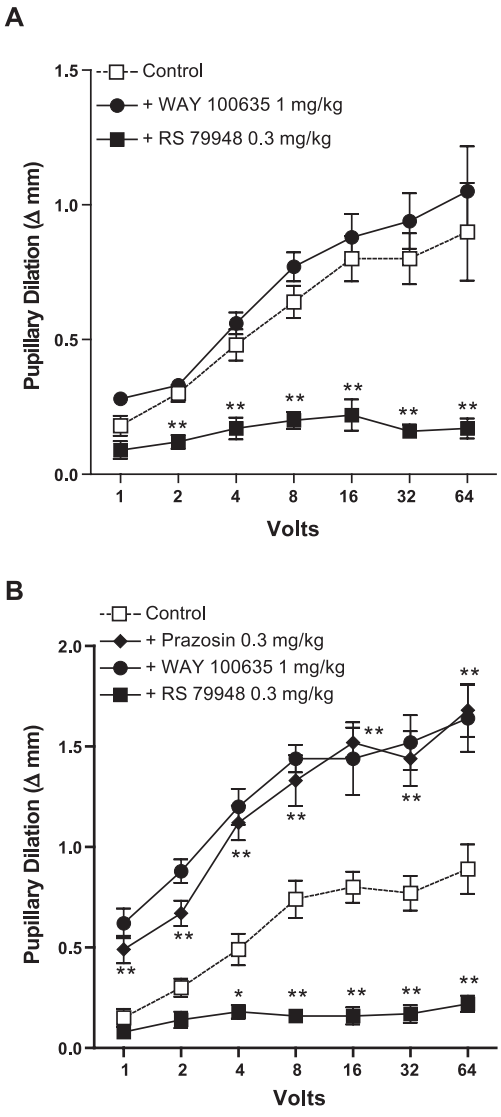

Fig. 5. Effects of the selective 5-HT_{1A} receptor antagonist, WAY 100635, and the selective α_2-adrenoceptor antagonist, RS 79948, on reflex pupillary dilation in response to electrical stimulation of an afferent sciatic nerve. The preganglionic cervical sympathetic nerve was sectioned. Voltage–response curves were generated before and 10 min after intravenous drug administration. Values represent means ± S.E.M. for five animals in each panel. Asterisks indicate levels of significance, compared with control values. $^{*}P<0.05$, $^{**}P<0.01$. In panel A, animals were first given WAY 100635 (1 mg/kg), followed by RS 79948 (0.3 mg/kg). In panel B, animals were sequentially given prazosin (0.3 mg/kg), WAY 100635 (1 mg/kg) and RS 79948 (0.3 mg/kg). Note that evoked reflex mydriasis was significantly potentiated by prazosin, and blocked by RS 79948, but not affected by WAY 100635.

4. Discussion

CNS serotonergic mechanisms are involved in pupillary control (Kramer et al., 1973; Saletu and Grünberger, 1988; Deijen et al., 1989; McGuirk and Silverstone, 1990). Although at least three serotonin receptor subtypes (5-HT_{1A}, 5-HT_2 and 5-HT_3) are suggested to alter pupillary size (Millson et al., 1992; Rizzi et al., 1993; Fanciullacci et al., 1995; Prow et al., 1996; Chidlow et al., 1999; Phillips et al., 1999), most attention has been directed to effects of 5-HT_{1A} receptor agonists. 5-HT_{1A} receptor agonists produce miosis in both humans (Fanciullacci et al., 1995; Phillips et al., 1999) and rabbits (Chidlow et al., 1999), but mydriasis in mice (Prow et al., 1996).

It is well established that central α_2-adrenoceptors modulate pupillary size. α_2-Adrenoceptor agonists produce pupillary dilation in cats, rats and mice by an inhibition of parasympathetic neuronal tone to the iris sphincter muscle (Koss and San, 1976; Gherezghiher and Koss, 1979; Koss, 1986; Heal et al., 1989). This action is produced by stimulation of postsynaptic α_2-adrenoceptors within the Edinger-Westphal nucleus (Koss, 1986; Heal et al., 1989). Interestingly, α_2-adrenoceptor agonists cause miosis, but not mydriasis, in rabbits, humans and dogs (Allen and Langham, 1976; Clifford et al., 1982; Sharpe and Pickworth, 1985). This species variation is similar to that seen with 5-HT_{1A} receptor agonists (Fanciullacci et al., 1995; Prow et al., 1996; Chidlow et al., 1999; Phillips et al., 1999). Therefore, it would seem likely that 5-HT_{1A} and α_2-adrenoceptor ligands act on the same central neural circuitry that modulates pupillary size.

In the present study in anesthetized rats, the selective 5-HT_{1A} receptor agonist, 8-OH-DPAT, produced dose-related mydriasis, similar to that of mice. The ED_{50} for this response was approximately 1 mg/kg, lower than that found in conscious mice (5.8 mg/kg; Prow et al., 1996). This potency difference may be partly due to that 8-OH-DPAT was administered by i.p. route in their study (Prow et al., 1996). The elicited pupillary dilation was significantly attenuated by the selective 5-HT_{1A} receptor antagonist, WAY 100635, confirming that 5-HT_{1A} receptors mediate the pupillary response.

The 8-OH-DPAT-elicited pupillary dilation in rats was not reduced by section of the cervical sympathetic nerve, suggesting that the sympathetic nerve is not involved. This is consistent with observations that activation of central 5-HT_{1A} receptors in general reduces sympathetic outflow (Van Zwieten and Chalmers, 1994), although in other studies a sympathoexcitation also is observed (Anderson et al., 1992).

Consistent with that found in mice (Prow et al., 1996), pupillary dilation elicited by 8-OH-DPAT was blocked by the selective α_2-adrenoceptor antagonist, RS 79948, which has no effects on 5-HT_{1A} receptors (Hume et al., 1996; Milligan et al., 1997). 8-OH-DPAT exhibits low binding affinity for α_2-adrenoceptors (Prow et al., 1996). In functional studies; however, it acts as a weak α_2-adrenoceptor antagonist (Winter, 1988). Therefore, the mydriasis produced by 8-OH-DPAT is not likely to be the result of a direct activation of α_2-adrenoceptors. A more likely explanation is that 8-OH-DPAT activates central 5-HT_{1A} receptors, which in turn triggers postsynaptic α_2-adrenoceptors in the Edinger-Westphal nucleus to reduce the parasympathetic outflow to the iris sphincter muscle. In this respect, it has been found that administration of 8-OH-DPAT in mice dose-dependently increases norepinephrine turnover in the brain (Prow et al., 1996). Studies using extracellular recordings in anesthetized rats also have shown that 8-OH-DPAT enhances the firing activity of norepinephrine neurons of the locus coeruleus (Szabo and Blier, 2001), which is believed to be the source of norepinephrine that activates postsynaptic α_2-adrenoceptors in the Edinger-Westphal nucleus (Szabadi and Bradshaw, 1996). Other evidence also supports such an indirect mechanism of action. First, 8-OH-DPAT exhibits much lower potency in producing pupillary dilation than seen with α_2-adrenoceptor agonists (Koss, 1986). Second, the Edinger-Westphal nucleus contains high concentrations of norepinephrine, while serotonin-containing neurons are not present (Dahlström et al., 1964).

Although 8-OH-DPAT has been reported to produce a relaxation of the rabbit isolated iris sphincter muscle (Barnett and Osborne, 1993), our finding that pupillary dilation elicited by 8-OH-DPAT was almost totally blocked by α_2-adrenoceptor antagonism suggests that a direct action on the iris smooth muscle is minimal. Activation of α_2-adrenoceptors in the iris does not cause significant pupillary dilation (Yu and Koss, 2003). Even topical clonidine to one eye produces mydriasis by a CNS mechanism, but not by a peripheral action on the iris (Koss, 1979). In addition, a direct effect of 8-OH-DPAT on irideal α_1-adrenoceptors can be excluded, as the mydriasis was not attenuated by the α_1-adrenoceptor antagonist, prazosin.

It is known that there is a complex, reciprocal interaction between norepinephrine and serotonin systems in the brainstem. Dorsal raphe serotonin neurons receive norpinephrine neuronal afferents originating from the locus coeruleus (Anderson et al., 1994), whereas the locus coeruleus also is under the modulation of serotonin systems (Haddjeri et al., 1997). Therefore, experiments were conducted to assess whether mydriasis elicited by α_2-adrenoceptor activation is modulated by 5-HT_{1A} receptors. The results showed that mydriasis elicited by the α_2-adrenoceptor agonist, guanabenz, was not antagonized by the 5-HT_{1A} receptor antagonist, WAY 100635, congruent with speculations that these α_2-adrenoceptors lie in the Edinger-Westphal nucleus (Koss, 1986), acting as a downstream pathway to the 5-HT_{1A} receptor activation.

The failure of WAY 100635 to produce significant pupillary constriction suggests that the 5-HT_{1A} receptor-mediated inhibition of the Edinger-Westphal nucleus is not tonic. A possible explanation is that in anesthetized rats the

basal level of norepinephrine inhibition on the Edinger-Westphal nucleus is low, as indicated by the small resting pupillary size. Although WAY 100635 has been shown to reduce the activity of the locus coeruleus neurons (Szabo and Blier, 2001), it may not have significant effects on the Edinger-Westphal nucleus.

Postsynaptic α_2-adrenoceptors in the Edinger-Westphal nucleus are of physiological significance in that they mediate reflex mydriasis elicited by electrical stimulation of the afferent sciatic nerve or the ascending reticular pathways in the lower brainstem in cats and rats (Koss et al., 1984; Hey et al., 1985). Both serotonin and norepinephrine are released in the CNS in response to sciatic nerve stimulation (Yaksh and Tyce, 1981). Therefore, we examined the possible role 5-HT_{1A} receptors in the reflex mydriasis evoked by electrical stimulation of the sciatic nerve. The results showed that evoked reflex mydriasis was not affected by WAY 100635, which, however, was abolished by α_2-adrenoceptor antagonism.

WAY 100635 has been reported to exhibit α_1-adrenoceptor antagonistic activities (Villalobos-Molina et al., 2002). α_1-Adrenoceptor antagonism potentiates reflex mydriasis in rats, presumably by a CNS presynaptic inhibition mechanism (Hey and Koss, 1988). Such an α_1-adrenoceptor-mediated potentiation might theoretically cancel the inhibitory effect of WAY 100635 on evoked reflex mydriasis. Therefore, the selective α_1-adrenoceptor antagonist, prazosin, was utilized to block α_1-adrenoceptors. As expected, prazosin significantly enhanced the mydriasis evoked by sciatic nerve stimulation. Again, WAY 100635 did not show any effect on the reflex mydriasis. It is therefore concluded that 5-HT_{1A} receptors are not involved in the mediation of reflex mydriasis in this species.

The functional linkage between 5-HT_{1A} receptors and α_2-adrenoceptors in modulation of pupillary size in the brain may explain the similar pattern of species variation of pupillary changes in response to 5-HT_{1A} receptor and α_2-adrenoceptor agonists. Although the mechanisms of how CNS α_2-adrenoceptors modulate pupillary size differently among species are still unclear (Szabadi and Bradshaw, 1996), it appears that the species difference with regard to 5-HT_{1A} receptor-mediated pupillary responses may be determined by that of α_2-adrenoceptors.

In summary, we examined the pharmacological mechanisms of 5-HT_{1A} receptor mediated pupillary dilation in anesthetized rats. The results suggest that the 8-OH-DPAT-elicited pupillary dilation is exclusively mediated by a parasympathetic inhibition. Activation of central 5-HT_{1A} receptors appears to trigger the release of norepinephrine in the brain. The latter reduces parasympathetic neuronal tone to the iris sphincter muscle by the stimulation of postsynaptic α_2-adrenoceptors within the Edinger-Westphal nucleus. Unlike α_2-adrenoceptors, 5-HT_{1A} receptors do not mediate reflex mydriasis evoked by sciatic nerve stimulation.

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