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Ventilatory stimulation by dopamine-receptor antagonists in the mouse

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1 Ventilation was measured by a plethysmographic method in awake mice before and after intraperitoneal injection of neuroleptic drugs to test the hypothesis that dopaminergic mechanisms modulate control of breathing in this species.

2 Dose-dependent augmentation of ventilation at rest and during hypoxia, and reduced ventilation during hypercapnia was demonstrated for haloperidol, droperidol, prochlorperazine and chlorpromazine ($P < 0.05$ or less for each drug).

3 Doses of drugs causing maximal increase of the ventilatory response to hypoxia were linearly related ($r = 0.98$, $P < 0.001$) to *in vitro* affinity of the drugs for dopamine receptors.

4 Despite presumed equal dopamine-receptor blockade, the drugs had unequal effects on the ventilatory response to hypoxia. Droperidol augmented hypoxic ventilation to 290% of the control value, chlorpromazine to 250% control, prochlorperazine to 190% control and haloperidol to 120% control. These differences in efficacy were in the same order as the affinities of the drugs for α-adrenoceptors.

5 The effect of combined haloperidol (90 nmol kg^{-1}) and varying doses of phentolamine (175–900 nmol kg^{-1}) was assessed to test the hypothesis that α-antagonism was a factor in determining the increase in ventilation following dopamine blockade. Phentolamine caused dose-dependent augmentation of the ventilatory effects of haloperidol ($P < 0.01$) but had no ventilatory effect when given alone.

6 Carotid body resection in anaesthetized mice abolished the stimulation of hypoxic ventilation caused by droperidol.

7 It is concluded that dopaminergic mechanisms in the carotid body modulate ventilatory control in the awake mouse. The drugs most effective in augmenting hypoxic ventilation are those that block both dopamine and α-adrenoceptors.

Introduction

Dopamine is the most abundant catecholamine in the carotid body and a great deal of recent work has been directed towards identifying its functional significance. Zapata (1975) showed that exogenously administered dopamine depressed the chemosensory activity of the carotid body, even when vascular effects were ruled out, and he and his co-workers have since shown that this is an action at specific dopamine receptors (Llados & Zapata, 1978a,b). Infused dopamine depresses ventilation in rats (Cardenas & Zapata, 1981), cats (Zapata & Zuazo, 1980; 1982), and man (Bainbridge & Heistad, 1980; Olson *et al.*, 1982b). Since dopamine is released by hypoxia from the glomus cells which store it (Hanbauer & Hellstrom, 1978), it has been suggested that endogenous dopamine mediates a negative feedback loop modulating the chemoreceptor sensitivity of the carotid body.

Many drugs are available which block dopamine-receptors, and their effects on carotid body discharge and on ventilation have been studied. Results have been conflicting however, some authors reporting stimulation of chemoreceptor discharge (Llados & Zapata, 1978a,b), others no change (Zapata, 1975; Docherty & McQueen, 1978; Mir *et al.*, 1984), and others observing stimulation with some drugs and depression with others (Aminoff *et al.*, 1978). Similar conflict exists regarding the effects of dopamine-receptor antagonists on ventilation. Bainbridge & Heistad (1980) could find no increase in resting or hypoxic

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ventilation with haloperidol in man, while we have recently reported that prochlorperazine increases resting ventilation and the ventilatory response to hypoxia (Olson *et al.*, 1982a). Others have reported findings in anaesthetized cats that are similar to our own (Zapata & Zuazo, 1982) whereas dopamine receptor blockade does not alter hypoxic ventilation in anaesthetized rats (Horn, 1982). While the effects of anaesthesia may explain some of these discrepancies (Smatresk *et al.*, 1983) they cannot account for all.

A major difficulty encountered in the study of dopamine-receptor blocking agents is that all have multiple actions, blocking to a varying extent α-adrenoceptors, muscarinic receptors, 5-hydroxytryptamine (5-HT) receptors and histamine receptors (Peroutka & Snyder, 1980). Since α-receptors have been proposed as the site of action of dopamine in the carotid body (Sampson, 1972), and muscarinic receptors can influence chemosensory activity (Eyzaguirre & Zapata, 1968), we wished to obtain clearer evidence that the ventilatory effects of drugs used as dopamine-antagonists were due principally to their action at dopamine-receptors. Therefore, we studied the ventilatory effects of a group of dopamine-receptor blocking drugs that are discordant in their effects at other receptor classes potentially involved in ventilatory control. We studied prochlorperazine which we have found previously to be effective in increasing ventilatory responsiveness to hypoxia in man (Olson *et al.*, 1982a), chlorpromazine, a potent α-receptor and muscarinic-receptor blocker, droperidol, a potent α-receptor blocker inactive at muscarinic receptors and haloperidol, a relatively pure dopamine-receptor blocker.

Methods

Animals used were adult male QS mice, weighing 30–35 g. They were unanaesthetized, apart from those studied following carotid body resection. Experiments were approved by the University of Newcastle Ethics Committee.

Ventilatory responses to hypoxia and hypercapnia

Ventilation was measured by the plethysmographic technique of Bartlett & Tenny (1970). Box pressure was measured with a Grass PT5A pressure transducer, the output of which was amplified (Grass 7PI) and displayed on an ink-pen recorder (Grass 7P). Calibration injections of 0.1 ml of air were made at the beginning and end of each experiment. Because this method has been validated only for relatively low respiratory frequencies (Drorbaugh & Fenn, 1967), experiments were performed to test the ability of the apparatus to follow accurately pressure changes at the respiratory frequency of mice (up to 7 Hz in our studies). The lid of the plethysmograph was replaced with a loudspeaker driven by a signal generator. The outputs of the signal generator and the pressure transducer were displayed on a dual channel oscilloscope (Tektronics 5A18N). No distortion of the waveform and no phase lag occurred between input signal and transducer signal up to and including a frequency of 8 Hz.

To study the ventilatory response to hypoxia, nitrogen was bled into the plethysmograph chamber at a rate sufficient to reduce inspired oxygen concentration successively from 21% to 15%, 12.5%, 11% and 10% O_2. Inspired oxygen concentration was measured with a Beckman OM11 oxygen analyser. At each level of hypoxia, ventilation was allowed to stabilize for 1 min before being recorded. No attempt was made to prevent the hypocapnia resulting from hyperventilation. Ventilation was measured in triplicate for 1 min during air breathing and at each level of hypoxia. Concentration of inspired oxygen was converted to inspired partial pressure of oxygen (P_IO_2) and ventilation was related to $1/P_IO_2$ by linear regression analysis to provide an expression of hypoxic responsiveness (the slope of the response, $\Delta V_I/\Delta 1/P_IO_2$ ml min^{-1} mmHg). Correlation coefficients of these regression lines were consistently > 0.90; responses with correlation coefficients < 0.80 were excluded from analysis. An example of tracings of ventilation in air and during hypoxia before and after droperidol obtained in one mouse are shown in Figure 1a; the values of ventilation obtained from these tracings are shown plotted against F_IO_2 and against $1/P_IO_2$ in Figure 1b.

Hypercapnia was induced by flushing the plethysmograph with 7% CO_2 in air at 4 l min^{-1} for 2 min. The half-time for replacement of resident gas in the plethysmograph with gas added at 4 l min^{-1} was 20–30 s. Ventilation was measured in triplicate for a period of 1 min, 1 min after flushing of the chamber with 7% CO_2 in air was complete.

Effects of dopamine antagonists

Droperidol (Janssen), haloperidol HCl (Searle), prochlorperazine edisylate (Smith, Kline and French), chlorpromazine (May and Baker) and phentolamine mesylate (Ciba) were standard pharmaceutical preparations. Drugs were administered intraperitoneally, diluted in normal saline so that volume injected was 0.1 ml.

Initially, five mice were studied at each of three or more drug doses; each dose was studied on a different day and at least two days separated studies in the same mouse. Once dose-response relationships were established, an additional five mice were studied for each drug at the dose found to cause maximal ventilatory stimulation during hypoxia. Different mice were

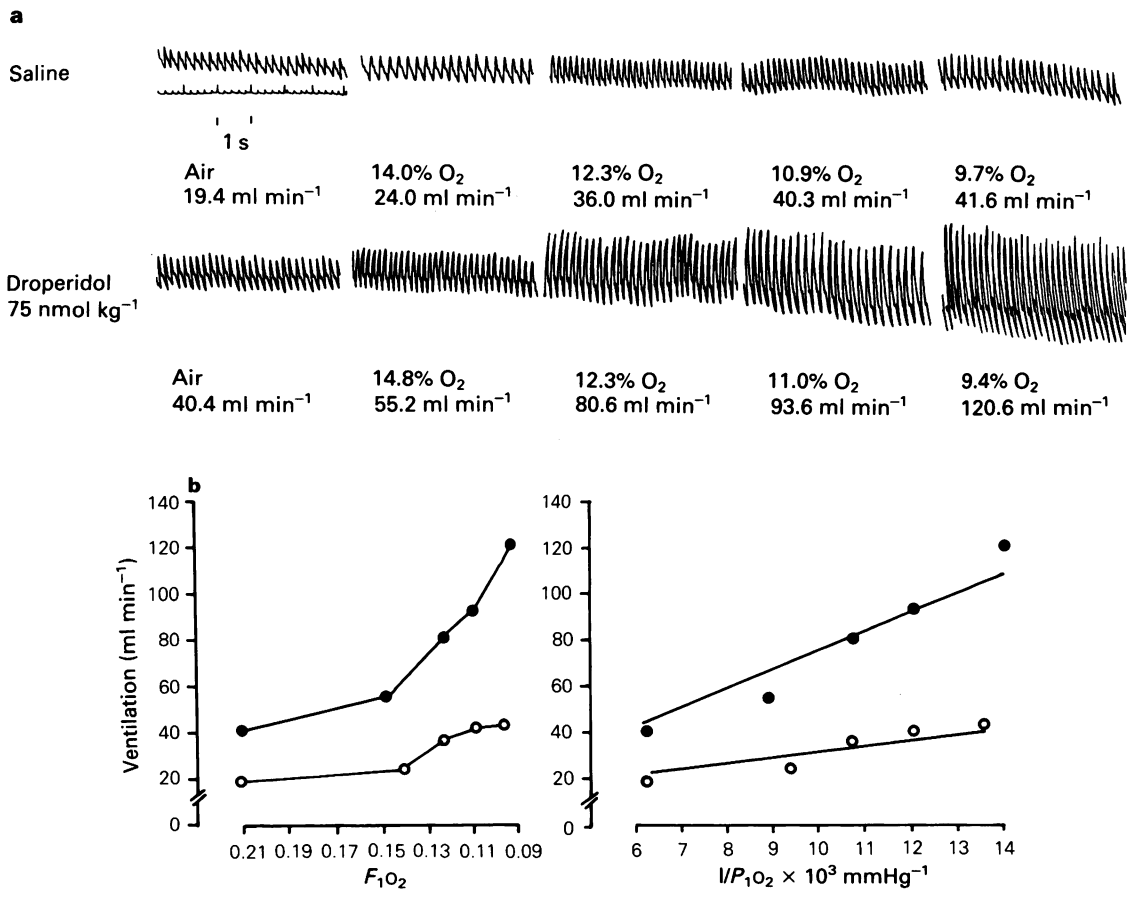

Figure 1 (a) Tracings of ventilation in one mouse during air breathing and successive levels of hypoxia before (upper panel) and after (lower panel) droperidol administration. (b) Calculation of hypoxic response. The curvilinear relationship between ventilation and F_IO_2 (left panel) is linearised by relating ventilation to $1/P_IO_2$ (right panel). The slope of this line ($\Delta V_I/\Delta\ 1/P_IO_2$ gives an expression of hypoxic responsiveness. Plots are derived from data presented in (a). Saline (○); droperidol (●).

studied with each drug. In each experiment, hypoxic responses were measured in triplicate 15 min after injection of 0.1 ml normal saline. Measurements were repeated in triplicate after drug injection. For droperidol, haloperidol and prochlorperazine, measurements were begun 15 min after injection, but 30 min were allowed to elapse after injection of chlorpromazine before measurements were made because of the slow onset of action of this drug (Dahl & Strandgord, 1977). Measurements of a single hypoxic response occupied about 10 min; slopes of first and last tests performed on a single mouse did not differ.

Ventilation during hypercapnia was measured in triplicate on a different day from hypoxic testing; each measurement was separated by 2 min of air breathing. Control measurements were made 15 min after injection of 0.1 ml normal saline and measurements after drug injection were made at the times described above.

Effect of combined α-receptor and dopamine-receptor blockade

A series of experiments was performed to see whether the addition of α-blockade would augment the small increase in ventilation caused by haloperidol. Ten mice were given the dose of haloperidol identified as optimal in the first series of experiments (90 nmol kg^{-1}). Fifteen minutes later, ventilation was measured in air and in 10% O_2 in N_2. One minute of air breathing separated triplicate measurements. Phen-

tolamine was administered in doses of 175, 200, 250, 360, 550 and 900 nmol kg^{-1}, and after a further 15 min, triplicate measurements of ventilation in air and in 10% O_2 were repeated. We have no evidence demonstrating that these doses of phentolamine were sufficient to cause blockade of α-receptors. However, the doses administered are very large; in man a dose of 0.2 nmol kg^{-1} blocks the hypertensive effect of exogenous noradrenaline (Heistad *et al.*, 1972). The same mice were used in experiments at each dose of phentolamine, studies being separated by at least two days. In control experiments, 0.1 ml normal saline replaced haloperidol.

Effects of droperidol after carotid body resection

Three groups of animals were studied. In Group 1, seven animals were anaesthetized with pentobarbitone (Abbott) 90 mg kg^{-1} intraperitoneally. The carotid bifurcations were exposed and the tissue lying between the internal and external carotid arteries, which contains the carotid body and any satellite collections of chemoreceptor cells (Clarke & de Burgh Daly, 1981), were excised. Ventilation was measured in 10% O_2. Droperidol (75 nmol kg^{-1}) was then given intraperitoneally. After 10 min, during which the animal breathed room air, ventilation in 10% O_2 was measured. In Group 2 (sham operation), six mice were anaesthetized with pentobarbitone 90 mg kg^{-1}. The carotid bifurcations were exposed but left intact and hypoxic ventilation was measured before and after droperidol administration. A further five mice (Group 3) were studied after pentobarbitone (45 mg kg^{-1}) intraperitoneally. This dose produced profound sedation but not anaesthesia. Ventilation was measured before and after droperidol as described previously.

Statistical methods

Statistical significance of drug effects, and effects of anaesthesia and carotid body resection on ventilation was assessed by one way analysis of variance and the Newman-Keul test as appropriate. Differences among doses of the same drug, and among drugs were examined in this manner. Significance of effects of droperidol before and after carotid body resection was assessed by paired Student's *t* test.

Results

Effect of dopamine-antagonists on ventilation

Figure 2 shows responses to hypoxia in four mice under control conditions and at a single dose of each drug studied. Ventilation increased progressively as inspired oxygen concentration was reduced. Each drug increased ventilation, although not equally (see below).

The relationship between administered dose of each

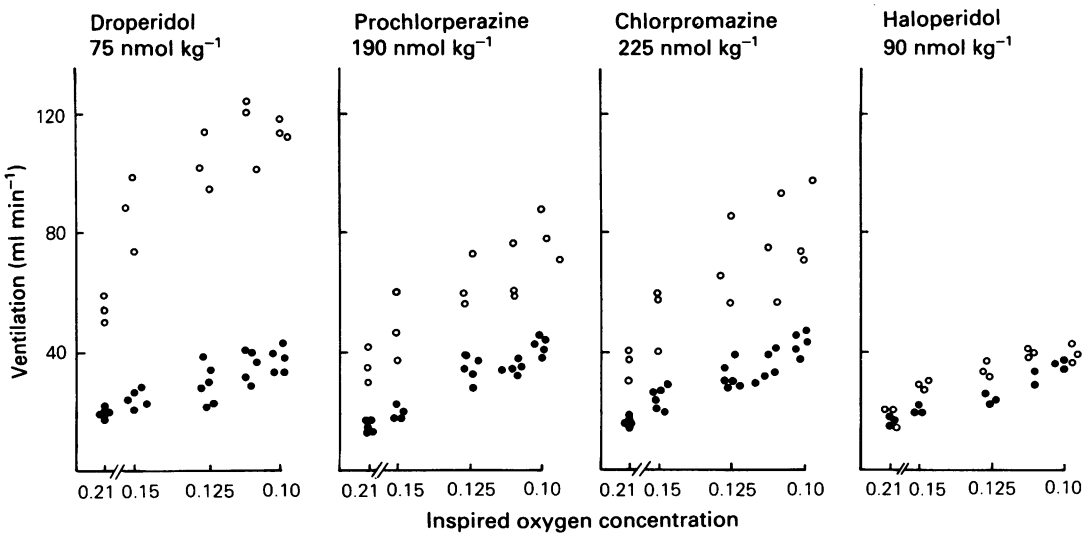

Figure 2 Ventilation breathing room air and during hypoxia after saline injection (●) and after drug administration (○) in four mice. Each panel shows triplicate measurements (at least) in one mouse before and after a single dose of drug.

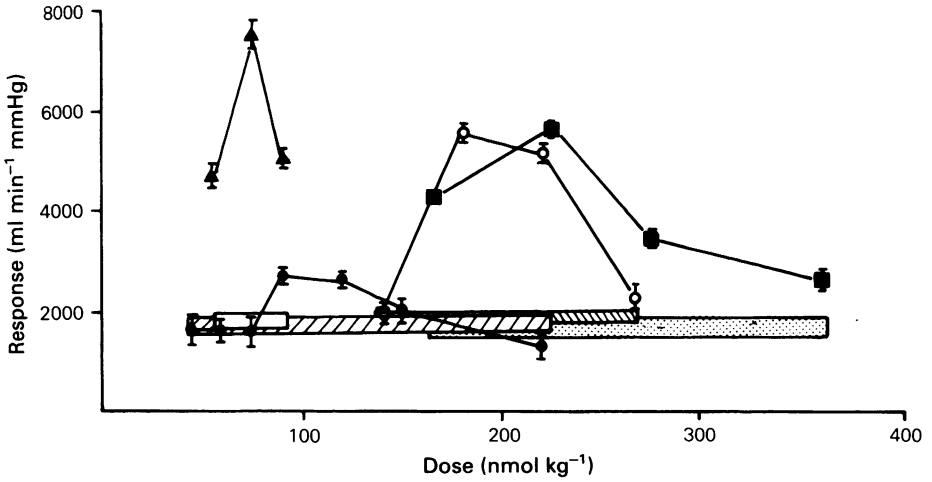

Figure 3 Dose-response curves for ventilatory response to progressive hypoxia. Values shown at each dose are mean for 5–10 mice; vertical lines show s.e.mean. Horizontal bars show the range of response slopes observed in saline injected controls. Droperidol (▲) and □; haloperidol (●) and ▨; prochlorperazine (○) and ▧; chlorpromazine (■) and ▩.

drug and the slope of response to hypoxia is shown in Figure 3. Dose-dependent increases in the response to hypoxia were demonstrated with all drugs (haloperidol $P<0.05$; other drugs $P<0.01$). The optimum dose of drug was clear cut for droperidol, chlorpromazine and prochlorperazine; the slope of the ventilatory response to hypoxia at this dose was significantly greater than the slope of response at doses on either side ($P<0.05$). The difference in slope of hypoxic responses between 90 nmol kg^{-1} and 110 nmol kg^{-1} haloperidol was not significant.

The increment in ventilation caused by these drugs during air breathing and hypoxia varied from slight with haloperidol to almost two fold with droperidol. Table 1 shows values of ventilation in air, 12.5% O_2 and 7% CO_2 at the dose of each drug that gave maximal increase in hypoxic response. Because not all responses included a value for ventilation recorded at precisely 12.5% O_2, values for 12.5% O_2 were interpolated from the calculated response slopes. Drug effects were significant under the three conditions ($P<0.01$). During hypoxia and air breathing, droperidol had a significantly greater stimulant effect than prochlorperazine and haloperidol ($P<0.05$), and both chlorpromazine and prochlorperazine had greater effects than haloperidol ($P<0.05$). The ratio of stimulated (drug) to control (saline) ventilation in 12.5% O_2 was 2.9 for droperidol, 2.5 for chlor-

Table 1 Ventilation at dose of drugs producing maximal increase in hypoxic ventilation

	Ki (nmol)	*Dose* (nmol kg^{-1})	*Ventilation* (ml min^{-1}) *Air*	*12.5% O_2*	*7% CO_2*
Control (saline)	—	—	17.0 ± 0.98	30.0 ± 1.56	77.8 ± 1.76
Droperidol	3.0	75	48.8 ± 3.71	86.4 ± 4.88	49.1 ± 2.73
Haloperidol	4.2	90	23.2 ± 1.76	34.9 ± 2.15	54.2 ± 2.54
Prochlorperazine	15	190	35.1 ± 2.54	56.0 ± 3.90	61.8 ± 2.54
Chlorpromazine	25	225	44.5 ± 3.51	75.9 ± 5.46	57.3 ± 3.51

Values are means ± s.e.mean from three tests each in 10 mice for air and hypoxia, and for three tests each in five mice for hypercapnia. All drugs increased ventilation during normoxia and hypoxia, and decreased ventilation during hypercapnia ($P<0.01$). Drug effects were unequal during normoxia and hypoxia (droperidol > prochlorperazine > haloperidol ($P<0.05$); chlorpromazine > haloperidol ($P<0.05$)) but equal during hypercapnia.
Ki values are those defined by Peroutka & Snyder (1980).

promazine, 1.9 for prochlorperazine and 1.2 for haloperidol. The ratios of stimulated to control ventilation during air breathing were very similar. Ventilation in 7% CO_2 was reduced by all drugs ($P<0.01$). The differences among the drugs during hypercapnia were not significant.

Effects of combined phentolamine and haloperidol

To test the hypothesis that α-receptor antagonism is necessary to allow the stimulant effect of dopamine antagonists to be expressed, varying doses of phentolamine were combined with the optimal dose of haloperidol (90 nmol kg^{-1}). Results of these experiments are shown in Figure 4. Phentolamine given alone in doses of 175, 200, 250, 360 and 900 nmol kg^{-1} did not alter resting ventilation or ventilation in 10% O_2. When combined with haloperidol, lower doses of phentolamine increased the ventilatory stimulant effect of haloperidol ($P<0.01$), although the combination was still less effective than the other dopamine-receptor blocking drugs studied. Doses of phentolamine of 200, 250 and 360 nmol kg^{-1} combined with haloperidol caused equal increments in ventilation. Higher doses of phentolamine caused a sharp fall in ventilation to control levels.

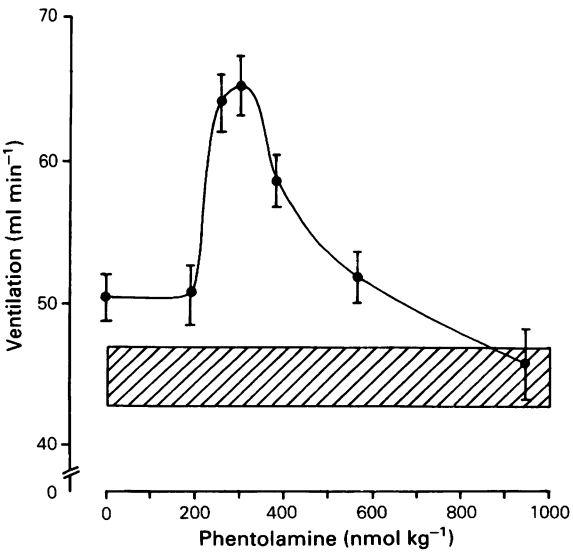

Figure 4 Dose-response curve for interaction of haloperidol (90 nmol kg^{-1}) with phentolamine. Hatched area shows range of ventilation observed during hypoxia (10% O_2) in animals injected with phentolamine alone. Means are shown with s.d. indicated by vertical lines.

Effects of droperidol after anaesthesia and carotid body resection

Ventilation in 10% O_2 before and after anaesthesia and carotid body resection, and the effects of droperidol under these conditions, are shown in Table 2. Anaesthesia caused dose-dependent depression of hypoxic ventilation; ventilation after 90 mg kg^{-1} pentobarbitone was significantly less than ventilation after 45 mg kg^{-1} ($P<0.05$), which was significantly less than control hypoxic ventilation ($P<0.05$). Carotid body resection caused a further fall in hypoxic ventilation ($P<0.01$) to a value below normoxic ventilation in awake intact mice (cf. Table 1). Droperidol had no significant effect on hypoxic ventilation in anaesthetized mice but in carotid body resected animals, it caused significant depression of ventilation. In sedated but unanaesthetized mice (pentobarbitone 45 mg kg^{-1}) droperidol minimally but significantly increased ventilation in 10% O_2 ($P<0.05$).

Discussion

This study has shown that dopamine antagonists influence ventilation and ventilatory responsiveness in the mouse. In awake mice, ventilation during air breathing and hypoxia was increased by the drugs and clear differences were observed between them both in terms of the dose required for maximal effect and the increase in ventilation elicited. Phentolamine, an α-receptor antagonist, had no effect on ventilation when given alone but when combined with haloperidol, it augmented the stimulant effect of haloperidol during air breathing and hypoxia. All dopamine-receptor blocking drugs studied reduced ventilation in 7% CO_2 to about 75% of the value reached after saline injection. In contrast with findings in awake chemoreceptor-intact mice, droperidol depressed ventilation in anaesthetized carotid body resected animals.

Two methodological limitations resulted from our failure to measure arterial blood gas tensions. Inspired gas tensions had to be used as an index of the stimulus to breathing and changes in P_{CO_2} consequent on hyperventilation could not be controlled during the experiments. It is unlikely that the differences among drugs in their ability to stimulate hypoxic ventilation is a spurious finding that can be explained by differences in the relationship between inspired and arterial P_{O_2}; a two to three fold difference in efficacy was observed between droperidol and haloperidol. The drugs reduced ventilation during hypercapnia to roughly equal degrees. If this effect interfered with O_2–CO_2 interactions, it should be equally distributed across the drugs. These issues do not alter our basic conclusion that

Table 2 Effects of anaesthesia and carotid body resection on ventilation in 10% O_2 before and after droperidol (75 nmol kg^{-1})

	(Ventilation ml min^{-1})			
	Awake	*Pentobarbitone* (45 mg kg^{-1})	*Pentobarbitone* (90 mg kg^{-1}) + *sham operation*	*CBR*
Control	45.2 ± 1.85 (6)	29.2 ± 1.93 (5)	21.4 ± 1.85 (6)	12.8 ± 1.60 (7)
Droperidol	—	34.9 ± 1.31 (5)	21.6 ± 1.72 (6)	7.4 ± 1.64 (7)
P	—	<0.05	NS	<0.05

Values are mean ± s.e.mean. *P* values relate to differences between control and droperidol values (paired Student's *t* test). See text for statistical significance of differences along rows. Numbers in parentheses are number of mice studied. CBR = carotid body resection.

these drugs increase ventilation because of dopamine-receptor blockade.

In order to explore possible mechanisms of actions of the drugs, we examined the relationship between dose of drug required to cause maximal stimulation of ventilation during hypoxia and the affinity of the drug for the dopamine-receptor as determined *in vitro* by others (Peroutka & Snyder, 1980). Figure 5 shows the relationship between log maximally effective dose and log dopamine receptor *Ki*, using *Ki* values determined by Peroutka & Snyder (1980) shown in Table 1. The equation of the corresponding linear/linear regression line is dose = 7.0 *Ki* + 62.6 nmol kg^{-1}. This close correlation ($P < 0.001$) suggests that the drugs tested in this study could be exerting their ventilatory effect by blocking dopamine-receptors. The correlation observed is similar to that found in studies of the

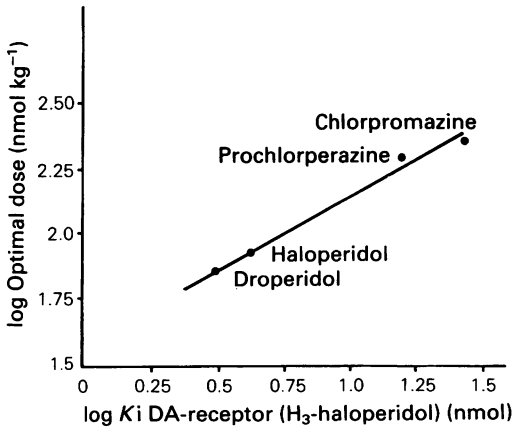

Figure 5 Relationship between log optimal dose and log dopamine-receptor *Ki* (Peroutka & Snyder, 1980). The equation for the line of best fit is log dose = 1.45 log *Ki* + 0.67 ($r = 0.98$).

antipsychotic properties of dopamine antagonists which led to the conclusion that the antipsychotic properties of these drugs are mediated by dopamine blockade (Creese *et al.*, 1976).

The fall in hypoxic ventilatory responsiveness with high doses of dopamine-receptor antagonists was a consistent finding but its interpretation is uncertain. The results agree with studies of the effects of dopamine-receptor blockers on carotid body discharge frequency. Aminoff and co-workers (1978) observed that doses of droperidol of 250 μg kg^{-1} administered by intracarotid injection in the cat depressed chemosensory discharges and that depression increased at higher doses. By contrast, doses of 10–50 μg kg^{-1} droperidol were stimulatory. Thus, the biphasic effect of dopamine-receptor blockers on ventilation may be an intrinsic property of the carotid body, reflecting a dual action of dopamine itself (Llados & Zapata, 1978a). Conventional dopamine antagonists are not known to block the putative excitatory dopamine-receptors (McQueen, 1983). An alternative explanation for the biphasic ventilatory response observed is that at high doses central dopamine-receptor blockade depressed the response of central respiratory neurones to the increased peripheral drive. Activation of central dopamine-receptors stimulates ventilation (Lundberg *et al.*, 1979).

We have observed that the drugs most effective in increasing ventilation during hypoxia are also those with the greatest α-adrenoceptor blocking effect. The most effective stimulants, droperidol and chlorpromazine, have an α-receptor *Ki* of 1.0 and 5.2 nmol respectively (i.e. they are three and five times respectively more potent as α-receptor blockers than as dopamine-receptor blockers, see Table 1) but haloperidol, the least effective drug, is a weak α-blocker (*Ki* = 10 nmol) (Peroutka & Snyder, 1980). The interaction between haloperidol and phentolamine that we observed, and between spiroperidol and dibenamine observed by others (Zapata & Zuazo,

1982), leads us to suggest that α-receptor blockade is a factor in determining the efficacy of a dopamine antagonist in increasing ventilation. The interaction between phentolamine and haloperidol is not likely to be explained by the known effects of changes in blood pressure on carotid sinus nerve discharge (Biscoe *et al.*, 1970). Phentolamine did not increase ventilation when given alone and it augmented the ventilatory effects of haloperidol when given in low, but not high doses. These findings provide strong evidence that phentolamine had effects independent of blood pressure changes.

We conclude that dopamine-receptor antagonists increase ventilation in the awake mouse by a carotid body dependent mechanism. This effect is probably due to dopamine-receptor blockade but is prominent only in those drugs that block α-receptors. Anaesthesia, dose-dependency of individual drug effects and differences among dopamine-receptor blockers in potency and efficacy may help explain previous conflicting results regarding the effect of these drugs on carotid sinus nerve discharge and ventilation.

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