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Studies on the Mechanism of Amphetamine Mydriasis in the Cat[1]

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ABSTRACT

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This study was undertaken in order to determine the relative extent to which amphetamine-induced mydriasis is of central nervous system (CNS) or of peripheral origin. Anesthetized cats were administered cumulative dosages of amphetamine given either intravenously (0.05–3.2 mg/kg) or directly into the third ventricle of the brain (500 μg i.c.v.). Pupillary dilation and ciliary nerve activity were monitored. In cats with only parasympathetic tone to the iris intact, i.v. amphetamine produced a dose-dependent mydriasis and decrease of ciliary nerve activity. Treatment with yohimbine (0.5 mg/kg i.v.), before amphetamine administration, blocked the amphetamine-induced reduction of parasympathetic nerve activity and partially antagonized the pupillary dilation. Both yohimbine pretreatment and CNS monoamine depletion (with reserpine 5 mg/kg i.p. and α-methyl-*p*-tyrosine 2 × 300 mg/kg i.p.) prevented the mydriatic and ciliary nerve activity lowering effects of i.c.v. amphetamine. These results suggest that amphetamine produces mydriasis in the cat primarily by means of CNS inhibition of tonic outflow from the oculomotor nucleus and to only a minor extent by acting as a peripheral sympathomimetic. This conclusion is consistent with the hypothesis that release of norepinephrine within the CNS inhibits tonic parasympathetic outflow to the iris.

Although it is well established that administration of amphetamine produces pupillary dilation in humans and animals (Martin *et al.*, 1971; Marley 1961, 1962; Sharpe *et al.*, 1977), the precise neural mechanism responsible for amphetamine-induced mydriasis is not well understood. Several studies suggest that amphetamine may act, at least in part, by means of inhibition of central nervous system (CNS) parasympathetic tone to the iris (Marley, 1961; Sharpe *et al.*, 1977). The present investigation was undertaken in order to determine the degree to which amphetamine-induced mydriasis in the cat is caused by a CNS action as compared to direct sympathomimetic effects on the iris. Additional experiments were performed to determine if a CNS adrenergic inhibitory mechanism may be involved as has been demonstrated for clonidine mydriasis (Koss and San, 1976; Koss and Christensen, 1979; Koss, 1979). Toward this end, yohimbine was utilized as a CNS adrenergic blocker as it has been established to antagonize the CNS sympathoinhibitory action of clonidine (Kobinger, 1978; Schmitt *et al.*, 1973) as well as the CNS-induced mydriasis of clonidine and depression of ciliary nerve activity (Koss and San, 1976; Koss, 1979).

Methods

General. Experiments were performed on adult cats of either sex anesthetized with α-chloralose (60–80 mg/kg i.p.). The animals used in the nerve recording experiments were paralyzed with gallamine triethiodide (2–4 mg/kg i.v.) to reduce artifacts produced by somatomotor activity and were artificially respired. Blood pressure and heart rate were monitored with a Statham P23Dd transducer and a Grass 7P4D tachograph, respectively. Rectal temperature was maintained at approximately 37°C with a heat lamp.

After cannulation of a femoral vein and the trachea, both cervical vagosympathetic nerve trunks were usually sectioned, and the animals were positioned in a David Kopf stereotaxic instrument. Pupillary responses were measured at the point of greatest horizontal diameter with a millimeter ruler. Ambient lighting conditions were the same for each cat.

Ciliary nerve recordings. Access to the short ciliary branches of the oculomotor nerve was achieved by a lateral approach. Fiber bundles concerned with pupilloconstriction were identified by crushing the fibers near their entry into the eye and observing the effect on pupillary diameter. The nerve bundle thus characterized was placed on a bipolar silver electrode and covered with warm mineral oil. Nerve activity was amplified and filtered by a Tektronix AM502 differential amplifier. The band pass was set at 100 to 3,000 Hz, and the amplifier gain was 50 to 100 *k*. Amplified potentials were displayed on a Tektronix SC502 oscilloscope and were processed through a Grass 7P10B integrator for display on a Grass 7D polygraph. A Hewlett Packard F-M tape recorder (3960) was used for data storage.

Induction of amine depletion. Some animals were injected intraperitoneally with reserpine (5 mg/kg) and two doses of the methyl ester of α-methyl-*p*-tyrosine (2 × 300 mg/kg) to deplete endogenous stores of noradrenaline, dopamine and serotonin. Reserpine and the first dose of α-methyl-*p*-tyrosine were administered approximately 16 hr before the experiment was begun. The second dose of α-methyl-*p*-tyrosine was given approximately 2 hr before amphetamine was administered. We

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have established in a previous report that this procedure reduces the CNS concentrations of noradrenaline, dopamine and serotonin to less than 3% of control levels in the cat (Koss and Christensen, 1979).

Drugs. All drugs, with the exception of reserpine, were dissolved in normal saline, and the doses are expressed in terms of their salts. Injections were made either intravenously by the femoral vein cannula or, in some cases, amphetamine was injected directly into the third ventricle (i.c.v.) through a metal cannula stereotaxically placed according to the coordinates of Snider and Niemer (1961). The tip of the cannula was positioned at coordinates A, 7.0; L, 0.0; and DV, 0.0 to −1.5. Volume of injection was 0.5 ml. Drugs used were: *d*-amphetamine sulfate, yohimbine hydrochloride, *ℓ*-epinephrine hydrochloride, physostigmine salicylate, hexamethonium chloride (C_6), reserpine (as Serpasil) and *d,ℓ*-α-methyltyrosine methyl ester hydrobromide.

Results

Effects of i.v. amphetamine on pupillary diameter. Cumulative doses of amphetamine (0.05–1.6 mg/kg) were administered, at 5 to 10-min intervals, to 14 cats in which the cervical vagosympathetic nerve trunks had been sectioned. As illustrated in figure 1, amphetamine produced a dose-dependent mydriasis in these preparations. The maximal response was usually reached within 3 min and remained unchanged until the next dose was injected. In four preparations, the sympathetic nerve on one side was left intact (dotted line in fig. 1). There was no significant difference in the mydriatic response to amphetamine in these animals when compared to the group in which the vagosympathetic nerve trunks were sectioned. (In these four animals, the mydriasis in response to amphetamine was identical on both sides). Subsequent administration of yohimbine (0.5 mg/kg i.v.) partially antagonized the amphetamine-induced mydriasis. In preparations in which the vagosympathetic nerves were cut, yohimbine administered after the largest dose of amphetamine (1.6 mg/kg) constricted the pupils from a mean diameter of 9.0 ± 0.7 to 3.2 ± 0.6 mm. In the four preparations, with both the sympathetic and parasympathetic nerves to the iris intact, amphetamine dilated the pupils to 7.8 ± 0.7 mm. After yohimbine the mean pupil size was reduced to 4.0 ± 1.1 mm. Yohimbine administered 10 to 15 min before amphetamine also greatly antagonized the pupillary effects of amphetamine in 11 other preparations. As can be seen in figure 1 (dashed line), an additional cumulative dose of amphetamine (to 3.2 mg/kg) resulted in mydriasis of only 3.5 mm above control in the animals initially treated with yohimbine.

Effects of i.v. amphetamine on ciliary nerve activity. In nine experiments, amphetamine-induced changes in activity of a branch of the lateral short ciliary nerve were monitored. Figure 2 shows examples of one control and one preparation given yohimbine before amphetamine. Figure 3 is a composite representation of these experiments. As can be seen, amphetamine caused a dose-related inhibition of tonic parasympathetic activity (fig. 3) which was associated with a concomitant dilation of the contralateral iris in the control group. As in the previous experiments, yohimbine partially antagonized these amphetamine-induced effects. As shown in figure 2, subsequent administration of yohimbine resulted in a return of both the nerve activity and pupil diameter toward the control level. In the five control animals, mean pupil diameter changed from 0.8 ± 0.6 to 9.9 ± 0.6 mm after the last dose of amphetamine. At this time, the mean ciliary nerve activity was 48.2 ± 8.9% of the initial level. Yohimbine administration (0.5 mg/kg i.v.) constricted the amphetamine dilated pupils to 0.1 ± 0.5 mm and returned the mean integrated nerve activity to 84.0 ± 7.7% of control.

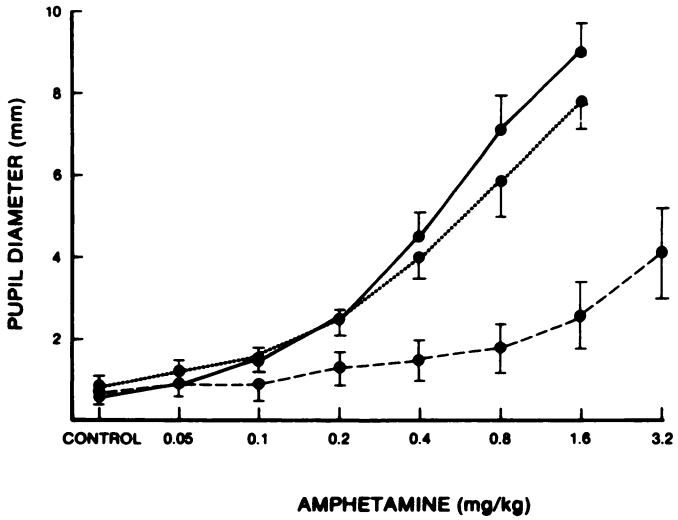

Fig. 1. Dose-response curves illustrating the mydriatic actions of cumulative dosages of i.v. amphetamine administered at 5 to 10-min intervals to chloralose anesthetized cats. Solid line (●——●) represents pupillary responses in cats with only parasympathetic innervation to the iris (n = 14). Dotted line (●...●) shows responses in animals with autonomic nervous control to pupil intact (n = 4). Dashed line (●– – –●) represents responses in preparations having only parasympathetic innervation (n = 11) which were pretreated with yohimbine (0.5 mg/kg i.v.) 10 to 15 min before amphetamine injection. Note that one additional dose of amphetamine was administered to this latter group. In the first two groups, subsequent yohimbine administration partially reversed the amphetamine mydriasis (see text for details). Values are means ± S.E.

In the group given yohimbine before amphetamine, there was no significant decrease in ciliary nerve activity, although the pupils did dilate by about 2 mm at the 3.2 mg/kg dosage level of amphetamine. In this latter group, yohimbine by itself produced no significant change in either pupil size or nerve activity.

Taken together, the above results suggest that amphetamine produces mydriasis primarily by CNS inhibition of parasympathetic tone to the iris and that the difference between the degree of mydriasis observed in the yohimbine treated *vs.* control cats represents, quantitatively, the degree of CNS parasympatho-inhibition produced by amphetamine (as shown in fig. 1).

Effect of i.c.v. amphetamine. In order to define more clearly the CNS mechanism involved, amphetamine (500 μg) was injected into the third ventricle in control cats as well as to preparations treated before amphetamine administration with yohimbine (0.5 mg/kg) and to others depleted of CNS monoamines with reserpine and α-methyl-*p*-tyrosine. As shown in the example presented in figure 4, the i.c.v. injection of saline (0.5 ml) frequently caused a transient depression of ciliary nerve activity which in all cases fully returned to control levels within 2 to 3 min. As can be seen in figure 4, and in the composite (fig. 5), i.c.v. amphetamine produced both a dramatic decrease in ciliary nerve activity, as measured on one side, as well as pupillary dilation of the opposite eye (both effects were antagonized by yohimbine). Unlike the i.v. administration, amphetamine by the i.c.v. route required approximately 15 to 20 min to exert a maximal and stable action. It is of interest that i.c.v. amphetamine administered to the yohimbine-treated group caused a slight pupillary constriction in two of four prepara-

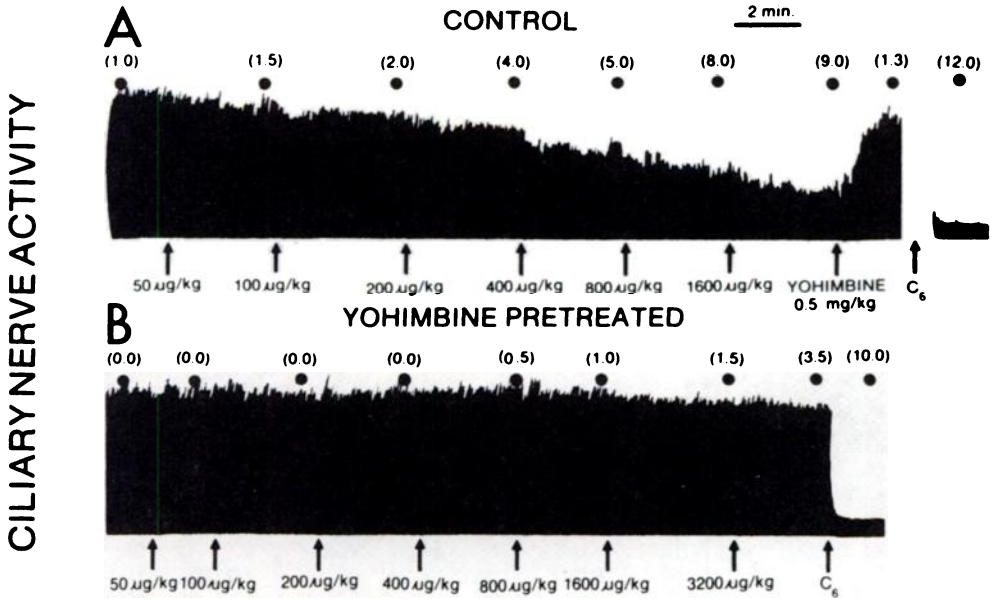

Fig. 2. Effect of cumulative i.v. injections of amphetamine on integrated short ciliary nerve activity in the anesthetized cat. Panel A represents control responses. Panel B shows responses in preparation treated with yohimbine (0.5 mg/kg i.v.) 10 to 15 min before amphetamine. Numbers below records are dosages of amphetamine, and numbers in parentheses indicate pupil diameter at point indicated. Recordings after hexamethonium (C_6; 20 mg/kg i.v.) show basal noise level in recordings.

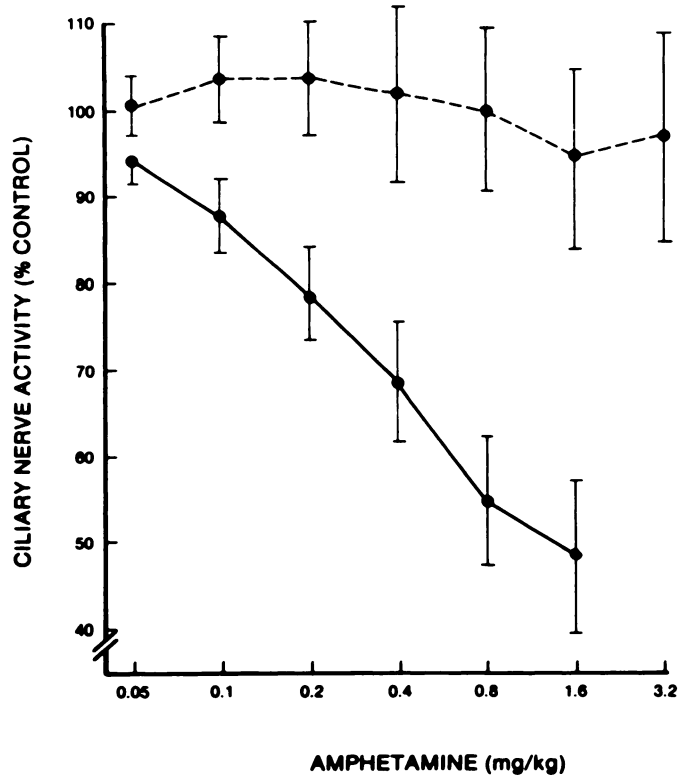

Fig. 3. Dose-response curves illustrating the effect of cumulative i.v. dosages of amphetamine on integrated potentials recorded from branch of lateral short ciliary nerve expressed as % control. Solid line (●——●) represents control preparations (n = 5). Dashed line (●- - -●) shows responses in preparations (n = 4) treated with yohimbine (0.5 mg/kg i.v.) before amphetamine. Note that one additional dose of amphetamine was administered to the group previously treated with yohimbine. Subsequent administration of yohimbine (0.5 mg/kg i.v.) reversed the amphetamine-induced depression of nerve activity in the control group. Values represent means ± S.E. In control animals, pupil diameter changed from 0.8 ± 0.6 to 9.9 ± 0.6 mm after the last dose (1.6 mg/kg) of amphetamine. Yohimbine constricted these amphetamine dilated pupils to 0.1 ± 0.5 mm. In the yohimbine pretreated group, initial mean pupil diameter was 0.0 and 1.3 ± 0.6 mm after amphetamine administration (3.2 mg/kg).

tions. A modest, although statistically insignificant, increase in nerve activity was observed in four of the five monoamine-depleted cats (fig. 5).

Effect of epinephrine on iris. In order to determine the effectiveness of yohimbine (0.5 mg/kg i.v.) in blocking the *alpha* adrenoceptors of the iris, epinephrine (0.3–10.0 µg/kg i.v.) was administered to four cats before and 10 to 15 min after being treated with yohimbine. As shown in table 1, epinephrine caused a dose-related pupillary dilation in these preparations which was not antagonized by this dose of yohimbine.

Discussion

The present results demonstrate that systemic administration of amphetamine to cats produces a dose-dependent mydriasis primarily by CNS inhibition of parasympathetic tone to the iris. This conclusion is in part based on the observations that yohimbine (0.5 mg/kg i.v.) effectively antagonized the amphetamine-induced pupillary dilation. Earlier studies have demonstrated a lack of effectiveness of small amounts of yohimbine in blocking the *alpha* adrenergic receptors of the iris. For example, Yonkman *et al.* (1944) reported that dosages of yohimbine of 5 to 6 mg/kg i.v. were necessary to antagonize epinephrine-induced mydriasis in the cat. The smallest effective dose was 2 mg/kg and the largest was 8 mg/kg. We have also reported that yohimbine (0.5 mg/kg) had no effect on neurally evoked nictitating membrane responses (Koss and Bernthal, 1979).

Existence of a CNS parasympatho-inhibitory action of amphetamine was further substantiated by nerve recording experiments. The observations that prior administration of yohimbine as well as CNS monoamine depletion prevent amphetamine depression of ciliary nerve activity and amphetamine mydriasis suggest that amphetamine acts indirectly to release a CNS inhibitory neurotransmitter (possibly norepinephrine).

Others, using less direct means, have suggested that the pupillary dilation seen after amphetamine administration is mediated, at least in part, by a CNS mechanism (Marley, 1961). Marley (1961) also demonstrated that high doses of amphet-

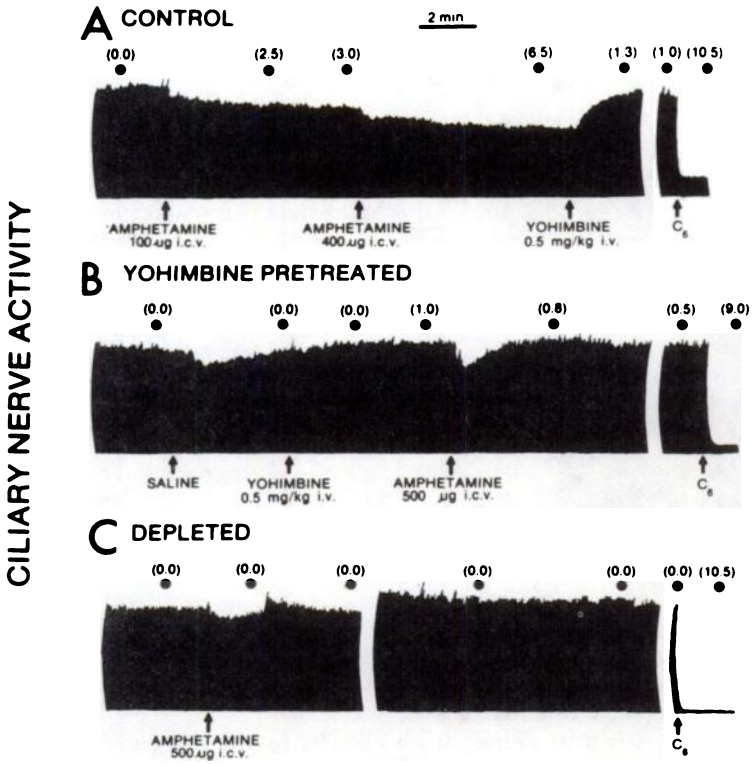

Fig. 4. Effect of i.c.v. amphetamine (500 µg in 0.5 ml) on integrated short ciliary nerve activity in chloralose anesthetized cats. Panel A is control. Note that in this one case the amphetamine dose was divided in order to demonstrate dose-related response. Panel B shows response in cat treated with yohimbine (0.5 mg/kg i.v.) before amphetamine and in panel C (depleted) the cat was previously depleted of CNS monoamines with reserpine (5 mg/kg i.p.) and α-methyl-p-tyrosine (2 × 300 mg/kg i.p.). The breaks in the record represent 10 to 15-min intervals. The C_6 (hexamethonium, 20 mg/kg i.v.) response is indicative of basal noise level in recording. Numbers in parentheses are pupil diameters read at point indicated.

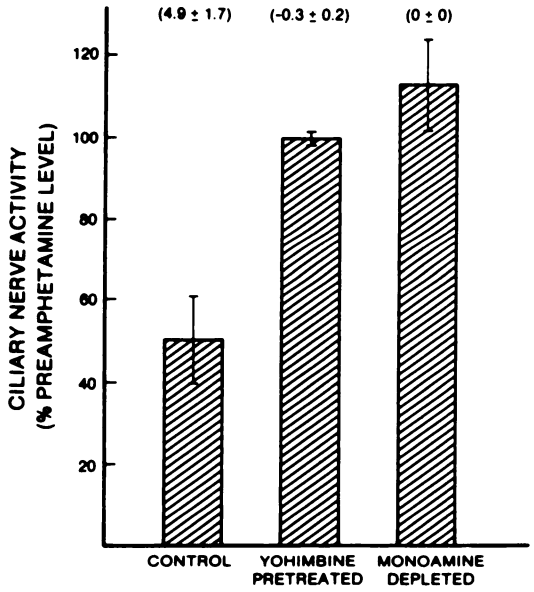

Fig. 5. Composite representation of effects of amphetamine (500 µg i.c.v.) on integrated ciliary nerve activity in nonpretreated control (n = 5), yohimbine pretreated (0.5 mg/kg i.v.; n = 4) and monoamine depleted (reserpine, 5 mg/kg i.p. and α-methyl-p-tyrosine, 2 × 300 mg/kg i.p.; n = 5) anesthetized cats. Yohimbine was administered 10 to 15 min before injection of amphetamine in the yohimbine pretreated group. Values represent means ± S.E. obtained approximately 15 to 20 min after amphetamine. Numbers in parentheses indicate change in pupil diameter at same time period. In the yohimbine pretreated group, yohimbine administration caused a slight but insignificant depression of nerve activity (to 86.5 ± 9.8% of initial value).

TABLE 1

Effect of epinephrine (0.3–10.0 µg i.v.) on pupillary diameter in control and yohimbine pretreated cats

Values represent mean pupillary dilation ± S.E.; dose of yohimbine pretreatment was 0.5 mg/kg i.v. administered 10 to 15 min before epinephrine, n = 4.

Dose of Epinephrine	Pupillary Dilation	
	Control	Yohimbine pretreated
µg i.v.	mm	
0.3	0.8 ± 0.6	1.5 ± 0.6
1.0	1.4 ± 0.8	2.1 ± 0.9
3.0	4.0 ± 0.5	4.3 ± 1.1
10.0	5.9 ± 0.6	6.0 ± 0.8

amine produced a further dilation of the pupils in anesthetized cats even after removal of parasympathetic tone to the iris. In this regard, it is likely that the direct effect of amphetamine on the iris could be potentiated in the absence of parasympathetic tone. In contrast to the present study, Marley (1961) claimed that after removal of the superior cervical ganglion, amphetamine produced mydriasis in unanesthetized but not in chloralose anesthetized cats. The reasons for such a discrepancy with the present results are not apparent.

Sharpe *et al.* (1977) observed that amphetamine (1.0 mg/kg i.v.) also produced pupillary dilation in unanesthetized, sympathectomized dogs. As the amphetamine mydriasis was only partially antagonized by a dose of phenoxybenzamine that completely blocked the effects of epinephrine and norepinephrine on the iris, they concluded that amphetamine must also be acting centrally to inhibit third nerve tone to the eye. If amphetamine is acting centrally, their reported lack of antagonism by phenoxybenzamine would be consistent with other findings. For example, the CNS sympatho-inhibitory action of clonidine (a putative stimulant of CNS *alpha* receptors) is antagonized by yohimbine and piperoxan (Kobinger, 1978; Schmitt *et al.*, 1973) but not by phenoxybenzamine. In one study, Schmitt and Schmitt (1970) found phenoxybenzamine to be almost without effect in blocking clonidine-induced depression of sympathetic nerve activity. We also have observed that yohimbine antagonizes the CNS-induced mydriasis of clonidine and depression of

ciliary nerve activity (Koss and San, 1976; Koss, 1979), but that 2 mg/kg i.v. phenoxybenzamine does not (unpublished observation).

The present observations regarding a CNS sympatho-inhibitory action for amphetamine are consistent with results using other drugs. For example, we have demonstrated that clonidine produces mydriasis by acting centrally to inhibit ciliary nerve tone and that it most likely exerts its action on central postsynaptic receptors (Koss and Christensen, 1979). It is possible that clonidine may be mimicking the action of an endogenous inhibitory neurotransmitter. In contrast, reserpine most likely produces miosis in the cat by removal of inhibitory influences to the Edinger-Westphal nucleus, as section of the parasympathetic (but not the sympathetic) innervation interrupted reserpine miosis (Hamel and Kaelber, 1961). Sigg and Sigg (1967) extended these findings by demonstrating that monoamine depletion prevented the inhibition of ciliary nerve potentials resulting from stimulation of several subcortical areas in spinalized cats. Nisida and Okada (1959) also reported that large doses of epinephrine decreased the firing of single fibers of the short ciliary nerve. In addition, Boakes *et al.* (1972) found that iontophoretic application of *d*-amphetamine mimicked the effects of norepinephrine on brain stem single neurons of acutely anesthetized rats. In these preparations, the action of amphetamine was abolished or reduced by pretreatment with either reserpine or α-methyl-*p*-tyrosine, suggesting that amphetamine acts by release of norepinephrine from presynaptic sites in the brain stem.

We have recently observed that clonidine (1–100 μg/kg i.v.) in the rat and α-methyldopa (30–100 mg/kg i.v.) in both the rat and cat caused a pupillary dilation which is yohimbine sensitive (unpublished observations). The mydriatic effect of clonidine was fully developed within 30 to 60 sec whereas the mydriasis in response to α-methyldopa required several hours to develop. These observations further support the conclusion that clonidine acts directly on CNS receptors and that α-methyldopa might be converted to an active metabolite. It is of interest that, in the rat, both serotonin and norepinephrine nerve terminals were found in the pretectal region whereas, of these two monoamines, only norepinephrine terminals were localized in the area of the Edinger-Westphal nucleus (Fuxe, 1965).

There are additional parallels between the effects of clonidine and amphetamine on the pupil and their respective actions on CNS sympatho-inhibition with regard to the cardiovascular system. For example, both clonidine and amphetamine (administered directly to the CNS) decreased sympathetic nerve activity and potentiated vagal reflexes in dogs and cats (Hoyer and van Zwieten, 1972; Schmitt *et al.*, 1973; Kobinger and Pichler, 1978) but only the effects of amphetamine were prevented by monoamine depletion (Hoyer and van Zwieten, 1972; Haeusler, 1974).

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