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Dexmedetomidine Produces a Hypnotic–Anesthetic Action in Rats via Activation of Central Alpha-2 Adrenoceptors

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Dexmedetomidine, a highly selective and potent alpha-2 adrenoceptor agonist, reduces halothane anesthetic requirements by over 90% in rats. The present study examined whether dexmedetomidine produces a hypnotic–anesthetic action in rats. Dexmedetomidine induced a hypnotic–anesthetic state in rats characterized by loss of righting reflex at doses ≥ 0.1 mg/kg. This response was dose-dependent between 0.1 and 3 mg/kg. Alpha-2 adrenoceptor antagonists that cross the blood-brain barrier (atipamezole and idazoxan) decreased the hypnotic–anesthetic action of dexmedetomidine in a dose-dependent fashion. In contrast, the alpha-2 antagonist, L-659,066, which does not penetrate into the CNS did not affect dexmedetomidine-induced hypnosis. Antagonists for the other adrenoceptors not only failed to reduce the hypnotic–anesthetic action of dexmedetomidine but in some cases even potentiated this effect. Thus, prazosin, an alpha-1 adrenoceptor antagonist, significantly enhanced the hypnotic–anesthetic property of dexmedetomidine. Antagonists with beta-2 receptor blocking properties also enhanced dexmedetomidine-induced hypnosis. Selective beta-1 receptor antagonists did not affect the hypnotic action of dexmedetomidine. These results suggest that dexmedetomidine produces a hypnotic–anesthetic action in rats *via* activation of central alpha-2 adrenoceptors. (Key words: Anesthesia: hypnosis. Receptors, adrenergic: alpha-2. Sympathetic nervous system, alpha-2 adrenoceptor agonist: dexmedetomidine. Sympathetic nervous system, alpha-2 adrenoceptor antagonist: atipamezole; idazoxan; L-659,066.)

THE ADRENERGIC SYSTEM is involved in the modulation of cortical arousal, wakefulness, and the processing of sensory stimuli.[1] It is also known to modulate anesthetic requirements.[1–3] The adrenergic system is comprised of distinct recognition sites, including alpha-1, alpha-2, beta-1, and beta-2 receptors, each of which is pharmacologically distinguished by its relative selectivity for agonists and antagonists. Of adrenergic agonists, only agonists for the alpha-2 adrenoceptor have been shown to potentiate anesthesia. Alpha-2 adrenoceptor agonists, such as clonidine, decrease anesthetic requirements for both inhalational anesthetics[4–6] and opioids,[7,8] and prolong barbiturate sleep time.[1] It has been suggested that the anesthetic-reducing properties of alpha-2 agonists are mediated by alpha-2 adrenoceptors in the CNS.[1,9]

Dexmedetomidine is a highly selective and specific, potent agonist at the alpha-2 adrenoceptor.[10,11] Compared with clonidine, it has a sevenfold greater selectivity for alpha-2 *versus* alpha-1 receptors.[11] Whereas clonidine can decrease volatile anesthetic requirements up to a maximum of 48%,[4] dexmedetomidine has been shown to reduce halothane anesthetic requirements by more than 90% in rats.[12]

The purpose of this study was to determine whether dexmedetomidine could produce a hypnotic–anesthetic action in rats in the absence of another anesthetic agent. Antagonists of the adrenergic receptors were also studied in this context to determine whether dexmedetomidine's actions were mediated *via* activation of central alpha-2 adrenoceptors.

Materials and Methods

The experimental protocol was approved by the Animal Care and Use Committee at the Palo Alto Veterans Administration Medical Center. Male Sprague-Dawley rats weighing 150–250 g were used throughout and housed in groups of four on a 12:12 h light-dark cycle with food and water *ad libitum*. All testing was performed between 10 A.M. and 6 P.M. Body temperatures were maintained throughout the experiment at 38° C with heating lamps and/or warming mattresses.

Loss of the righting reflex was used as an index of the hypnotic–anesthetic action, and its duration measured in minutes is referred to as duration of hypnosis. Hypnosis was determined when an animal became unresponsive to external stimulations and could be placed on its back without righting itself. To determine the dose-dependency and stereospecifity of the hypnotic–anesthetic actions of dexmedetomidine, rats were administered dexmedetomidine (0.01–10 mg/kg) or L-medetomidine (0.01–10 mg/kg), and the duration of hypnosis measured. Using information gained from these experiments, a separate series of investigations were then undertaken to determine the type and location of the adrenoceptor mediating the hypnotic–anesthetic action of dexmedetomidine.

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ADMINISTER CONTROL OR TREATMENT
TO RATS (n=10 per group)

15 min ↓ later

ADMINISTER DEXMEDETOMIDINE (0.5 mg/kg)
& MEASURE DURATION OF HYPNOSIS

CONTROL	TREATMENT	PURPOSE
saline	atipamezole	{ central alpha-2
saline	idazoxan	{ receptor blockade
saline	L-659,066	peripheral alpha-2 blockade
DMSO 5% water	prazosin	central alpha-1 blockade
DMSO 5% water	doxazosin	peripheral alpha-1 blockade
saline	propranolol	beta-1/beta-2 blockade
saline	atenolol	beta-1 blockade
saline	metoprolol	beta-1 blockade
dilute HCl saline	ICI-118,551	beta-2 blockade

FIG. 1. The hypnotic–anesthetic determinations and drug treatments used in the antagonism studies. Animals received either the vehicle control or the antagonist treatment compound(s) 15 min before the administration of dexmedetomidine. The duration of hypnosis was then measured.

Specific adrenergic receptor antagonists were given 15 min before the administration of a predetermined ED_{90} dose of dexmedetomidine and the duration of hypnosis measured (fig. 1). To determine the involvement of central alpha-2 adrenoceptors in mediating the hypnotic–anesthetic action of dexmedetomidine, atipamezole (0.01–1 mg/kg) and idazoxan (0.1–10 mg/kg), selective alpha-2 adrenergic receptor antagonists that cross the blood-brain barrier, were given 15 min before dexmedetomidine (0.5 mg/kg) administration, and the duration of hypnosis was then measured. To rule out the involvement of peripheral alpha-2 adrenoceptors, the alpha-2 antagonist L-659,066 (1–10 mg/kg), which does not readily penetrate into the CNS, was investigated using this same paradigm. To investigate the interaction with central and peripheral alpha-1 adrenoceptors, prazosin (0.01–1 mg/kg) and doxazosin (0.1–10 mg/kg), respectively, were studied. To determine the involvement of central beta-1 and beta-2 adrenergic receptors, propranolol (5–20 mg/kg), atenolol (10–40 mg/kg), metoprolol (20–80 mg/kg) and ICI-118,551 (5–20 mg/kg) were also all studied using this experimental design. In all of these studies, vehicle-treated control groups consisting of rats matched for age and weight were always studied at the same time to normalize day-to-day variations in the hypnotic–anesthetic action of dexmedetomidine.

In a separate investigation, the interaction of high-dose prazosin with dexmedetomidine was studied further to characterize the alpha-1 component of dexmedetomidine's actions. In these experiments, animals were given prazosin (3 mg/kg) followed by dexmedetomidine (0–5 mg/kg) and the duration of hypnosis then measured.

All drug solutions were made up immediately prior to their injection and were administered by the intraperitoneal (ip) route. Injection volumes were adjusted to 0.5 ml/100 g of body weight in all instances. Drug dosages were calculated on the basis of the weights of their salts. The drugs used in this study and their sources were as follows: dexmedetomidine HCl (dextrorotatory isomer of medetomidine or MPV-1440, Farmos-Group Ltd., Turku, Finland), L-medetomidine HCl (levorotatory isomer of medetomidine or MPV-1441, Farmos), atipamezole HCl (MPV-1248, Farmos), idazoxan HCl (Reckitt & Colman, Kingston-upon-Hull, England), L-659,066 HCl (Merck Sharp & Dohme, West Point, Pennsylvania); prazosin HCl (Pfizer, Sandwich, Kent, England), doxazosin mesylate (Pfizer), DL-propranolol HCl (Sigma Chem. Co., St. Louis, Missouri), atenolol HCl (Sigma), metoprolol tartrate (Sigma), and ICI-118,551 HCl (I.C.I., Macclesfield, Cheshire, England). All drugs were soluble in saline except for prazosin and doxazosin, which were dissolved in DMSO 5% in sterile water, and ICI-118,551, which was dissolved in dilute hydrochloric acid in saline.

The dose–response data were analyzed for statistical significance using one-way ANOVA. Probability (P) less than 0.05 was considered significant. Standard error was calculated from the residual error term of the appropriate ANOVA. In the antagonism studies, the duration of hypnosis is expressed as a percentage of the control group that received dexmedetomidine alone. Differences between the mean values of the control and antagonist-treated groups were evaluated using the paired t test.

Results

Dexmedetomidine induced a hypnotic–anesthetic behavioral state in rats characterized by muscle flaccidity, a

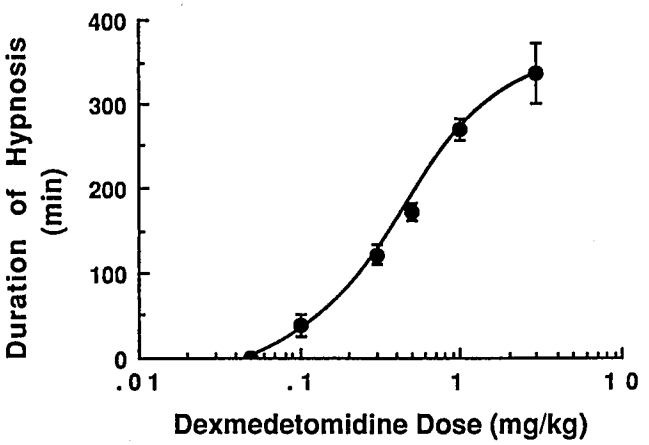

FIG. 2. Log dose–response curve for the hypnotic–anesthetic action of dexmedetomidine. Dexmedetomidine (0.01–10 mg/kg) was injected ip into rats and the duration of hypnosis measured. Each value represents the mean ± SEM for n = 7–10 animals.

loss of eyelid reflexes, and hypnosis. Duration of hypnosis was dose-dependent between 0.1 and 3 mg/kg (fig. 2). Administration of 0.5 mg/kg dexmedetomidine produced a hypnotic–anesthetic action in 91% ± 10% of the animals. Onset of action was within 2–5 min at this dose. At doses ≥3 mg/kg, evidence of behavioral excitation (*i.e.*, piloerection, hyperactivity, and rapid respirations) was observed, and at 5 mg/kg, the duration of hypnosis was actually decreased compared with that following 3 mg/kg. Administration of 10 mg/kg dexmedetomidine was associated with a high incidence of lethality (>LD_{50}) and was not tested further. I-Medetomidine was devoid of hypnotic–anesthetic activity over this same dose range.

The alpha-2 adrenoceptor antagonists atipamezole[13] and idazoxan,[14] both of which cross the blood-brain barrier, decreased the hypnotic–anesthetic action of dexmedetomidine in a dose-dependent fashion (fig. 3). Atipamezole was more potent than idazoxan as a blocker of the hypnotic response to dexmedetomidine. Pretreatment with either atipamezole (1 mg/kg) or idazoxan (10 mg/kg) abolished the hypnotic–anesthetic action of dexmedetomidine. In contrast, the alpha-2 antagonist L-659,066, which is as potent as idazoxan at blocking alpha-2 adrenoceptors *in vitro* but does not cross the blood-brain barrier at the doses tested (1–10 mg/kg),[15] did not antagonize the hypnotic response to dexmedetomidine (fig. 3).

Prazosin, a selective alpha-1 adrenergic receptor antagonist with central activity,[16] enhanced the hypnotic–anesthetic actions of dexmedetomidine in a dose-dependent fashion (table 1). In addition, pretreatment with prazosin abolished the behavioral excitation and reversal of the hypnotic response that occurred at the 3 and 5 mg/kg doses of dexmedetomidine, respectively (fig. 4). In contrast, the alpha-1 receptor antagonist doxazosin, which lacks CNS activity,[17] did not enhance the hypnotic–anesthetic actions of dexmedetomidine (table 1).

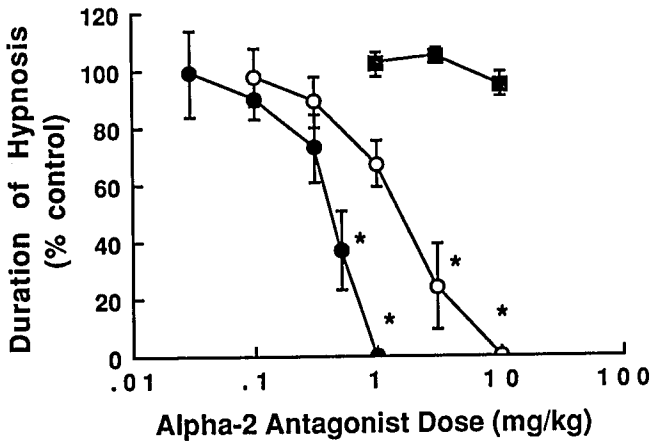

FIG. 3. Influence of alpha-2 adrenoceptor antagonists on the hypnotic–anesthetic action of dexmedetomidine. Atipamezole (●), idazoxan (○), or L-569,066 (■) was administered ip 15 min before the administration of dexmedetomidine (0.5 mg/kg), and the duration of hypnosis was then measured. The duration of hypnosis is expressed as a percentage of that produced by dexmedetomidine (control) alone. Each value represents the mean ± SEM for n = 7–10 animals. *Statistically significant *versus* the dexmedetomidine alone control, $P < 0.05$.

TABLE 1. Effects of Alpha-1 and Beta Adrenergic Receptor Antagonists on the Hypnotic–Anesthetic Action of Dexmedetomidine

Pretreatment (drug)	Receptor Antagonism (primary)	Dose (mg/kg)	Duration of Hypnosis* (% control)
Vehicle	None	—	100
Prazosin	Alpha-1	0.01	106 ± 9
		0.03	110 ± 4
		0.1	115 ± 4
		0.3	116 ± 5
		1.0	135 ± 9†
Doxazosin	Alpha-1	0.1	102 ± 4
		0.3	97 ± 7
		1.0	94 ± 6
		3.0	93 ± 5
		10.0	81 ± 6†
Propranolol	Beta-1/Beta-2	5.0	109 ± 4
		10.0	118 ± 7
		20.0	144 ± 4†
Atenolol	Beta-1	10.0	111 ± 4
		20.0	111 ± 6
		40.0	110 ± 4
Metoprolol	Beta-1	20.0	107 ± 9
		40.0	100 ± 5
		80.0	115 ± 6
ICI-118,551	Beta-2	5.0	107 ± 6
		10.0	117 ± 8
		20.0	123 ± 8†

Each value represents the mean ± SEM for n = 7–10 animals. The variance in the control group is not shown because it consists of the normalized value (100%) from ten experiments.

Antagonists were given ip 15 min before dexmedetomidine (0.5 mg/kg).

* Duration of hypnosis is expressed as a percentage of that produced by dexmedetomidine alone (150–170 min).

† Significantly different from the dexmedetomidine control, $P < 0.05$.

Centrally active beta receptor blocking agents did not antagonize the dexmedetomidine-induced hypnotic–anesthetic action (table 1). Propranolol, a beta-1 and beta-2 antagonist, at doses of 10 and 20 mg/kg actually prolonged dexmedetomidine's duration of hypnosis. The selective beta-1 receptor blockers, atenolol and metoprolol, had no effect on dexmedetomidine-induced hypnosis even at doses as high as 40 and 80 mg/kg, respectively. However, the selective beta-2 receptor antagonist, ICI-118,551,[18] prolonged the hypnotic duration of dexmedetomidine in a similar dose-dependent fashion to that seen with propranolol. At the doses studied, none of the adrenergic antagonists, when given alone, produced a hypnotic–anesthetic action.

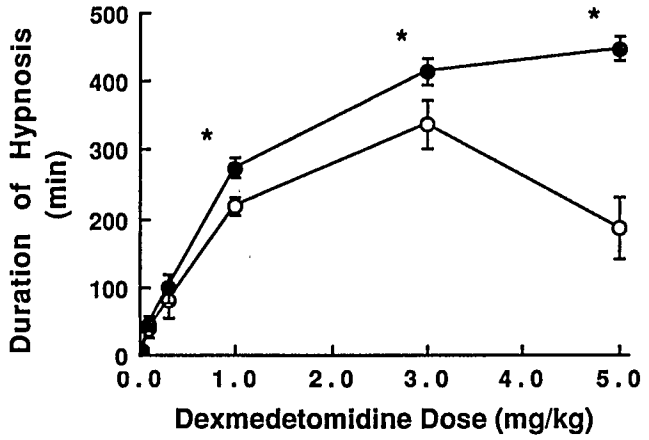

FIG. 4. Influence of central alpha-1 adrenoceptor blockade on the hypnotic–anesthetic action of dexmedetomidine. Animals were given prazosin (3 mg/kg) followed by dexmedetomidine (0–5 mg/kg). Each value represents the mean ± SEM for n = 7–10 animals. *Treatment values (●) significantly different from the dexmedetomidine (○) control, $P < 0.05$.

Discussion

The present study shows that dexmedetomidine, a highly selective and potent agonist for alpha-2 adrenoceptors, dose-dependently produces a hypnotic–anesthetic action in the rat. The fact that the hypnotic–anesthetic action of medetomidine was stereospecific, with activity residing in the D-isomer (dexmedetomidine) but not in the L-isomer, suggests that this action is mediated *via* a discrete receptor population.

The results of the adrenergic receptor antagonism studies establish the involvement of central alpha-2 adrenoceptors in the hypnotic action of dexmedetomidine with no mediating role for peripheral alpha-2 or other central adrenoceptors. The centrally active alpha-2 adrenergic antagonists dose-dependently attenuated the hypnotic action of dexmedetomidine in the order of their potency for displacing ligands at the alpha-2 adrenoceptor (atipazemole > idazoxan).[13,14] The peripherally acting alpha-2 adrenergic antagonist, L-659,066, did not antagonize the hypnotic–anesthetic action of dexmedetomidine.

Adrenergic antagonists without alpha-2 blocking activity not only failed to reduce the hypnotic–anesthetic actions of dexmedetomidine but in some cases even potentiated this effect. Prazosin, a centrally active alpha-1 adrenergic receptor antagonist, enhanced the hypnotic–anesthetic properties of dexmedetomidine in a dose-dependent fashion and abolished the behavioral excitation and hypnotic reversal observed at the higher doses of dexmedetomidine. These effects were probably mediated *via* alpha-1 receptor blockade because activation of alpha-1 receptors is known to produce arousal.[19] Alpha-1 adrenergic receptor agonists, such as ST-587, will antagonize thiopental-induced loss of righting reflex in rats.[1] From the interpretation of these data, it appears that no appreciable alpha-1 agonist effect is produced at the lower dose range of dexmedetomidine (≤1 mg/kg); however, at higher doses (≥3 mg/kg) a functionally antagonistic alpha-1 receptor-mediated effect predominates. Because the alpha-1 receptor antagonist, doxazosin, which is devoid of central activity, did not potentiate the hypnotic action of dexmedetomidine, the functionally antagonistic alpha-1 action of dexmedetomidine is mediated *via* central alpha-1 adrenoceptors.

The potentiation of dexmedetomidine's hypnotic–anesthetic effects by the nonselective beta adrenergic blocking drug, propranolol, is likely to be due to propranolol's action at the beta-2 receptor because the selective beta-2 receptor antagonist, ICI-118,551, but not the selective beta-1 receptor blocking drugs, atenolol and metoprolol, enhanced dexmedetomidine-induced hypnosis. A likely explanation for this is that beta-2 adrenoceptor antagonists inhibit the presynaptic beta-2 receptor-mediated release of norepinephrine, which normally activates postsynaptic alpha-1 receptors.[20]

Another possible explanation for these effects by propranolol and ICI-118,551 may relate to the fact that these drugs have membrane stabilizing properties.[21] High doses of propranolol but not of atenolol and metoprolol have also been shown to enhance the hypnotic actions of thiopental.[1]

Dexmedetomidine's greater selectivity for alpha-2 *versus* alpha-1 receptors is the most likely reason for its increased anesthetic properties when compared with the effects of other alpha-2 agonists, such as clonidine. In radioligand binding assays, the alpha-2/alpha-1 selectivity ratio of medetomidine was 1,620 compared with 220 for clonidine.[11] Thus, it is possible that an opposing alpha-1 receptor-mediated action, similar to that observed at high doses of dexmedetomidine, may account for the inability of clonidine to produce hypnosis. Alpha-1 receptor blockade with prazosin has been reported to enhance clonidine-induced sedation in chicks.[22] Another possible explanation for the increased anesthetic properties of dexmedetomidine compared with that of clonidine and other alpha-2 agonists may relate to its greater efficacy at the alpha-2 adrenoceptor that produces the hypnotic–anesthetic action (*i.e.*, clonidine may be a partial agonist at this receptor, whereas dexmedetomidine may be a full agonist). Partial agonists can also possess antagonist properties with a "ceiling" effect.

In summary, the present study suggests that dexmedetomidine produces its hypnotic–anesthetic action in rats *via* activation of central alpha-2 adrenoceptors. Furthermore, centrally active alpha-2 receptor antagonists can

be used to attenuate or reverse the hypnotic–anesthetic properties of dexmedetomidine. Additional investigations are needed to characterize the central alpha-2 adrenoceptor–effector mechanism responsible for the hypnotic–anesthetic action of dexmedetomidine.

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