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Bulbocapnine is not a selective DA_1 receptor antagonist

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Antagonist activity of bulbocapnine on DA_1 versus DA_2 dopamine receptors was studied simultaneously in a dog under pentobarbitone anaesthesia and without phenoxybenzamine pretreatment. Fenoldopam (SK&F 82526) injected into the renal artery was the DA_1 agonist and dipropyl dopamine or piribedil injected into the femoral artery were the DA_2 agonists. Both at 0·5 and 1 mg kg^{-1} doses intravenous bulbocapnine caused nearly equal inhibition of DA_1 and DA_2 dopamine receptor-mediated responses. Our results show that under these experimental conditions bulbocapnine is not a selective DA_1 dopamine antagonist.

Bulbocapnine was among the first generation of dopamine (DA) antagonists used to distinguish DA receptor-mediated vasodilation from vasodilation caused by action on other receptors (for references, see Goldberg 1972). Setler et al (1975) reported that bulbocapnine (3 mg kg^{-1} i.v.) antagonized DA-induced renal vasodilation but did not inhibit apomorphine-induced emesis, suggesting that vascular DA receptors may be different from DA receptors located in the area postrema. During the last five years, DA receptors have been divided into two subtypes. Renal vasodilation is mediated by DA_1 receptors, while emesis, inhibition of the sympathetic nervous system, and inhibition of prolactin release are mediated by DA_2 receptors (see Goldberg & Kohli 1983; Stoof & Kebabian 1984). Reviewing the literature based on the DA_1/DA_2 classification, we found conflicting data concerning the DA antagonist actions of bulbocapnine. Ilhan et al (1975) and Lokhandwala & Jandhyala (1979) reported that approximately the same doses of bulbocapnine (2–5 mg kg^{-1}) that blocked DA_1-mediated renal vasodilation also blocked DA_2 neuroinhibitory effects. In contrast, Shepperson et al (1982) reported that bulbocapnine was a preferential DA_1 antagonist. Because of these contrary data, we studied the effects of intravenously administered bulbocapnine on DA_1 and DA_2 receptors in an anaesthetized dog in order to determine accurately the range of its selectivity between the two subtypes of DA receptors.

Methods

Studies were conducted in seven pentobarbitone-anaesthetized dogs in which renal and femoral blood flow and arterial blood pressure were measured simultaneously, as previously described (Kohli et al 1980), except that phenoxybenzamine was not administered. DA_1 responses were obtained by intra-arterial (i.a.) injections of the selective DA_1 agonist, fenoldopam (SK&F 82526) (Hahn et al 1982), in doses of 3–12 nmol into the renal artery. DA_2 responses were obtained alternately by injections of dipropyl dopamine (DPDA) (Kohli et al 1983), 12–48 nmol, or piribedil, 3–48 nmol, into the femoral artery (Laubie et al 1977). Bulbocapnine hydrochloride was injected i.v. in doses of 0·5 and 1 mg kg^{-1}. Ten minutes after the injection of bulbocapnine, the DA_1 and DA_2 agonists were again administered into the respective arteries. In 4 separate ganglion-blocked dogs (hexamethonium, 10 mg kg^{-1} i.v.) noradrenaline (NA), 3–12 nmol, was injected into the femoral artery before and 10 min after bulbocapnine, 1 mg kg^{-1} i.v., to exclude the α-adrenoceptor blocking activity of this dose of bulbocapnine.

Results and discussion

Fig. 1 illustrates an experiment in which 1 mg kg^{-1} of bulbocapnine inhibited both DA_1 and DA_2 receptor-mediated responses. The per cent inhibition by 0·5 and 1 mg kg^{-1} of bulbocapnine responses elicited by the DA_1 and DA_2 agonists was calculated from this type of experiment. The results obtained in 5–7 experiments are shown in Table 1. With the 0·5 mg kg^{-1} dose, bulbocapnine caused similar inhibition of the responses mediated by DA_1 and DA_2 receptors in the two vascular beds. At the 1 mg kg^{-1} dose, it appeared to be more effective against DA_2 receptor-mediated femoral vasodilation than against DA_1-mediated renal vasodilation; however, the difference was not significant. At this higher dose, bulbocapnine had no α-adrenoceptor blocking activity. NA, 3–12 nmol, given i.a. into the

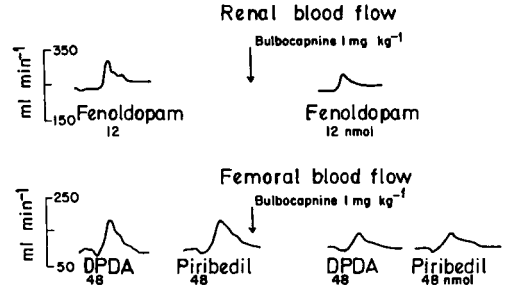

FIG. 1. Effect of bulbocapnine, 1 mg kg^{-1} intravenously, on vasodilator responses elicited by fenoldopam in the renal vascular bed and *N,N*-di-n-propyl dopamine (DPDA) or piribedil in the femoral vascular bed of a pentobarbitone-anaesthetized dog. Agonists were injected into the respective arteries before and 10 min after bulbocapnine.

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Table 1. Per cent inhibition by bulbocapnine of DA_1 and DA_2 receptor agonists in pentobarbitone-anaesthetized dogs.

Bulbocapnine i.v. dose	Renal vascular bed (DA_1 receptor)	Femoral vascular bed (DA_2 receptor)
0·5 mg kg^{-1}	Fenoldopam 25·4 ± 6·57	DPDA 23·6 ± 7·30 Piribedil 19·0 ± 7·60
1·0 mg kg^{-1}	Fenoldopam 35·4 ± 5·36	DPDA 49·9 ± 0·90 Piribedil 42·6 ± 9·38
	(n = 5–7)	(n = 5–7)

femoral artery produced a decrease of 54 ± 6·0 ml min^{-1} in the femoral blood flow before and a decrease of 57 ± 5·9 ml min^{-1} after 1 mg kg^{-1} i.v. bulbocapnine (n = 4).

Our results do not support the conclusion of Shepperson et al (1982) that bulbocapnine is a preferential DA_1 antagonist. These investigators reported that the ID50 of bulbocapnine as a DA_1 antagonist was about 0·3 mg kg^{-1} and that doses as high as 2 mg kg^{-1} did not exert a significant effect on DPDA-induced inhibition of sympathetic transmission. In that study, mesenteric blood flow was used for measurement of DA_1-mediated activity and electrically stimulated response of the heart or nictitating membrane was utilized for measurement of DA_2 receptor activity. The two receptor subtypes, however, were studied in separate groups of animals. In the present study both DA_1 and DA_2 activities were measured in the same animal using physiological nerve activity compared with electrically stimulated neuronal activity used in the Shepperson study. More importantly, the dose of DPDA used in the Shepperson study was 25–100 μg kg^{-1} min^{-1} for 4 min compared with a single dose of 12–48 nmol (3·7 to 14·9 μg) used in the present study. These methodological and dosage differences could have been responsible for the lack of DA_2 block by bulbocapnine observed by Shepperson et al (1982).

Lack of selectivity in bulbocapnine, similar to the present results, was reported recently by Plantjé et al (1984) for D_1 and D_2 dopamine receptors in the rat neostriatum. Many studies tend to show similarity or identity between either subtype (D_1/DA_1 and D_2/DA_2) recognized by the two classifications of DA receptors (Goldberg & Kohli 1983; Stoof & Kebabian 1984). Therefore, the reason for lack of antagonism by bulbocapnine of the emetic effect of apomorphine (Setler et al 1975), a D_2/DA_2 receptor-mediated effect, is not clear.

In the present study α-adrenoceptor-mediated effects of physiological neuronal activity as modified by a DA_2 receptor agonist (DPDA) were used as the test procedure. In this procedure bulbocapnine could modify effects of nerve activity by a post-synaptic α-adrenoceptor blocking action which could be mistaken for its DA_2 antagonist activity at the nerve terminals. However, such a possibility is excluded by the observation that at the 1 mg kg^{-1} dose, bulbocapnine had no effect on NA-induced vasoconstriction. Moreover, as shown by Shepperson et al (1982) in 2 mg kg^{-1} doses (2–4 times higher than the dose used in the present study) bulbocapnine had no effect on pre- or post-synaptic α-adrenoceptors.

The results of the present study demonstrate that bulbocapnine cannot be used when administered i.v. to separate DA_1 and DA_2 receptors, even though it has relatively more DA_1 than DA_2 antagonist activity compared to most DA antagonists (Shepperson et al 1982; Goldberg et al 1984). Fortunately, a much more selective DA_1 antagonist, SCH 23390 [*R*(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7-ol] is available (Goldberg et al 1984; Hilditch et al 1984). SCH 23390 is about one thousand times more potent as a DA_1 antagonist than as a DA_2 antagonist.

In conclusion, it was not possible to use i.v. administration of bulbocapnine to distinguish between two subtypes of DA receptors. In addition, bulbocapnine has a non-specific vasoconstrictor activity and some α-adrenoceptor blocking activity (Setler et al 1975) which would also limit its use as a DA antagonist.

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