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EFFECT OF INTRACISTERNAL 5,7-DIHYDROXYTRYPTAMINE ON THE ACUTE ANTIHYPERTENSIVE ACTION OF PROPRANOLOL IN THE SINO-AORTIC DENERVATED ANAESTHETIZED DOG

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1 The anti-hypertensive effects of intravenously and intracisternally administered (±)-propranolol were studied in anaesthetized dogs with acute neurogenic (sino-aortic denervation) hypertension. The animals were pretreated 7 days earlier with intracisternally administered 5,7-dihydroxytryptamine (5,7-DHT 200 μg/kg plus desipramine 5 mg/kg i.v.).

2 5,7-DHT (plus desipramine) failed to decrease both basic blood pressure and heart rate measured before sino-aortic denervation. After 5,7-DHT (plus desipramine) pretreatment, acute sino-aortic denervation induced a rise in blood pressure and stimulated the heart rate, these effects being similar (in intensity and duration) to those observed in control (saline-pretreated) debuffered dogs during the first hour following the deafferentation.

3 In debuffered dogs, (±)-propranolol given by intracisternal (50 μg/kg) or intravenous (300 μg/kg) routes descreased both blood pressure and heart rate.

4 5,7-DHT (plus desipramine) pretreatment abolished the antihypertensive effect of intracisternal propranolol whereas the action of intravenous propranolol was only delayed. In contrast, this pretreatment failed to reduce and even sometimes enhanced the negative chronotropic response induced by propranolol.

5 These results suggest that central 5-hydroxytryptaminergic pathways play an important role in the acute hypotension elicited by intracisternal (±)-propranolol in debuffered hypertensive anaesthetized dogs, but little, if any in propranolol-induced bradycardia.

Introduction

A number of recent studies suggested that the 5-hydroxytryptaminergic pathways within the brain may contribute to central cardiovascular control. This is partly based on the observations (although sometimes contradictory) that intraventricular administration of 5-hydroxytryptamine (5-HT) or its precursor 5-hydroxytryptophan (5-HTP) induced an increase in both blood pressure and heart rate (for references see Chalmers, 1975; Lambert, Friedman, Buchweitz & Gershon, 1978). Conversely, the central administration of the neurotoxic agent 5,6-dihydroxytryptamine (5,6-DHT), a drug known to produce a degeneration of central 5-hydroxytryptaminergic nerve terminals (Baumgarten, Lachenmayer & Schlossberger, 1972a; Daly, Fuxe & Jonsson, 1973; Baumgarten, Björklund, Nobin, Rosengren & Schlossberger, 1975); and a depletion of central 5-HT stores (Baumgarten, Björklund, Lachenmayer, Nobin & Stenevi, 1971; Baumgarten, Evetts, Holman, Iversen, Vogt & Wilson 1972b; Wing & Chalmers, 1974) produced a decrease in both arterial blood pressure and heart rate of normotensive rabbits (Wing & Chalmers, 1974) and a fall in blood pressure in conscious hypertensive rats (Finch, 1975). Wing & Chalmers (1974) have shown that pretreatment with intracisternal, 5,6-DHT prevented the increase in blood pressure seen in chronic sino-aortic denervated conscious rabbits.

Furthermore, it has been postulated that at least part of the antihypertensive action of propranolol may be due to a central effect, since the administration of this drug into the cerebrospinal fluid or into the vertebral arteries decreased blood pressure in various species of animals (for references see Lewis, 1976; Scriabine, 1979). In addition, pharmacological (Schechter & Weinstock, 1974; Weinstock & Schechter 1975), biochemical (Alsasua, Montanes, Pelayo & Garcia de Jalon, 1977; Middlemiss, Blakeborough & Leather, 1977) and behavioural studies (Green & Grahame-Smith, 1976; Weinstock, Weiss & Gitter, 1977) have suggested that propranolol may interact with some 5-HT receptors or 5-HT processes

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in the central nervous system although Fillion, Fillion, Goiny & Jacob (1978) found no evidence for such a biochemical interaction.

Previous findings from our laboratory (Montastruc, Montastruc, Moatti & Mauco, 1978) indicated that the acute neurogenic hypertension which follows the section of the four buffer nerves consitutes a relevant model for studying the antihypertensive effect of intravenously or intracisternally administered (±)-propranolol in the anaesthetized dog. The present experiments, using 5,7-dihydroxytryptamine as a central neurotoxic agent (Baumgarten *et al.*, 1975; Gerson & Baldessarini, 1975) were designed to investigate the role of central 5-hydroxytryptaminergic processes in the antihypertensive effect of systemically and centrally administered (±)-propranolol in anaesthetized dogs with acute neurogenic hypertension.

Methods

General procedure

Adult male or female dogs (42 in all) weighing 10 to 20 kg were used. They were housed in individual cages with free access to food and water.

Dogs were anaesthetized with intravenous sodium thiopentone (12.5 mg/kg), curarized with gallamine triethiodide (2 mg/kg, i.v.), and ventilated with an Ideal-Palmer respirator. Small doses (2.5 mg/kg) of intravenous sodium thiopentone were injected every 30 min for maintenance of anaesthesia. Previous experiments, in the absence of gallamine, have shown that this pattern of thiopentone administration produced complete anaesthesia throughout the period of the experiment. Gallamine does not affect sympathetic nerve function but has vagolytic properties in keeping with which tachycardia, without modification of the carotid arterial pressure, was noted in some experiments. Because of the paralysis of the respiratory muscles, variations of the carotid arterial pressure, induced by respiratory irregularities are suppressed. Under these conditions, ventilation was correct over a long period as previously reported (Montastruc *et al.*, 1978). A polythene tube was secured in the right brachial vein for intravenous injection. Blood pressure was recorded by means of a catheter introduced into the aorta via the femoral artery and connected to a Statham P 23 Db pressure transducer and a Philips recorder. Heart rate was counted with a heart (pulse interval)-meter triggered by the electrocardiogram (lead II).

Experimental hypertension

Acute neurogenic hypertension was produced in all the dogs by surgical procedure as previously described (Montastruc *et al.*, 1978). Briefly, the inhibitory nervous pathways were severed, the sino-cartoid nerve at the carotid artery bifurcation and the vago-sympathetic trunk in the cervical region. The section of the fourth buffer nerve was immediately followed by a rise in blood pressure and tachycardia.

Drugs

One week before the induction of this experimental acute neurogenic hypertension, a single injection into the cisterna magna of 5,7-dihydroxytryptamine (5,7-DHT) creatinine sulphate (Serva, 200 μg/kg free base freshly dissolved in sterile saline with 1 mg/ml ascorbic acid) was given to dogs pretreated 45 to 60 min before hand with desipramine (5 mg/kg i.v.; Ciba-Geigy, Switzerland). The dose of 5,7-DHT was chosen in accordance with the results of Baumgarten *et al.* (1971; 1972a,b; 1975) and Gerson & Baldessarini (1975). Preliminary experiments showed that most of the dogs died within 36 h following the intracisternal administration of 300 μg/kg of 5,7-DHT. Desipramine was used in order to improve the selectivity of 5,7-DHT for central 5-HT neurones as described by Björklund, Baumgarten & Rensch, 1975. The intracisternal administration of 5,7-DHT was performed under light sodium thiopentone anaesthesia by transcutaneous puncture into the atlo-occipital space with a spinal needle as previously described (Montastruc & Montastruc, 1979). The injection volume was 100 μl. Control dogs received an intracisternal injection of saline-ascorbic acid vehicle under the same conditions. A leak of cerebro-spinal fluid through the extremity of the spinal needle confirmed that the injection had been made in the correct position. Animals showing blood in the cerebro-spinal fluid after transcutaneous puncture were not used. During the days following intracisternal injection of 5,7-DHT, the dogs did not show any major neurological or neuro-vegetative disorders.

(±)-Propranolol hydrochloride (ICI-Pharma) was taken from sterile ampoules. After stabilization of the systemic hypertension (30 to 40 s after the section of the last buffer nerve) a single injection (5 s) of the drugs was given by intravenous (300 μg/kg) or intracisternal routes (50 μg/kg in a volume of 100 μl). Debuffered control dogs received an injection of the same volume of saline by the intravenous or intracisternal route. At the end of each experiment, the correct position of the spinal needle in the cisterna magna was checked. All the experiments were carried out for at least 1 h after sino-aortic denervation.

Statistical analysis

Statistical evaluations between the different groups of dogs were made by Student's *t* test. Mean values are given in the text with standard error of the mean (± s.e. mean). *P* values of less than 0.05 were considered significant.

Results

Effect of sino-aortic denervation 5,7-dihydroxytryptamine pretreatment

In debuffered control dogs (n=6) pretreated with intracisternal saline, sino-aortic denervation induced a 12.5% increase (1 min after deafferentation) in heart rate which remained stable for at least 1 h (Figure 1). Ventricular arrhythmias often occur during the 10 min following the deafferentation. In the five 5,7-DHT (plus desipramine) pretreated dogs, basic heart rate was not statistically different from that of controls. Sino-aortic denervation always induced an increase in heart rate (27%, $P < 0.02$, 1 min after the buffer nerves section) and often extrasystoles. During the period of the experiment, this induced tachycardia was the same as that in control debuffered animals (Figure 1).

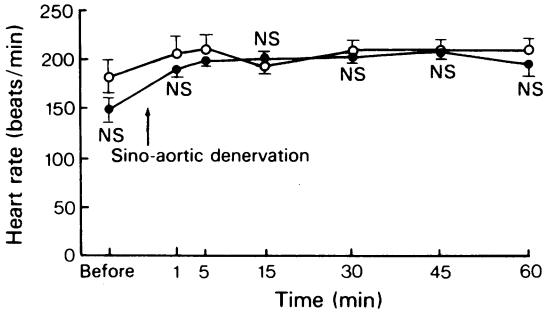

Figure 1 Effect of sino-aortic denervation on heart rate (beats/min) in control dogs (saline pretreated, n = 6) and in dogs pretreated with 5,7-dihydroxytyptamine (5,7-DHT 200 μg/kg intracisternally, 7 days earlier) plus desipramine (5 mg/kg i.v., 45 to 60 min prior to 5,7-DHT) (n = 5). (○) Control dogs; (●) 5,7-DHT plus desipramine-treated dogs. The values of heart rate (measured before and 1, 5, 15, 30, 45 and 60 min after denervation) were not statistically different in the two groups of animals. Comparison with control group at each time using Student's t test; NS = Not significant. Mean values are shown; vertical lines indicate s.e. mean.

Deafferentation induced a significant increase (61%; $P < 0.001$, 1 min after the buffer nerves section) in mean blood pressure of the control dogs. Although blood pressure tended to decrease slowly, it remained high for 3 to 4 h under out experimental conditions. The time course of the blood pressure changes in controls during the first hour is shown in Figure 2. After 5,7-DHT (plus desipramine) treatment, basic blood pressure measured before deafferentation was not statistically different from that of control dogs. Deafferentation always induced a very marked rise (69%, $P < 0.001$, at 1 min) in blood pressure and the time course of this hypertension was found to be identical to that in control dogs. During the first hour there was no statistical difference in blood pressure between the two groups of animals, except at the 15th and 30th min when the values for blood pressure were higher (21% and 17%; $P < 0.05$) in the 5,7-DHT-treated group than in control dogs (Figure 2).

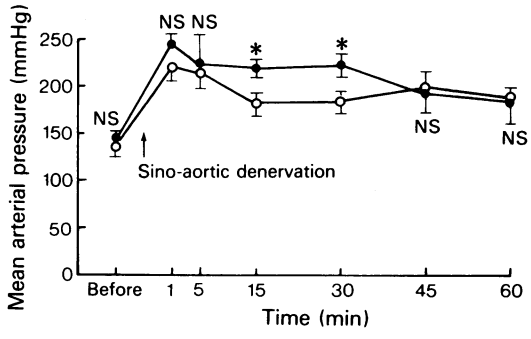

Figure 2 Effect of sino-aortic denervation on mean blood pressure (mmHg) in control dogs (saline pretreated, n = 6) and in dogs pretreated with 5,7-dihydroxytryptamine (5,7-DHT 200 μg/kg intracisternally 7 days earlier) plus desipramine (5 mg/kg i.v. 45 to 60 min prior to 5,7-DHT) n = 5. (○) Control dogs; (●) 5,7-DHT plus desipramine-treated dogs. The blood pressure was measured before and 1, 5, 15, 30, 45 and 60 min after denervation. Comparison with control group at each time using Student's t test; NS = Not significant *$P<0.05$. Mean values are shown; vertical line indicates s.e. mean.

Effect of 5,7-dihydroxytryptamine pretreatment on the response to intravenous propranolol

The basic values (before deafferentation) for heart rate (Figure 3) and blood pressure (Figure 4) were identical in the three groups of animals; deafferentation induced a similar increase in heart rate (Figure 3) and blood pressure (Figure 4) in all animals.

In debuffered hypertensive dogs (n = 7) intravenous injection of (±)-propranolol (300 μg/kg) induced a significant decrease in heart rate (49%; $P < 0.001$, 5 min after the injection) which persisted for at least 1 h (Figure 3). Pretreatment with 5,7-DHT (plus desipramine) did not abolish propranolol-induced bradycardia. There was no statistical difference between propranolol and 5,7-DHT plus propranolol-treated dogs (Figure 3).

Intravenous injection of (±)-propranolol (300 μg/kg) reduced the rise in blood pressure of the debuffered dogs (Figure 4). There was a 21% decrease ($P < 0.01$) in mean blood pressure at the 5th min after the administration of the drug and this remained statistically significant during the whole experiment. Pre-

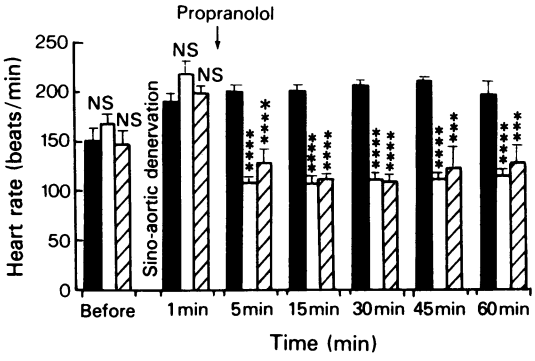

Figure 3 Effect of intracisternal application of 5,7-dihydroxytryptamine (5,7-DHT plus desipramine) on the heart rate response to intravenous (300 μg/kg) (±)-propranolol in debuffered hypertensive dogs. The columns are the values for heart rate (beats/min) measured before, 1, 5, 15, 30, 45 and 60 min after sino-aortic denervation in the three groups of animals. Solid columns: intracisternal 5,7-DHT (200 μg/kg) plus desipramine (5 mg/kg i.v. 45 to 60 min prior to 5,7-DHT) given 7 days earlier plus intravenous saline 30 s after denervation (n = 5). Open columns: intracisternal saline-ascorbic acid given 7 days earlier plus intravenous 300 μg/kg) (±)-propranolol 30 s after denervation (n = 7). Hatched columns: 5,7-DHT (200 μg/kg intracisternally) 7 days previously plus desipramine (5 mg/kg i.v. 45 to 60 min prior to 5,7-DHT) plus intravenous (300 μg/kg) (±)-propranolol 30 s after deafferentation (n = 6). Statistical evaluations were made at each time with 5,7-DHT (plus desipramine)-treated animals (solid columns) by Student's t test. Mean values are shown; vertical lines indicate s.e. mean: ***P<0.01; ****P<0.001; NS = Not significant.

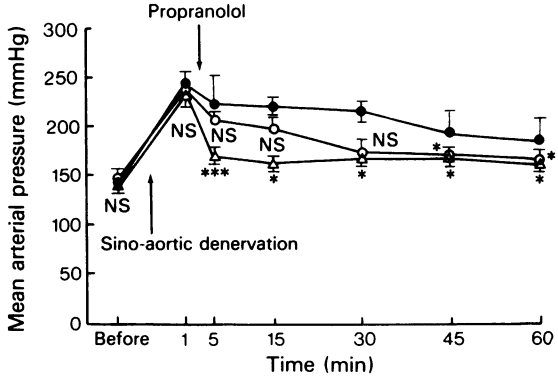

Figure 4 Effect of intracisternal application of 5,7-dihydroxytryptamine (5,7-DHT) plus desipramine on the blood pressure response to intravenous (300 μg/kg) (±)-propranolol in debuffered hypertensive dogs. The values of mean blood pressure (mmHg) were measured before, 1, 5, 15, 30, 45 and 60 min after sino-aortic denervation in the three groups of animals. For description of the experimental protocol and the groups of animals see Figure 3. (●) 5,7-DHT plus desipramine; (○) 5,7-DHT plus desipramine and i.v. propranolol; (△) intracisternal saline plus i.v. propranolol. Statistical comparisons were made at each time with 5,7-DHT (+ desipramine) treated group by Student's t test: *P<0.05; ***P<0.01; NS = Not significant. Mean values are shown, vertical lines indicate s.e. mean.

treatment with 5,7-DHT (plus desipramine) abolished the anti-hypertensive effect of propranolol only during the 30 min immediately following the sino-aortic denervation (Figure 4).

Effect of 5,7-dihydroxytryptamine pretreatment on the action of intracisternal propranolol

There was no difference between the values of either heart rate (Figure 5) or blood pressure (Figure 6) in the three different groups of animals before and just after (1 min) deafferentation.

At a dose of 50 μg/kg (which was inactive by the systemic route) (Montastruc *et al.*, 1978) intracisternal propranolol reduced the tachycardia (22%; $P < 0.01$, 5 min following the injection) of debuffered dogs pretreated with saline (n = 6). The duration of this bradycardia was 45 min, the heart rate not being significantly different from control at the 60th min (Figure 5). In 5,7-DHT (plus desipramine) pretreated animals (n = 4), intracisternal propranolol always induced a decrease (27%; $P < 0.01$ at the 5th min) in heart rate which after 1 h was more marked ($P < 0.05$) than in saline pretreated debuffered dogs (Figure 5).

Intracisternal propranolol significantly reduced (23%; $P < 0.05$ at the 5th min) mean blood pressure in saline pretreated debuffered dogs (Figure 6). After treatment with 5,7-DHT (plus desipramine) intracisternal propranolol failed to decrease the rise in blood pressure of debuffered dogs (Figure 6).

Discussion

The present findings suggest that central 5-hydroxytryptaminergic pathways play an important role in the acute hypotension produced by intracisternal propranolol in debuffered hypertensive anaesthetized dogs but little, if any, in the negative chronotropic response induced by this drug. In fact, Wing & Chalmers (1974) have suggested that 5-HT containing bulbospinal fibres (Fuxe, Hökfelt & Ungerstedt, 1968) may be involved in the central cardiovascular regulation. Although we did not measure 5-HT levels, it is probable that destruction of these fibres (Baumgarten *et al.*, 1975; Gerson & Baldessarini, 1975) was obtained after 5,7-DHT (plus desipramine) pretreatment. Since the combination of such treatment with desipramine reduced noradrenergic damage induced by 5,7-DHT (Björklund *et al.*, 1975)

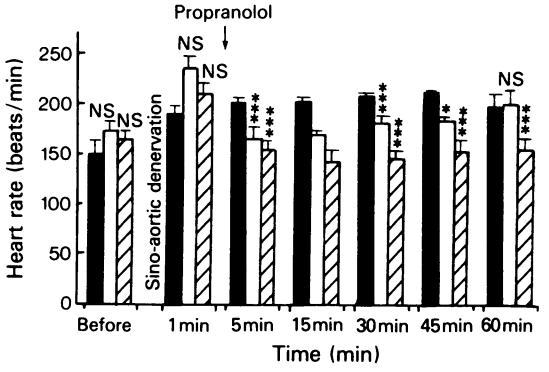

Figure 5 Effect of intracisternal application of 5,7-dihydroxytryptamine (5,7-DHT plus desipramine) on the heart rate response to intracisternal (50 μg/kg) (±)-propranolol in debuffered hypertensive dogs. The columns are the values of heart rate (beats/min) measured before, 1, 5, 15, 30, 45 and 60 min after sino-aortic denervation in the three groups of animals. Solid columns: intracisternal 5,7-DHT (200 μg/kg) plus desipramine (5 mg/kg i.v. 45 to 60 min prior to 5,7-DHT) given 7 days earlier plus intracisternal saline 30 s after denervation (n = 5). Open columns: intracisternal saline-ascorbic acid one week previously plus intracisternal (50 μg/kg) (±)-propranolol 30 s after denervation (n = 6). Hatched columns: 5,7-DHT (200 μg/kg intracisternally) 7 days previously plus desipramine (5 mg/kg i.v. 45 to 60 min prior to 5,7-DHT) plus intracisternal (50 μg/kg) (±)-propranolol 30 s after denervation (n = 4). Statistical evaluations were made at each time with 5,7-DHT plus desipramine treated group (solid columns) by Student's t test; $^{*}P<0.05$; $^{***}P<0.02$; $^{***}P<0.01$; N S = Not significant. Mean values are shown; vertical lines indicate s.e. mean.

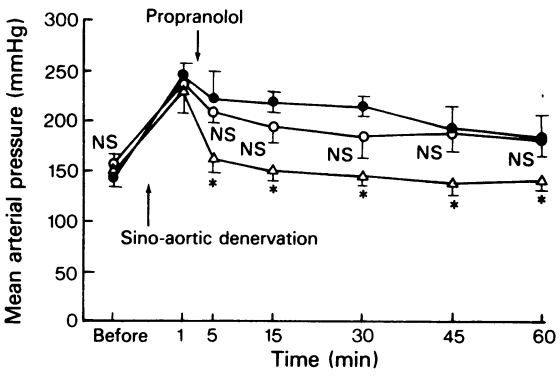

Figure 6 Effect of intracisternal application of 5,7-dihydroxytryptamine (5,7-DHT plus desipramine) on blood pressure response to intracisternal (50 μg/kg) (±)-propranolol in debuffered hypertensive dogs. The values of mean blood pressure (mmHg) were measured before, 1, 5, 15, 30, 45 and 60 min after sino-aortic denervation. For details of experimental protocol and groups of animals see methods and legend to figure 5. (●) 5,7-DHT plus desipramine; (○) 5,7-DHT plus desipramine plus intracisternal propranolol; (△) intracisternal saline plus intracisternal propranolol. Statistical evaluations were made at each time with 5,7-DHT plus desipramine-treated group. Mean values are shown; vertical lines indicate s.e. mean. $^{*}P<0.05$; NS = Not significant.

without altering its neurotoxic activity on 5-HT neurones (Björklund *et al.*, 1975), it is reasonable to assume that the effects we obtained are due to 5-HT-neuronal degeneration. However, it is not possible to exclude completely the possibility that such treatment may have a small effect (as suggested by Nelson, Herbert, Bourgouin, Glowinski & Hamon, 1979) on some dopaminergic and/or noradrenergic neurones.

In our anaesthetized dogs one week after 5,7-DHT (plus desipramine) basic blood pressure and heart rate were not significantly different from controls. This result conflicts with the findings of Wing & Chalmers (1974) who have shown in conscious normotensive rabbits that intracisternal 5,6-DHT results in a reduction of mean arterial blood pressure and heart rate. The differences observed between their study and ours may be due to species differences, anaesthesia or differences between the two experimental protocols. Indeed 5,6-DHT also affected the catecholaminergic stores particularly in the medulla-pons (Wing & Chalmers, 1974; Björklund *et al.*, 1975).

Deafferentation induced a marked increase in both blood pressure and heart rate of control and 5,7-DHT (plus desipramine) pretreated dogs. The values for heart rate and blood pressure were the same in the two groups of animals during the whole experiment except for blood pressure at the 15th and 30th min after deafferentation, which remained higher in the 5,7-DHT (plus desipramine) pretreated group. We have no explanation for this unexpected observation.

These data must be compared with the findings of Wing & Chalmers (1974) in conscious debuffered rabbits. These authors found that pretreatment with intracisternally administered 5,6-DHT prevented the sustained increase in blood pressure seen on the second, sixth, eleventh and fourteenth days after sino-aortic dernervation and only prevented the increase in heart rate after the second day following the buffer nerves section. However, these authors did not report the effects of acute denervation following destruction of central 5-hydroxytryptaminergic neurones. Our study shows that this acute experimental hypertension is not prevented by previous intracisternal administration of 5,7-DHT (plus desipramine). Our results, although they do not rule out a role for central 5-hydroxytryptaminergic pathways in the sustained rise in blood pressure as suggested in chronic debuffered rabbits by Wing & Chalmers (1974) indicate that central 5-hydroxytryptaminergic neurones play little part in the early stages of such experimental hypertension in the dog.

In their study, Wing & Chalmers (1974) also found that the integrity of these neurones appears to be of minimum importance in experimental renal hypertension in the rabbit.

The acute neurogenic hypertension elicited by sino-aortic denervation in the anaesthetized dog is a convenient model for studying the anti-hypertensive effect of propranolol. Using this model, we have previously shown that both the rise in blood pressure and the tachycardia were decreased by intravenous or intracisternal (±)-propranolol, whereas the isomer (±)-propranolol, a drug without β-adrenoceptor blocking potency, was inactive by these two routes (Montastruc *et al.*, 1978). The correction of this acute hypertension by intracisternal (±)-propranolol used at a dose (50 μg/kg) inactive by the systemic route (Montastruc *et al.*, 1978) (suggesting at least a central component in the antihypertensive action of propranolol) is in agreement with previous studies in normotensive animals (for references see Lewis 1976; Scriabine 1979). In the present study, the decrease in blood pressure elicited by intravenous propranolol was delayed by pretreatment with 5,7-DHT (plus desipramine). Furthermore, after 5,7-DHT (plus desipramine) intracisternal propranolol failed to suppress this form of acute experimental hypertension.

These results show that the integrity of central 5-hydroxytryptaminergic neurones appears to be necessary for the antihypertensive effect of propranolol in debuffered dogs. They are in agreement with previous biochemical pharmacological and behavioural studies (for references see introduction) suggesting that propranolol may interact not only with β-adrenoceptors but also with central 5-HT mechanisms.

Bradycardia induced by both intravenous and intracisternal propranolol was not suppressed by pretreatment with 5,7-DHT (plus desipramine). The maintenance of the negative chronotropic effects of propranolol after intracisternal 5,7-DHT (plus desipramine) suggests that the central 5-hydroxytryptaminergic neurones are not directly involved in the decrease in heart rate elicited by the β-blocking agent, propranolol. Moreover, intracisternal propranolol induced a more marked bradycardia in 5,7-DHT (plus desipramine) pretreated dogs than in dogs with intact 5-HT innervation. One can suggest that blockade by propranolol of 5-HT receptors (Middlemiss *et al.*, 1977) or other receptors in the brain and/or spinal cord triggers a compensatory feed-back stimulation of 5-HT processes. According to the works listed above (Chalmers, 1975; Lambert *et al.*, 1978) this mechanism may contribute to a partial antagonism of the bradycardia induced by the β-blocking agent in normal dogs. However, 5,7-DHT (plus desipramine) pretreatment failed to enhance the bradycardia caused by intravenous propranolol. This suggests that the bradycardia effects of intravenous or intracisternal propranolol are not completely under the same 5-HT regulatory control. Possibly propranolol did not reach the same central sites to an equal extent after intravenous as compared to intracisternal administration. This may also be true for the antihypertensive effects of intravenous or intracisternal propranolol, since the former was only delayed whereas the latter was suppressed after 5,7-DHT pretreatment.

In conclusion, these results support the hypothesis that in debuffered anaesthetized dogs, acute hypertension observed after both intracisternal and intravenous propranolol is dependent on the integrity of central 5-hydroxytryptaminergic neurones. In contrast, these central mechanisms did not seem to be crucially involved in the decrease in heart rate elicited by both intracisternal and intravenous propranolol suggesting that the central mechanisms which regulate blood pressure and heart rate are probably different. In a previous study (Montastruc & Montastruc, 1980b) we have found that the destruction of central catecholaminergic neurones with 6-hydroxydopamine suppressed the antihypertensive effect of both intravenous and intracisternal propranolol in debuffered hypertensive dogs. From the results of this study and the present paper, it is tempting to speculate that in debuffered anaesthetized animals, both noradrenergic and 5-hydroxytryptaminergic bulbospinal fibres participate in the hypotensive action of the β-blocking agent, propranolol. However, such a mechanism cannot explain the antihypertensive properties of all the β-blocking agents since many β-adrenoceptor blocking drugs do not penetrate the blood-brain barrier (Scriabine 1979) and are inactive when administered by the intracisternal route in the acute debuffered hypertensive dog (Montastruc & Montastruc 1979; 1980a).

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