In summary, α-adrenergic stimulation elicited a rapid release of K^+ from dispersed parotid acinar cells in the presence of external Ca^{2+}. A recent classification of α-adrenergic receptors proposed that α_1 receptors facilitate Ca^{2+} entry while α_2 receptors interact with adenylate cyclase. We tested this proposal by studying the ability of selective α-adrenergic antagonists to prevent epinephrine-induced release of K^+ from parotid cells. The α_1 agents, WB 4101 and prazosin, were less potent than the α_2 antagonist yohimbine. These data suggest that α_2-adrenergic receptors in the parotid might facilitate the entry of Ca^{2+}.

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Effect of haloperidol pre- and post-treatment on the ability of pergolide and bromocriptine to antagonize the γ-butyrolactone-induced increase in brain dopamine in rats

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Recently, Marek and Roth [1] reported that the ability of dopamine agonists to counteract the increase in dopamine formation produced by administration of γ-butyrolactone (GBL) was prevented by haloperidol under some but not all conditions. GBL blocks impulse flow and causes accumulation of dopamine, which is counteracted by dopamine agonists acting presynaptically. Haloperidol given prior to the dopamine agonists prevented the effects of apomorphine and bromocriptine, whereas haloperidol given after the dopamine agonist prevented the effect of apomorphine but not of bromocriptine. Marek and Roth [1] suggested that bromocriptine may interact irreversibly or noncompetitively with presynaptic dopamine receptors. The experiments described here compare the effects of pergolide, a new potent dopamine agonist [2–5] being used in the treatment of Parkinson's disease [6] and hyperprolactinemia [7]. Pergolide is an ergoline that shows potent dopamine agonist activity *in vitro* [3–5] and *in vivo* [2–4] and has a long duration of action [2–4]. Since Bannon *et al.* [8] have suggested that irreversible interactions with dopamine receptors may account for the long duration of some ergots, we were interested in evaluating whether pergolide resembled bromocriptine in respect to reversibility by post-treatment with haloperidol.

The experimental design was based on the work of Marek and Roth [1], but we measured dopamine rather than the accumulation of dopa following decarboxylase inhibition to avoid having to give a fourth drug, the decarboxylase inhibitor. Our measurements were made in whole brain whereas Marek and Roth [1] had measured in two brain regions, the striatum and the olfactory tubercle. In our studies, male Wistar rats weighing 140–210 g were obtained from Harlan Industries, Cumberland, IN. GBL (Eastman Chemical Products, Kingsport, TN) was injected at a dose of 500 mg/kg i.p., 35 min before the rats were killed. Pergolide mesylate (Lilly Research Laboratories, Indianapolis, IN), 0.3 mg/kg i.p., and bromocriptine mesylate (Sandoz Pharmaceuticals, East Hanover, NJ), 10 mg/kg i.p., were injected 1 hr prior to GBL. Haloperidol (McNeil Laboratories, Fort Washington, PA), 1 mg/kg i.p., was injected 5 min before or 50 min after pergolide or bromocriptine. Rats were decapitated, and whole brains were quickly removed, frozen on dry ice, and stored at −15° prior to analysis. Dopamine concentration in whole brain was measured by liquid chromatography with electrochemical detection [9].

The results are shown in Fig. 1. Dopamine concentration was increased ($P < 0.1$) by GBL injection (compare two left columns). The injection of either pergolide or bromocriptine (third and sixth columns from left) significantly antagonized the accumulation of dopamine. Haloperidol given before bromocriptine completely prevented the antagonistic effect of bromocriptine (second column from right), but haloperidol given subsequent to

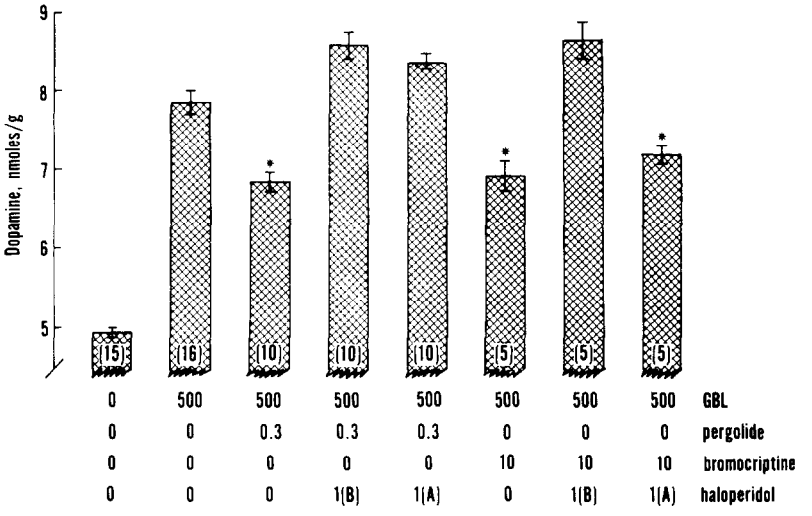

Fig. 1. Dopamine concentration in whole brain. Rats were treated as indicated at the bottom of the graph. Haloperidol was injected before (B) or after (A) the dopamine agonists as described in the text. Drug doses are shown in mg/kg. The values are means ± standard errors for the numbers of rats shown at the base of each bar. An asterisk indicates a significant difference ($P < 0.05$) from the group treated with GBL alone (second from left).

bromocriptine had no effect (right column). In contrast, haloperidol blocked the effect of pergolide regardless of whether it was given before or after pergolide (two middle columns).

The findings with bromocriptine are in agreement with those of Marek and Roth [1]. Although we measured dopamine rather than dopa accumulation after decarboxylase inhibition and we measured in whole brain rather than in striatum, our data and theirs show that haloperidol prevented the effect of bromocriptine when it was given before but not when it was given after bromocriptine. The results with pergolide are in contrast to those with bromocriptine, but similar to those with apomorphine [1]. Haloperidol prevented the effect of pergolide whether it was given before or after pergolide.

The inability of post-treatment with haloperidol to reverse the GBL-antagonizing effect of bromocriptine is consistent with other biochemical and electrophysiological evidence for an irreversible interaction of bromocriptine with some central dopamine receptors [8]. Bannon *et al.* [8] suggested that the irreversibility of bromocriptine was related to the peptide chain present in bromocriptine, and our data would be compatible with that idea since pergolide does not have a peptide moiety.

If the interpretation of Marek and Roth [1] is correct, that bromocriptine combines noncompetitively or irreversibly with presynaptic dopamine receptors, then one could infer that pergolide combines reversibly and competitively as does apomorphine. The pharmacologic significance of this apparent difference between the two dopamine agonists is not presently known. Bannon *et al.* [8] suggested that the irreversible interaction of bromocriptine with dopamine receptors might help to explain the long action of bromocriptine in experimental animals and in humans. Clearly this irreversibility is not required for a long duration of action, since pergolide acts at least as long as bromocriptine in animals [2–4, 10] and in humans [7, 11].

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