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Droperidol, a Selective Antagonist of Postsynaptic α-Adrenoceptors in the Canine Saphenous Vein

Mark Hyatt, B.S., Sheila M. Muldoon, M.D.,† Duane K. Rorie, M.D., Ph.D.‡*

Droperidol antagonizes postsynaptic α-adrenoceptors in blood vessels, yet clinical doses of this drug can induce hypertension when a pheochromocytoma is present. Whether droperidol can block presynaptic α-adrenoceptors, causing increased release of norepinephrine from adrenergic nerve endings, was examined in isolated canine saphenous vein segments using standard superfusion techniques. The helical strips of vein were first incubated in [7-^{3}H]*dl*-norepinephrine (2×10^{-7} M), then mounted for superfusion and isometric tension recording. [^{3}H]Norepinephrine and its metabolites were measured in superfusate collected during basal conditions and during release of [^{3}H]norepinephrine evoked by electrical stimulation (10 V; 2 msec duration; 1 or 2 Hz). In unstimulated veins, droperidol (3.9×10^{-7} M) increased the efflux of total radioactivity and of the norepinephrine metabolite, 3,4-dihydroxyphenylglycol; in addition to these changes, 3.9×10^{-6} M droperidol increased the efflux of norepinephrine and 3,4-dihydroxymandelic acid. Tension did not change. The increased efflux of norepinephrine and its metabolites was due to droperidol-induced nonexocytotic release of norepinephrine from intraneuronal storage vesicles. When electrically stimulated veins were exposed to droperidol (3.9×10^{-6} M), tension decreased, although [^{3}H]norepinephrine efflux was not different. During electrical stimulation of veins, addition of unlabeled norepinephrine to the superfusing fluid inhibited the overflow of total radioactivity; treatment of veins with droperidol (3.9×10^{-6} M) did not alter this effect. These studies indicate that droperidol, in the concentrations used, is an antagonist of the postsynaptic, but not of the presynaptic, α-adrenoceptor. Moreover, droperidol promotes a leakage of norepinephrine from intraneuronal storage vesicles. Indeed, this may be the mechanism by which this agent produces hypertension in patients who have pheochromocytoma. (Key words: Anesthetics, intravenous; droperidol. Receptors: sympathetic nervous system. Sympathetic nervous system: adrenergic transmission; alpha-adrenergic receptors; catecholamines, norepinephrine.)

DROPERIDOL has been shown to cause blockade of postsynaptic α-adrenergic responses in blood vessels *in vivo*[1,2] and *in vitro*.[3–5] It is unknown whether droperidol can cause blockade of presynaptic α-adrenoceptors. Because blockade of presynaptic α-adrenoceptors causes increased release of norepinephrine (NE) from sympathetic nerve terminals,[6,7] a presynaptic α-blocking action by droperidol is of particular interest, since droperidol has been shown to cause hypertension in patients who have proven pheochromocytoma.[8,9] Moreover, the cerebral vasoconstriction associated with droperidol[10] could be related to this action.

The present study was undertaken to determine whether droperidol could antagonize the presynaptic α-adrenoceptor. The canine saphenous vein was chosen to test this hypothesis because the existence of both pre- and postsynaptic α-adrenoceptors in this tissue has been demonstrated.[11]

Materials and Methods

The experiments were performed on helical strips (75–125 mg) of saphenous veins taken from dogs (15–25 kg) anesthetized with pentobarbital (30 mg/kg, iv). The vein strips were incubated for two hours in Krebs-Ringer's bicarbonate solution containing 2×10^{-7} M [7-^{3}H]*dl*-norepinephrine (NE) (specific activity: 8–13 Ci/mmol) (supplied by New England Nuclear, Boston, Mass.), disodium ethylenediaminetetraacetate (EDTA) (0.1 mg/ml), and ascorbic acid (0.2 mg/ml). At the end of incubation the strips were rinsed in Krebs-Ringer's bicarbonate solution; in certain experiments the latter contained cocaine (10^{-5} M). The veins were then mounted for superfusion. The preparations were suspended in a moist tunnel-shaped chamber maintained at 37 C. Each strip was superfused at 3 ml/min by a constant-flow roller pump with Krebs-Ringer's bicarbonate solution (*p*H 7.4), which was maintained at 37 C and aerated with 95 per cent O_2 and 5 per cent CO_2. The preparations were connected to a strain gauge for isometric tension recordings, the initial tension being set at 5.0 g. Tension gradually decreased and stabilized at approximately 3.0 g within 30 minutes. After stabilization, collection of the superfusate was started, and samples were taken at 2-minute intervals for direct estimation of total radioactive efflux. At selected 12-minute intervals, samples of the superfusate were collected into flasks that contained 10 μg of each of the following carriers: norepinephrine (NE), normetanephrine (NMN), 3,4-dihydroxymandelic acid (DOMA), 3,4-dihydroxyphenyl glycol (DOPEG), 3-methoxy-4-hydroxyphenyl glycol (MOPEG), 3-methoxy-4-hydroxymandelic acid (VMA). Also added to the collection flask was 1.0 mg

* Student, Mayo Medical School.

† Associate Professor of Anesthesiology. Present address: Uniformed Services University of the Health Sciences, Bethesda, Maryland 20014.

‡ Associate Professor of Anesthesiology.

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Address reprint requests to Doctor Rorie.

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TABLE 1. Effects of Droperidol on Tension, [^{3}H]NE, and [^{3}H]NE Metabolite Efflux* in the Unstimulated Saphenous Vein

	Tension (g)	Total ^{3}H	[^{3}H]NE	[^{3}H]NMN	[^{3}H]DOPEG	[^{3}H]DOMA	[^{3}H]OMDA
Control†	3.16 ± 0.21	14.70 ± 1.09	0.87 ± 0.06	0.57 ± 0.05	5.08 ± 0.45	0.60 ± 0.03	5.64 ± 1.00
Droperidol (3.9×10^{-6} M)	3.12 ± 0.21	21.90‡ ± 1.26	1.68‡ ± 0.08	0.62 ± 0.02	10.28‡ ± 0.62	0.95‡ ± 0.11	5.41 ± 0.78
Control	3.55 ± 0.29	19.94 ± 0.40	1.68 ± 0.23	1.20 ± 0.13	8.67 ± 0.85	1.25 ± 0.22	6.20 ± 0.13
Droperidol (3.9×10^{-7} M)	3.52 ± 0.31	21.71‡ ± 0.63	1.96 ± 0.22	1.14 ± 0.11	10.67‡ ± 0.93	1.18 ± 0.21	6.47 ± 0.46

* Values expressed as 10^3 dpm/6 ml of superfusate, mean ± SEM, n = 6 in each group.
† Control values represent averages of data obtained before and after administration of droperidol.
‡ Significant difference from the control, $P < 0.01$, Student t test for paired data.

sodium metabisulfite and 0.1 ml 2 N HCl. The samples were frozen at −23 C until column chromatographic analysis was performed.

ELECTRICAL STIMULATION

For electrical stimulation (ES) of the preparations, two platinum wire electrodes (0.5 mm wide, 10 cm long) were placed parallel to the preparations as previously described.[4,11] Electrical stimulation consisted of unidirectional rectangular impulses of 10 V, 2 msec pulse duration, and 1 or 2 Hz, provided by a direct-current power supply and a switching transistor (RCA 2N 3034) triggered by a Grass stimulator (Model S44). Both the electrodes and the vein strips were superfused continuously. Two 24- or 44-minute intervals of continuous ES were used.

COLUMN CHROMATOGRAPHY

Norepinephrine was separated from its metabolites in the superfusate by a modification[12] of the column chromatographic method of Graefe *et al.*[13] Briefly, this involves adsorption of catechols on alumina at *p*H 8.4, followed by a differential elution from the alumina of NE and DOPEG in the same fraction, and then DOMA. Subsequently, amines are separated from neutral and acidic compounds in the effluent and the eluate by using the cation-exchange resin, Dowex 50®. The O-methylated deaminated metabolites, MOPEG and VMA, were collected together and are referred to as OMDA. Recoveries of 20 μg [^{3}H]NE, [^{3}H]NMN, [^{14}C]DOPEG, [^{14}C]VMA, [^{14}C]MOPEG, and DOMA (fluorometric assay), and their interferences in other fractions, were determined previously.[12] Recoveries were as follows: [^{3}H]NE, 84.5 per cent ± 0.3; [^{3}H]-NMN, 83 per cent ± 1.3; [^{14}C]DOPEG, 73.6 per cent ± 1.3; [^{14}C]MOPEG, 96 per cent ± 1.2; [^{14}C]VMA, 69.0 per cent ± 1.1; DOMA, 81.1 per cent ± 0.5. The results are corrected for these recoveries.

RADIOACTIVITY MEASUREMENTS

Aliquots (1 ml) of superfusate and of the effluents and eluates from the columns were added to 10 ml Insta-Gel® (Packard Instrument Co., Inc., Downers Grove, Illinois), and the radioactivity was measured in a liquid scintillation counter. Corrections for quenching were made with an external standard. The counting efficiency was approximately 35 per cent. Most of the samples were counted for 10 minutes, but the

TABLE 2. Effects of MAO Inhibition by Pargyline, and of Pargyline Plus Droperidol, on Tension, Spontaneous Efflux of [^{3}H]NE, and [^{3}H]NE Metabolites* in Unstimulated Veins

	Tension (g)	Total ^{3}H	[^{3}H]NE	[^{3}H]NMN	[^{3}H]DOPEG	[^{3}H]DOMA	[^{3}H]OMDA
Control	2.85 ± 0.31	14.89 ± 1.26	1.23 ± 0.24	0.91 ± 0.15	5.28 ± 0.44	0.92 ± 0.12	4.65 ± 0.63
Pargyline (1.5×10^{-4} M)	2.78 ± 0.32	7.09† ± 0.52	1.24 ± 0.18	1.30† ± 0.08	0.72† ± 0.11	0.70 ± 0.11	2.39† ± 0.31
Droperidol (3.9×10^{-6} M) and pargyline (1.5×10^{-4} M)	2.79 ± 0.33	13.34‡ ± 0.35	6.43‡ ± 0.63	2.19‡ ± 0.16	0.57 ± 0.10	0.70 ± 0.08	1.94 ± 0.32

* Values expressed as 10^3 dpm/6 ml of superfusate, mean ± SEM, n = 5 in each group.
† Significantly different from control, $P < 0.01$, Student t test for paired data.
‡ Significantly different from pargyline-treated preparations, $P < 0.01$, Student t test for paired data.

TABLE 3. Effects of Phenoxybenzamine (PBZ) and Droperidol on Tension, the Efflux of [^{3}H]NE, and [^{3}H]NE metabolites* during Electrical Stimulation-evoked Release

	Tension (g)	Total ^{3}H	[^{3}H]NE	[^{3}H]NMN	[^{3}H]DOPEG	[^{3}H]DOMA	[^{3}H]OMDA
Control	3.58 ± 0.33	20.41 ± 2.07	1.63 ± 0.14	0.73 ± 0.09	8.46 ± 1.50	1.11 ± 0.07	9.03 ± 1.05
Electrical stimulation (2 Hz, 10 V)	7.90† ± 0.55	48.10† ± 3.71	10.47† ± 0.91	7.44† ± 0.26	10.09† ± 1.25	2.90† ± 0.95	19.50† ± 1.32
Electrical stimulation (2 Hz, 10 V) and PBZ (1.8×10^{-4} M)	4.35‡ ± 0.30	108.23‡ ± 12.95	55.14‡ ± 7.09	9.71‡ ± 0.96	13.74 ± 2.38	4.11 ± 1.71	29.37‡ ± 3.82
Control	3.17 ± 0.10	18.94 ± 2.72	1.11 ± 0.16	0.72 ± 0.12	7.17 ± 1.12	1.37 ± 0.29	6.37 ± 1.40
Electrical stimulation (2 Hz, 10 V)	6.91† ± 0.79	47.90† ± 5.91	7.61† ± 1.19	5.30† ± 0.61	9.50† ± 1.16	3.49† ± 0.66	15.56† ± 2.87
Electrical stimulation (2 Hz, 10 V) and droperidol (3.9×10^{-6} M)	4.83‡ ± 0.41	57.05‡ ± 7.68	7.34 ± 1.33	3.69 ± 0.35	15.35‡ ± 1.88	4.92‡ ± 1.18	18.61‡ ± 3.73

* Values expressed as 10^3 dpm/6 ml of superfusate, mean ± SEM, n = 4 in each group.
† Significantly different from control, $P < 0.05$, Student t test for paired data.
‡ Significantly different from stimulation phase, $P < 0.05$, Student t test for paired data.

samples that contained [^{3}H]NE were counted long enough to reach 10,000 counts.

DRUGS

The following pharmacologic agents were used: cocaine hydrochloride (10^{-5} M), pargyline hydrochloride (1.5×10^{-4} M), and phenoxybenzamine (1.8×10^{-4} M). Droperidol concentrations (3.9×10^{-6} M and 3.9×10^{-7} M) used were made by adding aliquots of a 1.3×10^{2} M droperidol stock solution dissolved in 2.5×10^{-2} M tartaric acid to Krebs-Ringer's bicarbonate solution. The final molar concentrations of tartaric acid achieved were 7.5×10^{-6} M and 7.5×10^{-7} M. Preliminary experiments (n = 6) indicated that these concentrations of tartaric acid had no effect on α-adrenoceptors or on release of [^{3}H]NE or ^{3}H metabolites of NE. The concentration of droperidol used in these studies was selected because previous organ bath studies indicated that this concentration caused a marked shift to the right of the NE dose–response curve and a slight flattening of the maximal response when NE was added.[4] Clinical doses of droperidol range from 0.075 to 0.15 mg/kg.[2,14] It is calculated that these doses would yield plasma concentrations of droperidol from 10^{-6} M to 10^{-5} M in a 70-kg adult.

ANALYSIS OF DATA

For each group of experiments the number of strips reported is also the number of dogs used. The data are expressed as means ± SEM. For statistical evaluation of the data, the Student t test for paired observations was used. $P < 0.05$ was considered significant.

Results

UNSTIMULATED PREPARATIONS

Effects of Droperidol on Basal Efflux of [^{3}H]NE and [^{3}H]NE Metabolites. The efflux of total ^{3}H from six strips in the superfusate was greater after treatment with droperidol (3.9×10^{-6} M) for 10 minutes than during the control periods (table 1). Column chromatographic analysis of the superfusate revealed that the increase with droperidol treatment was due to a significant augmentation in efflux of [^{3}H]NE, [^{3}H]-DOPEG, and [^{3}H]DOMA. The O-methylated metabolites were not significantly altered. A lower concentration of droperidol (3.9×10^{-7} M) caused a smaller increase in the efflux of total ^{3}H; this was due to an increased efflux of [^{3}H]DOPEG.

Effect of Droperidol on Basal Efflux of [^{3}H] and [^{3}H]-NE Metabolites in the Presence of Monoamine Oxidase Inhibition. Five strips were superfused with pargyline (1.5×10^{-4} M) for 20 minutes and then exposed to a combination of pargyline and droperidol (3.9×10^{-6} M; table 2). During pargyline treatment, the efflux of total ^{3}H, and efflux of the deaminated metabolites [^{3}H]-DOPEG and [^{3}H]OMDA, were decreased; the efflux of [^{3}H]NMN was increased. Addition of droperidol increased effluxes of total ^{3}H, [^{3}H]NE and [^{3}H]-

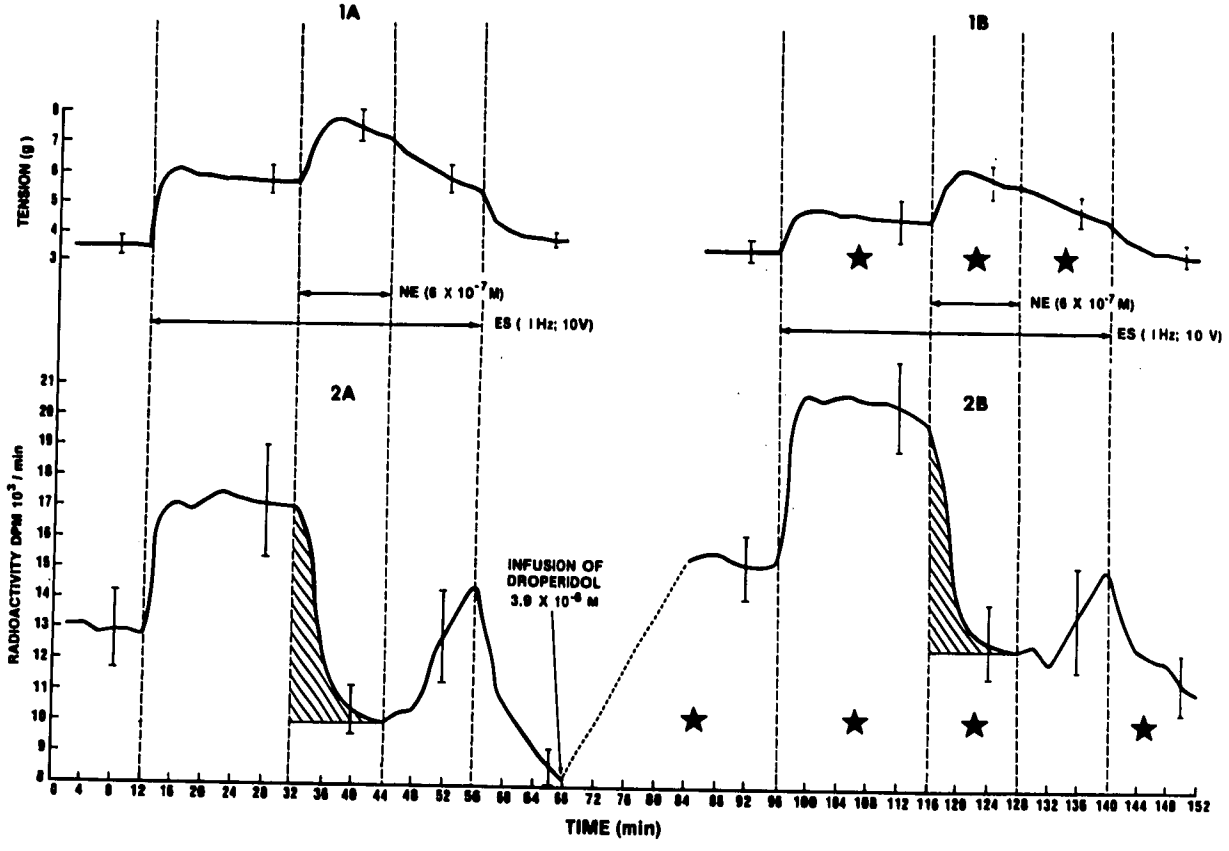

FIG. 1. The effect of exogenous NE (6×10^{-7} M) on the tension and efflux of total radioactivity in four canine saphenous vein strips prelabeled with [^{3}H]NE and stimulated at 1 Hz in the presence (*1B*, *2B*) and absence (*1A*, *2A*) of droperidol (3.9×10^{-6} M). These strips were treated with cocaine (10^{-5} M) throughout the experiment. Notice the increased basal efflux of total radioactivity after addition of droperidol to the superfusing fluid. The shaded portions are approximately equal in area and represent nearly identical negative feedback responses to exogenous NE. Values are expressed as means ± SEM. * Denotes a significant difference from control (*1A*, *2A*), $P < 0.05$, Student *t* test for paired data.

NMN. Despite the fivefold increase in [^{3}H]NE output with droperidol, tension did not change.

Stimulated Preparations

Droperidol and α-Receptor Antagonist Activity. Studies were designed to compare the actions of droperidol and the classic α-adrenoceptor blocker phenoxybenzamine (PBZ) on [^{3}H]NE release and metabolism in the saphenous vein (table 3). When PBZ (1.8×10^{-4} M) was infused between the 30th and the 48th minute during 2 Hz ES, it caused a marked augmentation in the release of [^{3}H]NE, which was accompanied by a significant increase in all O-methylated metabolites and a significant decrease in tension. When droperidol (3.9×10^{-6} M) was used instead of PBZ in the superfusing fluid, a smaller, yet significant, decrease in tension occurred, although [^{3}H]NE efflux did not increase. A concomitant small increase in total ^{3}H was observed, and this was due solely to increases in the deaminated and O-methylated deaminated metabolites.

Effects of Exogenous NE on Electrically Evoked Release of [^{3}H]NE in the Absence and Presence of Droperidol. After prelabeling with [^{3}H]NE, four saphenous veins were incubated for 20 minutes and then superfused with Krebs-Ringer's bicarbonate solution containing cocaine (10^{-5} M). When NE (6×10^{-7} M) was added to the superfusing fluid between the 20th and 32nd minute of ES (1 Hz), a marked inhibition of total ^{3}H release occurred, while tension increased further (fig. 1). Discontinuing NE infusion resulted in reversal of these effects.

When droperidol (3.9×10^{-6} M) was added to the Krebs-Ringer's bicarbonate superfusing fluid containing 10^{-5} M cocaine and these same strips of vein were superfused during basal condition with this solution for 20 minutes, increasing amounts of total ^{3}H were released during this interval, although no change in tension occurred. When 1 Hz ES was applied to the cocaine- and droperidol-treated strips, the tension response was depressed significantly, although inhibition by exogenous NE of the efflux of total ^{3}H was not altered (fig. 1).

Discussion

The present studies indicate that droperidol, in the concentrations used, (1) promotes a non-exocytotic efflux or "leakage" of NE, presumably from intraneuronal NE storage vesicles, and 2) is an antagonist of the postsynaptic α-adrenoceptor, but is not an antagonist of the presynaptic α-adrenoceptor.

Presynaptic α-adrenoceptors have been proposed to be part of a negative-feedback system through which NE modulates its own release.[6,7] It has been suggested that NE accumulates in the synaptic cleft until a concentration is reached that is capable of activating presynaptic α-adrenoceptors. Activation of these receptors then leads to attenuation of further NE release.[6,7] In contrast, blockade of presynaptic α-adrenoceptors results in uninhibited NE release.[6,7]

The attenuated tensions that developed in electrically stimulated, droperidol-treated, canine saphenous veins in the absence of decreased [^{3}H]NE release (table 3) substantiate previous observations indicating that droperidol is an antagonist of the postsynaptic α-adrenoceptor. Since the release of [^{3}H]NE did not increase during ES in the presence of droperidol treatment, these studies suggest that droperidol does not antagonize the presynaptic α-adrenoceptor. Additional evidence suggesting that droperidol is not an antagonist of the presynaptic α-adrenoceptor is provided by the studies demonstrating the existence of a presynaptic regulation of NE release through a negative-feedback mechanism (fig. 1). In these, infusion of droperidol did not prevent unlabeled NE from inhibiting total radioactivity entering the superfusate. This indicates that presynaptic α-adrenoceptors were not antagonized. In contrast, PBZ, a known antagonist of both pre- and postsynaptic α-adrenoceptors,[6] caused a reduction in tension with ES and a concomitant increase in the release of [^{3}H]NE (table 3). This indicates that the effect of presynaptic α-adrenoceptor blockade (increased release of NE) is prevented from causing an increased contractile response due to the potent blockade of postsynaptic α-adrenoceptors by PBZ. That PBZ preferentially antagonizes the postsynaptic α-adrenoceptor has been reported previously.[6]

In order to detect activation of presynaptic α-adrenoceptors, it was necessary to enhance the accumulation of NE at receptor sites in the vein preparations by blocking neuronal uptake of NE with cocaine, 10^{-5} M, a concentration of cocaine shown by Hughes[15] to be without a local anesthetic effect. If cocaine is present during infusion of exogenous NE, the synaptic cleft concentration of NE will rise, and activation of presynaptic α-adrenoceptors with inhibition of NE release will occur. When cocaine is absent, the exogenous NE will be taken up and some [^{3}H]NE will be displaced from its intraneuronal stores by the exogenous NE.[11] Thus, the net result will be to mask the effect of activation of presynaptic α-adrenoceptors.

Increases were observed in the efflux of total ^{3}H from unstimulated (table 1) as well as from electrically stimulated veins (table 3) upon addition of droperidol. It appeared unlikely that these effects could be attributed to blockade of presynaptic α-adrenoceptors, and an action of droperidol in addition to its effects on postsynaptic α-adrenoceptors became apparent. Analyses of superfusates collected during ES of droperidol-treated veins indicated that the increase in total ^{3}H overflow was due primarily to [^{3}H]-DOPEG, with lesser increases in [^{3}H]DOMA and [^{3}H]-OMDA (table 3). That the increased total ^{3}H release consisted predominantly of deaminated metabolites suggested that increased amounts of NE were being acted upon by monoamine oxidase (MAO). Direct evidence supporting this theory came from studies in which MAO was inhibited with pargyline (table 2). When veins were superfused with pargyline alone, total ^{3}H release decreased due to decreases in [^{3}H]-DOPEG and [^{3}H]OMDA. In contrast, a combination of pargyline and droperidol increased the total ^{3}H release into the superfusate with marked increases in [^{3}H]NE and [^{3}H]NMN, with no change in deaminated metabolites. Tension did not change. That droperidol renders the membrane of intraneuronal NE storage vesicles "leaky" so that increased amounts of NE escape into the cytoplasm from these vesicles and come in contact with MAO has been proposed previously.[4] These data support this concept.

That reported instances of hypertension developing after administration of droperidol might be secondary to a blockade of neuronal uptake of NE has been proposed previously.[8] Although this postulate was not examined directly in our studies, the lack of a potentiation of the efflux of [^{3}H]NE when droperidol was added to the superfusate during ES (table 3) indicates that in the concentrations used, droperidol does not block neuronal uptake of NE.

Since we were unable to demonstrate a droperidol antagonism of presynaptic α-adrenoceptors, we concluded that this mechanism must be considered to be an unlikely cause of cases of hypertension associated with this agent. However, we found that droperidol did induce a leakage of NE, presumably from intraneuronal storage vesicles. Although this action did not cause vasoconstriction in our preparation (due to the presence of postsynaptic α-adrenoceptor blockade and to deamination of released NE by intraneuronal MAO), it could induce an outpouring of catecholamines in patients with pheochromocytoma. The increased catecholamine release comes either from the

tumor or from expanded releasable stores of catecholamines in the sympathetic nerve endings, as has been suggested,[16] due to the constant exposure of the nerve endings to abnormally high concentrations of catecholamines in plasma. Moreover, this increase in releasable stores of catecholamines may explain why droperidol causes hypertension in some patients who have pheochromocytoma and does not in normal patients.

The results of this study indicate that, because of the propensity of patients with pheochromocytoma to become hypertensive upon receiving droperidol, neuroleptanalgesia with droperidol should be used with caution in these patients or in patients with hypertension.

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