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Mechanism of the Effect of Droperidol to Induce Catecholamine Efflux from the Adrenal Medulla

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The study was undertaken to determine whether droperidol had an effect to induce catecholamine efflux from the adrenal medulla as a mechanism for the possible pressor effect of droperidol in patients with pheochromocytoma and, if so, to ascertain the site of action of this compound. The efflux of catecholamines from perfused dog adrenals was increased from control level, 0.15 μg/min, to 0.66 μg/min by the administration of droperidol 6.6 μM. This effect of droperidol was not dependent on extracellular Ca^{++}, in contrast to acetylcholine. The concomitant secretion of catecholamines and dopamine-β-hydroxylase was observed in response to acetylcholine and caffeine. However, droperidol-, histamine-, and reserpine-induced catecholamine efflux was not accompanied by dopamine-β-hydroxylase release. In additional studies, chromaffin granules were isolated with a Millipore® filter technique from the bovine adrenal medulla and were incubated for 10 min in an isotonic medium to examine the direct effects of droperidol. Droperidol did not enhance the efflux of catecholamines from the granules in contrast to histamine. The upake of ^{14}C-norepinephrine into the granules was inhibited by droperidol in a manner comparable to reserpine. The results suggest that droperidol induces catecholamine efflux from adrenal medullary cells and the efflux probably is caused by a nonexocytotic mechanism. A contributing mechanism was an inhibition of catecholamine uptake into chromaffin granules, resulting in an increased diffusion of catecholamines out of the cell. (Key Words: Anesthetics, intravenous: droperidol. Sympathetic nervous system: adrenal medulla; catecholamines; chromaffin granule.)

IT HAS BEEN REPORTED that droperidol occasionally is associated with extreme hypertension in patients with pheochromocytoma.[1-3] Although it has not been well established whether this hypertension could be caused by a specific pharmacologic action of droperidol, it is considered possible, as a mechanism of this action, that droperidol might promote catecholamine release from the tumor cells or sympathetic nerve endings,[2,4] or might inhibit the uptake of catecholamines into the nerve terminals,[2,5] resulting in a hypertensive response. Further investigations are necessary to obtain conclusive answers.

The present study was undertaken to determine whether droperidol induces catecholamine efflux from adrenal medullary cells and, if so, to ascertain the site of action of this compound.

Materials and Methods

Perfusion Experiment

The details of the procedure for perfusing dog adrenals have been described previously.[6] In brief, mongrel dogs of either sex weighing 9–13 kg were anesthetized with sodium pentobarbital (30 mg/kg iv or ip). Both adrenals were exposed through a midline abdominal incision and isolated outside the body together with the adrenolumbar vein. The adrenolumbar vein was cannulated, and the glands were perfused retrogradely at a pressure ranging from 45 to 80 cmH_2O with a warmed (37° C) modified Locke's solution aerated with 95% O_2 and 5% CO_2. The solution was composed as follows (in mM): NaCl 154, KCl 5.6, $CaCl_2$ 2.2, glucose 10 and TRIS–HCl buffer 40–pH 7.4. In some experiments, a solution free of $CaCl_2$ was used. Perfusion was carried out at a constant rate, ranging from 0.9 to 1.3 ml/min, in each experiment. About 80 min were allowed to elapse before any treatment for reduction of the spontaneous efflux of catecholamines. Drugs dissolved in Locke's solution were administered by continuous infusion by switching a valve on the tubing leading to the glands. The adrenals were perfused with the following drugs: droperidol 1.7–13.2 μM, histamine 1 mM, reserpine 10 μM, acetylcholine 3 μM, and caffeine 10 mM. The perfusion period was 10 min. The perfusions with histamine, caffeine, and reserpine were carried out in the absence of extracellular Ca^{++} to confirm that the catecholamine effluxes induced by these compounds were not dependent on extracellular Ca^{++}, while those of droperidol and acetylcholine were carried out both in the presence and absence of extracellular Ca^{++}. Only one drug was examined in each adrenal, and at least

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three experiments were done for each drug and for each concentration using different adrenals.

The effluent from the adrenals was collected into glass tubes kept on ice at 2-min intervals that started 2 min prior to the drug administration, and lasted for 12 min. Catecholamine content was measured by the trihydroxyindole method without further purification on alumina[6,7] (analysis 1). In some experiments, the catecholamines also were measured by semiautomated fluorimetric analysis after purification on alumina[8] (analysis 2) to exclude a contaminated analysis of catechol-o-methylated metabolites and DOPA. Dopamine-β-hydroxylase (DBH) activity in the effluent was measured by the method of Nagatsu and Udenfriend,[9] in which tyramine was used as substrate, and the octopamine formed was assayed by spectrophotometry. A 0.8-ml aliquot of each fraction was used for the assay, and DBH activity was expressed as nanomoles of product (octopamine) formed per milliliter of effluent per hour ($nmol \cdot ml^{-1} \cdot h^{-1}$). It was ascertained that the drugs used did not interfere with the assay of catecholamines and DBH activity. Drug-induced catecholamine efflux was calculated as the difference between spontaneous catecholamine efflux and efflux during drug administration.

Granule Experiment

Chromaffin granules were prepared from fresh bovine adrenal medulla as described previously[10] and were suspended with isotonic sucrose solution (0.3 M sucrose, 40 mM TRIS–HCl buffer, *p*H 7.4). The methodologic details for determining catecholamine uptake and efflux in isolated granules have been described previously.[11]

The incubation medium for measuring the uptake of norepinephrine consisted of 0.3 M sucrose, 4 mM adenosine triphosphate (ATP), 2 mM $MgSO_4$, 40 mM TRIS–HCl buffer (*p*H 7.4), 4 μM dl-[7-^{14}C]-norepinephrine (6.24×10^5 cpm) in the presence or absence of 3.3 – 13.2 μM droperidol and 0.12 μM reserpine, at a volume of 3 ml in 7-ml polyethylene centrifuge tubes. Six experiments were performed for each drug concentration. The tubes were kept at 37° C for 5 min in a water bath, and the reaction was started by adding 0.1 ml granule preparation (2.5 mg protein, 450 μg catecholamines) to the medium and was carried out at 37° C for 10 min without shaking. After incubation, the tubes were cooled in an ice water bath, and the granules were precipitated by centrifugation at 20,000 $\times g$ for 10 min at 2° C. Radioactive norepinephrine was extracted from the precipitate with 0.4 N perchloric acid and counted in a liquid scintillator. The identity of the labeled material in the tubes after incubation was examined with adsorbtion on Dowex-50 column,[12] and 98% of radioactivity was recovered as norepinephrine.

To determine catecholamine efflux, granules were suspended with isotonic KCl solution (150 mM KCl, 40 mM TRIS–HCl buffer, *p*H 7.4). The incubation medium contained isotonic KCl solution in the presence or absence of 3.3 – 13.2 μM droperidol and 1 mM histamine at a final volume of 3 ml in 7-ml centrifuge tubes. Six experiments were performed for each drug concentration. After the tubes had been held in a water bath at 37° C for 5 min, the reaction was initiated by the addition of 0.1 ml of the granule preparation. The reaction was carried out at 37° C for 10 min. After incubation, the tubes were cooled in an ice water bath and centrifuged at 20,000 $\times g$ for 10 min at 2° C. The supernatant was made up to 0.4 N perchloric acid to precipitate protein, and catecholamine content was measured fluorimetrically by the trihydroxyindole method with purification on alumina.[6,7] It was ascertained that the drugs used did not interfere with the assay. This protocol could assay the catecholamine efflux separately from the uptake, because, in the absence of ATP-Mg^{++}, catecholamines were not taken up into granules, whereas efflux could occur.[11]

Statistical Analysis

The data were expressed as mean ± SE. The results of repeated measures and multiple groups were analyzed by one-way analysis of variance. Multiple pairwise comparisons between groups were assessed by a Bonferroni *t* test. A P value < 0.05 was considered significant.

Results

The results of the two kinds of catecholamine analysis were compared as shown in table 1. Analysis 1 is the trihydroxyindole method without purification on alumina and has a sensitivity of 2 ng.[7] Analysis 2 is a semiautomated method using high-performance liquid chromatography with purification on alumina and has a high specificity and a sensitivity of 20 pg.[8] Analysis 1 also measures catechol-o-methylated metabolites and DOPA in addition to catecholamines, however, the results show that there was no significant contamination of such metabolites in analysis 1. The catecholamine efflux in the perfusion experiment routinely was assayed with analysis 1.

Catecholamine and DBH Efflux from the Perfused Adrenals

Spontaneous efflux of catecholamines during the 2-min period prior to drug administration amounted to 0.15 ± 0.04 μg/min (mean ± SE, n = 5). During

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TABLE 1. Comparison of the Two Kinds of Analysis for Basal, Droperidol-induced, and Acetylcholine-induced Efflux of Epinephrine (E) and Norepinephrine (NE) (Mean ± SE; n = 3 for Each Value) (Analysis 1 is the trihydroxyindole method without purification on alumina. Analysis 2 is a semiautomated method with purification on alumina.)

	Peak Efflux of Catecholamines (ng/min)					
	Basal		Droperidol Induced		Acetylcholine Induced	
	E	NE	E	NE	E	NE
Analysis 1	147 ± 23	21 ± 3	512 ± 69	78 ± 12	933 ± 158	162 ± 27
Analysis 2	163 ± 27	20 ± 3	539 ± 73	75 ± 13	1004 ± 184	175 ± 31

the drug administration period with droperidol, 6.6 μM, the catecholamine efflux increased gradually and attained its maximum within 4–6 min. The peak rate of efflux was 0.66 ± 0.08 μg/min. DBH activity in the perfusate before administration was 5.7 nmol · ml^{-1} · h^{-1}, and this showed no change during the droperidol administration period (fig. 1). Histamine and reserpine also enhanced catecholamine efflux, and, in the same manner as droperidol, did not cause DBH release. Both acetylcholine- and caffeine-induced catecholamine efflux were accompanied by simultaneous DBH release. The peak rate of DBH release was 21.7 nmol · ml^{-1} · h^{-1} with acetylcholine and 17.3 nmol · ml^{-1} · h^{-1} with caffeine, respectively (fig. 1).

Catecholamine effluxes induced by acetylcholine and droperidol were examined in the presence and absence of extracellular Ca^{++}. As shown in table 2, acetylcholine failed to induce catecholamine efflux in the absence of extracellular Ca^{++}, whereas droperidol-induced catecholamine efflux was not affected by the absence of extracellular Ca^{++}.

The dose–effect relationship regarding the effect of droperidol on catecholamine efflux was examined (fig. 2). Droperidol exhibited the effect at concentrations of

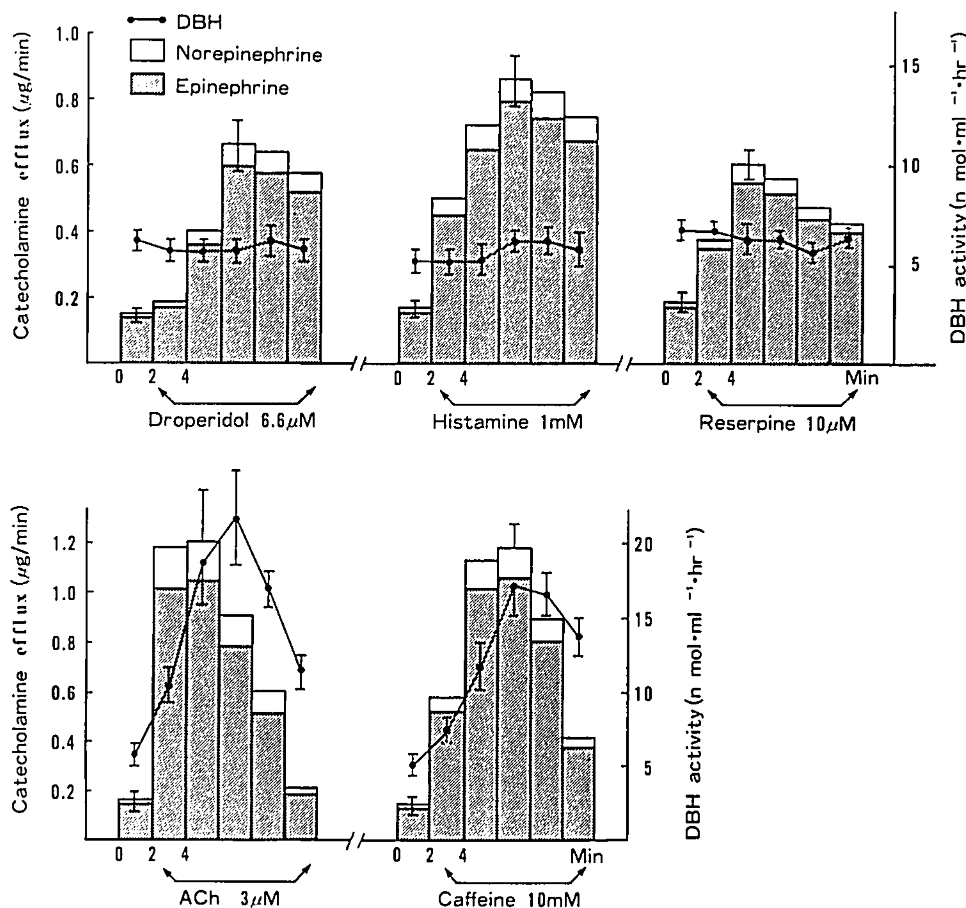

FIG. 1. The efflux of catecholamines and dopamine-β-hydroxylase (DBH) from the dog adrenal medulla by the administration of droperidol, histamine, reserpine, acetylcholine, and caffeine. Isolated dog adrenals were perfused retrogradely with a modified Locke's solution at 37° C, and one of these drugs was administered for 10 min. The ordinates represent both the rate of catecholamine efflux during a 2-min period and DBH activity of the effluent. Activity of DBH is expressed as nanomoles of octopamine formed from tyramine per milliliter of effluent per hour (n = 4 for each value, mean ± SE). Catecholamine efflux was increased significantly ($P < 0.01$) by each of five drugs. DBH efflux was increased significantly ($P < 0.01$) by acetylcholine and caffeine but not by the others.

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TABLE 2. Acetylcholine- and Droperidol-Induced Catecholamine Release from the Dog Adrenal Medulla in the Presence or Absence of Extracellular Ca^{++}

	Catecholamine Release (μg/10 min, Mean ± SE)	
	2.2 mM [Ca^{++}]	0 mM [Ca^{++}]
Acetylcholine 3 μM	6.5 ± 0.6 (n = 4)	1.5 ± 0.3* (n = 3)
Droperidol 6.6 μM	3.3 ± 0.4 (n = 4)	3.1 ± 0.4 (n = 3)

* Statistically significant change ($P < 0.01$ from the 2.2 mM [Ca^{++}] value.

more than 3.3 μM, attaining its maximum effect at 6.6 μM.

Catecholamine Uptake and Efflux in Isolated Chromaffin Granules

Droperidol at concentrations of 3.3 μM or more inhibited the uptake of ^{14}C-norepinephrine into the granules in a dose-dependent manner, *i.e.*, the uptake was decreased to 86% of control by 3.3 μM droperidol and to 67 and 56% of control by 6.6 and 13.2 μM droperidol, respectively. Reserpine, 0.12 μM, also decreased the uptake to 43% of control (fig. 3).

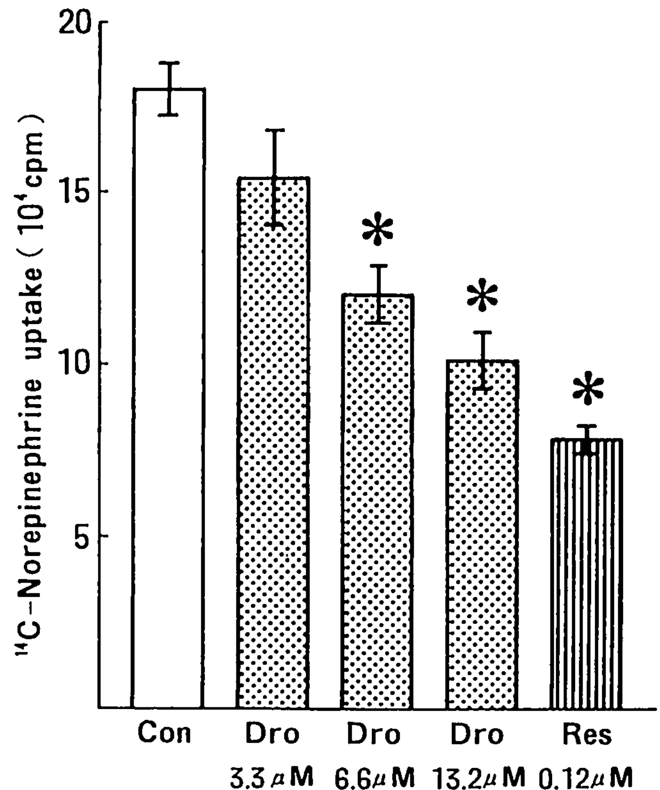

FIG. 3. Effect of droperidol (Dro) and reserpine (Res) on ^{14}C-norepinephrine uptake into the chromaffin granules in comparison with control (Con) condition ($n = 6$ for each value, mean ± SE). Granules were incubated at 37° C for 10 min with dl-[7-^{14}C]-norepinephrine, ATP-Mg^{++}, and various concentrations of droperidol and reserpine in isotonic sucrose medium. *$P < 0.01$, compared with control.

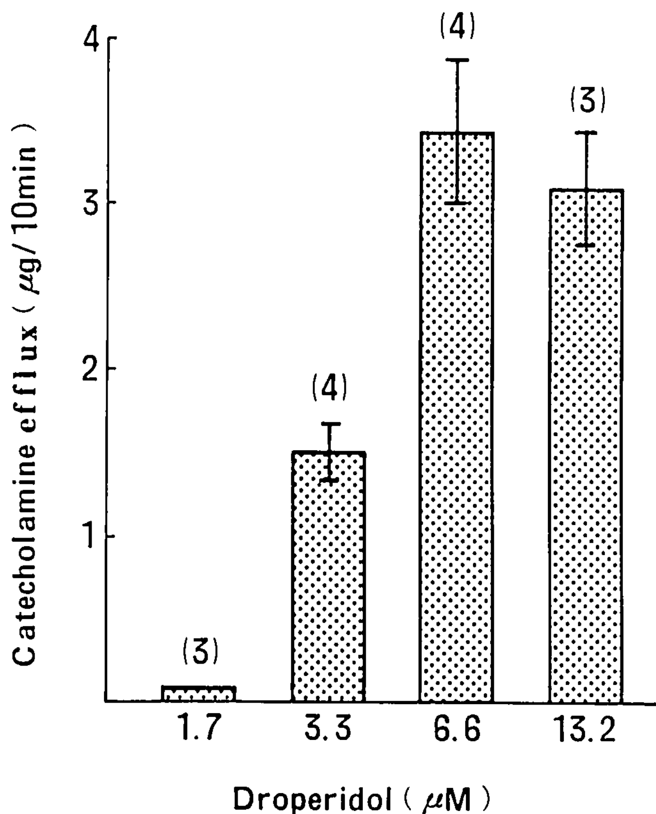

FIG. 2. Effect of droperidol on catecholamine efflux from the perfused dog adrenal medulla (mean ± SE). The ordinate represents the efflux of catecholamines during a 10-min administration period. The number of experiments is indicated by the figure in parentheses. Catecholamine efflux was increased significantly ($P < 0.01$) by 3.3–13.2 μM droperidol.

Spontaneous catecholamine efflux from isolated chromaffin granules incubated in isotonic KCl solution for 10 min at 37° C amounted to 24.5% of the total catecholamines in the granules. Droperidol at concentrations of from 3.3 to 13.2 μM exerted no action on catecholamine efflux from the granules. On the other hand, histamine, 1 mM, enhanced the catecholamine efflux significantly (fig. 4).

Discussion

The present results show that droperidol increases the efflux of catecholamines from the adrenal medulla. This effect of droperidol does not depend on extracellular Ca^{++} in contrast to acetylcholine, which is the physiologic transmitter for the adrenal medulla and needs extracellular Ca^{++} to exert its action. It has been well established that Ca^{++} is the coupler for the stimulus-secretion coupling of the adrenal medullary cells and that the entry of Ca^{++} into the cell triggers exocy-

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totic secretion of catecholamines.[13] In order to determine whether exocytosis is involved in the droperidol-induced catecholamine efflux in spite of a lack of dependency on extracellular Ca^{++}, the effect of droperidol on DBH release was examined and compared with the effects of acetylcholine, caffeine, histamine, and reserpine, since DBH release with catecholamines has been regarded as biochemical evidence for the exocytotic release of catecholamines.[13] The concomitant secretion of catecholamines and DBH was observed in response to stimulation by caffeine and acetylcholine. However, histamine-, reserpine-, and droperidol-induced catecholamine efflux was not accompanied by DBH release. It was suggested that caffeine evoked catecholamine release by mobilization of intracellular Ca^{++},[14] and the present results support this concept, *i.e.*, caffeine induces exocytotic release of catecholamines using intracellular Ca^{++}. On the other hand, it is considered probable that droperidol-, histamine-, and reserpine-induced catecholamine efflux involves a nonexocytotic mechanism.

These results have confirmed those of Muldoon *et al.*[15] and Hyatt *et al.*[4] Muldoon *et al.*[15] demonstrated that, in the absence of nerve stimulation, droperidol augmented the efflux of deaminated metabolites in isolated canine pulmonary arteries previously incubated with ^{3}H-norepinephrine. Recently, Hyatt *et al.*[4] also observed a similar phenomenon, *i.e.*, in canine saphenous veins, droperidol increased the efflux of ^{3}H-norepinephrine and its metabolites. Contrary to their results, we did not observe a significant efflux of metabolites. The reasons for this discrepancy might be ascribed to differences in organs and catecholamines used in these experiments, *i.e.*, they measured an exogenous catecholamine and its metabolites, whereas we measured endogenous catecholamines. In fact, there is ample evidence that blood vessels are equipped with enzymatic mechanisms that dispose in an efficient way of exogenous catecholamines.[16]

It has been suggested that droperidol might induce a nonexocytotic efflux of norepinephrine from the sympathetic nerve endings,[4,15] however, the mechanism of action remained unknown until now. In the present experiments, in order to determine the site of action of droperidol in the adrenal medullary cells, we have examined the direct effect of droperidol on the adrenal medullary granules as compared with those of histamine and reserpine. Droperidol does not enhance the efflux of catecholamines from the granules, in contrast to histamine. Although the mechanism of histamine-induced catecholamine efflux from the chromaffin granules is not clear, it seems likely that histamine may change places with catecholamines in the storage complex composed of catecholamines, ATP, and chromogranin because of its similar structure to catecholamines. On the other hand, the uptake of norepinephrine into the granules was inhibited by droperidol in a manner comparable to reserpine. This inhibition of catecholamine uptake would cause a change in the dynamic equilibrium between the efflux and uptake of catecholamines in the chromaffin granules, resulting in an increase in catecholamine concentration in the cytoplasm and greater exposure of catecholamines to the action of metabolic enzymes. Thus, this finding would explain the phenomenon observed by Muldoon *et al.*[15] and Hyatt *et al.*[4] Furthermore, the increased amount of catecholamines in the cytoplasm would lead to the diffusion of these catecholamines out of the cell. This mechanism of efflux could explain the results of the perfusion experiment in which the catecholamine efflux induced by droperidol was not accompanied by DBH release.

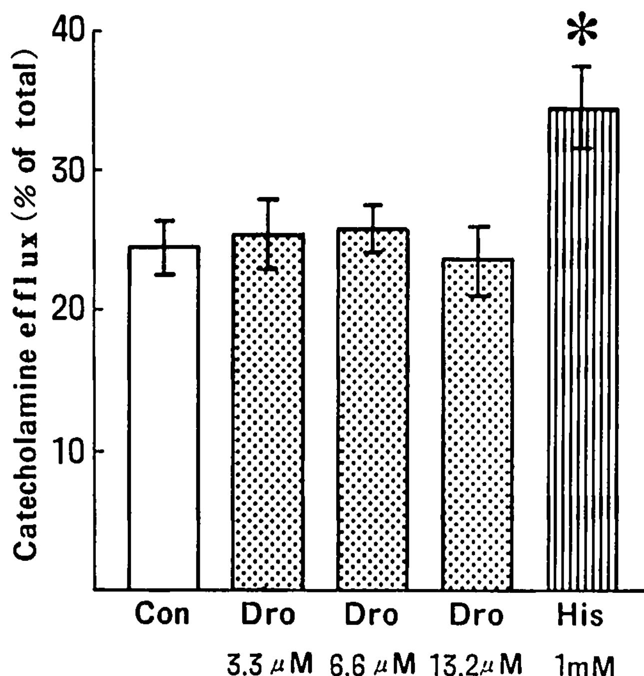

FIG. 4. Effect of droperidol (Dro) and histamine (His) on catecholamine efflux from the chromaffin granules in comparison with control (Con) condition ($n = 6$ for each value, mean ± SE). Granules were incubated at 37° C for 10 min in isotonic KCl medium containing various concentrations of droperidol and histamine. The ordinate represents the efflux of catecholamines as a percentage of the total catecholamines in the granules. *$P < 0.05$, compared with control.

This mechanism of action of droperidol might appear in pheochromocytoma cells in an amplified manner because the turnover of catecholamines in the pheochromocytoma cells is far more rapid than that in the normal adrenal medulla,[17] *i.e.*, the amount of catecholamines secreted per day is 3% of the catecholamine content of the normal human adrenal medulla,[17] whereas higher amounts are secreted from pheochromocytomas, and, indeed, values of up to 768% have

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been reported.[18] Furthermore, in pheochromocytoma cells, catecholamines possibly are released by diffusion across the cytoplasm out of the cell because tumor cells are devoid of innervation.[17] We speculate that this mechanism of release in tumor cells might be enhanced by droperidol and that the higher the turnover rate of catecholamines, the more pronounced the effect of droperidol on the cells.

It has been proposed previously that the pressor effect of droperidol might be secondary to a blockade of neuronal uptake of norepinephrine.[2] Satoh *et al.*[19] have demonstrated by fluorescent histochemistry using the left atrial strip of the rabbit that droperidol had an inhibitory action on norepinephrine uptake into the adrenergic terminal. Using a similar method, Oh *et al.*[5] also have demonstrated that droperidol is an inhibitor of neuronal uptake of norepinephrine in the perfused rabbit ear artery. However, on the basis of the experiment with an animal model of pheochromocytoma in which droperidol was compared with desmethylimipramine, they have concluded that it is unlikely that blockade of norepinephrine uptake is the major mechanism of droperidol-induced hypertension. The reason why this effect of droperidol was not exhibited *in vivo* could be attributed to the far higher concentration of droperidol used in the *in vitro* study, *i.e.*, the concentration used to inhibit the neuronal uptake of norepinephrine was 500 μM,[5] whereas it was calculated that clinical doses of droperidol range from 0.075 to 0.15 mg/kg in Japan, although these might be larger doses than customary in the United States, and would yield plasma concentrations of 1–10 μM.[4] By contrast, the concentrations used in the present study do not deviate from the clinical dose range of droperidol.

In conclusion, droperidol promotes catecholamine efflux from adrenal medullary cells. The efflux probably is caused by a nonexocytotic mechanism. The mechanism does not involve an enhancement of catecholamine efflux from chromaffin granules but rather an inhibition of catecholamine uptake into the granules. Such inhibition changes the dynamic equilibrium between the efflux and uptake of catecholamines in the granules, resulting in an increase in the diffusion of catecholamines out of the cell. This phenomenon might occur in an exaggerated manner in pheochromocytoma cells.

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