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# CARDIOVASCULAR EFFECTS OF HYPERTONIC SODIUM CHLORIDE SOLUTIONS WHEN INJECTED INTO THE LIQUOR SPACE OF ANAESTHETIZED CATS

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**1** In cats anaesthetized with chloralose, hyper- and hypotonic solutions were injected into the cisterna magna (in 0.5 ml) or into a lateral cerebral ventricle (in 0.2 to 0.3 ml), with aqueduct cannulated to prevent the injected solution from entering the subarachnoid space, and the effects on blood pressure and heart rate were examined.

**2** Cisternal injections of hyper- and hypotonic solutions of NaCl (0.51 M and 0.05 M), glucose (1.03 M and 0.10 M), or sucrose (1.02 M and 0.10 M), as well as distilled water produced a rise in arterial blood pressure with tachycardias. Isotonic solutions of NaCl, glucose or sucrose were ineffective.

**3** Ventricular injections of the hypertonic NaCl solution, also produced a pressor response with tachycardia as did an equally hypertonic solution of $NaHCO_3$ but the other solutions produced no circulatory effects when injected in this way.

**4** The pressor responses and the tachycardias occurred after bilateral vagotomy and resulted from a sympathetic discharge which, on cisternal injection, originated from structures reached from the subarachnoid space, and on ventricular injection, from structures in the ventricular walls, probably in the hypothalamus.

**5** The stimuli responsible for the discharge, were, on cisternal injection, the changes in osmolarity, and on ventricular injection, the sodium ions.

## Introduction

When examining the cardiovascular effects produced by the injection of peptides with morphine-like activity into the cisterna magna of anaesthetized cats, a sample of C-fragment ($\beta$-endorphin) was found to produce a rise in blood pressure with tachycardia instead of the expected fall in blood pressure with bradycardia normally produced when the peptide was injected in this way (Feldberg & Wei, 1978). On enquiry, the sample was found not to have been desalted but to contain 30 mg/ml of NaCl. When such a hypertonic (0.51 M) NaCl solution was injected intracisternally it produced a pressor response with tachycardia. This led to an examination of the effects which might be produced on circulation by both hyper- and hypotonic solutions injected not only into the cisterna magna but also into a lateral cerebral ventricle. So far, only the pressor response to hypertonic NaCl solution injected into the third ventricle appears to have been observed. It was obtained by Andersson, Eriksson, Fernández, Kolmodin & Oltner (1972) in conscious goats, by Chiu & Sawyer (1974) in anaesthetized cats and by Zucker, Levine & Kaley (1974) in anaesthetized dogs.

## Methods

Male cats weighing between 2.5 and 7.5 kg were anaesthetized with chloralose injected intravenously after induction of anaesthesia with ethyl chloride. The dose of chloralose injected was 60 mg/kg, except in cats weighing 5 kg or more when the dose was reduced to 50 mg/kg. Blood pressure was recorded from the cannulated right femoral artery on a Smith's Servoscribe potentiometric recorder with a transducer connected through a Cambridge amplifier (Type 72342). The trachea was cannulated and the cats were artificially ventilated.

The method for cannulating the cisterna magna was that described by Feldberg, Gupta, Milton & Wendlandt (1973) and for cannulating the left lateral ventricle, that described by Feldberg & Shaligram (1972). In order to prevent the fluid injected into the lateral ventricle from entering the subarachnoid

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space, the aqueduct was cannulated with a fine polythene tube inserted through the opened cisterna along the floor of the fourth ventricle into the middle of the aqueduct as described by Bisset, Feldberg, Guertzenstein & Rocha e Silva Jr (1975).

The chemicals used for the cisternal and ventricular injections were sodium chloride, D-glucose, sucrose and $NaHCO_3$ (A.R. BDH Chemicals Ltd).

## Results

*Injections into the cisterna magna*

An injection into the cisterna magna of 0.5 ml isotonic NaCl solution (0.15 M) had no effect on blood pressure and heart rate, or at most produced a just perceptible rise of a few mmHg with an acceleration of a few heart beats per min. But the injection of 0.5 ml of a hypertonic NaCl solution (0.51 M) resulted in a pressor response associated with tachycardia which began within 30 s of the injection and lasted a few minutes. In nine cats the variations of the pressor effect to this hypertonic NaCl ranged from 25 to 85 mmHg, and of the tachycardia, from 20 to 80 beats per min.

In Figure 1 the top and middle records illustrate, at (b), pressor responses obtained in two cats to the cisternal injection of 0.5 ml of the 0.51 M NaCl solution. In the one (top record) pressure rose by 85 mmHg and heart rate increased by 43 beats per min; in the other (middle record) blood pressure increased by 40 mmHg and heart rate by 49 beats per min. Similar pressor responses with tachycardia were obtained when the injections were repeated a few hours later but in neither cat did the injection of isotonic NaCl (a) produce more than a just perceptible response on blood pressure and heart rate.

By decreasing the hypertonicity of the 0.51 M NaCl solution to 0.25 M or increasing it to 0.77 M the response decreased or increased respectively.

A pressor response with tachycardia of about the same magnitude as obtained with the 0.51 M NaCl solution occurred on cisternal injection of an equally hypertonic solution of glucose (1.03 M) or sucrose (1.02 M). Figure 1 illustrates the glucose effect on two cats (top and middle records) by comparing the effect of a 0.51 M solution of NaCl (b) with that of a 1.03 M solution of glucose (c). Similar results were obtained in two other experiments with cisternal injections of 0.5 ml of 1.02 M sucrose. For glucose it was further shown that an increase in the tonicity of the solution from 1.03 to 1.57 M increased the cardiovascular response. In isotonic solution, cisternal injections of 0.5 ml of either glucose or sucrose had no effect on blood pressure and heart rate.

Hypotonic solutions of NaCl (0.05 M) or glucose (0.1 M) or simply distilled water, injected cisternally in a volume of 0.5 ml, also produced increases in blood pressure and heart rate of about the same magnitude as obtained with 0.51 M NaCl. This is illustrated in the top and middle records of Figure 1 at (d) and (e).

The hyper- and hypotonic solutions produced their pressor responses with tachycardia also after cutting the vagi in the neck. This is illustrated at (f) in Figure 1 for hypertonic NaCl (top record) and for distilled water (middle record). In both experiments the blood pressure effects were about the same as before the vagotomy. In the experiment with hypertonic NaCl, strong vagal tone had developed before the vagi were cut which itself caused an acceleration of 100 beats per min. Before the vagi were cut the hypertonic NaCl solution had been injected cisternally three times and heart rate increased from 218 to 238 after the first, from 180 to 232 after the second, and from 168 to 224 beats per min after the third injection, as compared to an increase from 268 to 300 beats per min (at f) when the injection was repeated after the vagotomy. In the other experiment the cisternal injection of distilled water had produced an increase in heart rate of 20 beats per min (from 242 to 262) before, and of 26 beats per min (from 252 to 278) after the vagotomy.

None of the hyper- or hypotonic solutions which produced pressor responses with tachycardia on cisternal injection in a volume of 0.5 ml had any effect on blood pressure and heart rate when injected intravenously in this volume.

*Injections into a lateral ventricle*

In six cats intraventricular injections of 0.2 to 0.3 ml of hypertonic NaCl (0.51 M) produced rises in blood pressure ranging from 25 to 80 mmHg, with tachycardias ranging from 40 to 110 beats per min; in addition there was vigorous widespread shivering. Similar effects were obtained in three cats after bilateral vagotomy. Even the tachycardia appeared to be scarcely, if at all, affected by the vagotomy. In one experiment in which the effect of injecting 0.2 ml of the hypertonic NaCl solution was compared before and after cutting the vagi, the acceleration amounted to 80 beats per min (from 250 to 330) before and to 78 per min (from 262 to 340) after the vagotomy.

The same effects as obtained with the 0.51 M NaCl solution were obtained on intraventricular injections of 0.2 to 0.3 ml of hypertonic $NaHCO_3$ solution (0.5 M). But none of the effects was produced when equally hypertonic solutions of glucose (1.03 M) or of sucrose (1.02 M) were injected intraventricularly in a volume of 0.2 to 0.3 ml, nor were hypotonic solutions of NaCl (0.05 M) or of glucose (0.10 M) or distilled water effective when injected in this way. Some of these results

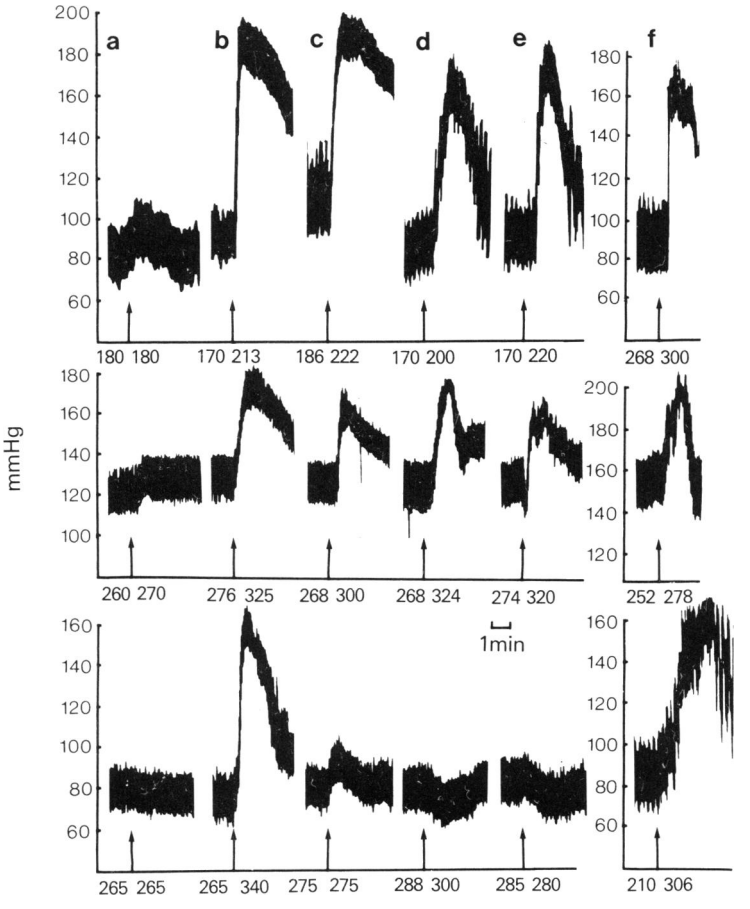


**Figure 1** Arterial blood pressure obtained from six cats anaesthetized with intravenous chloralose. Top record: (a to e) from a 6 kg cat; (f) from a 2.8 kg cat with vagi cut. Middle record: (a to e) from a 2.7 kg cat; (f) from a 2.5 kg cat with vagi cut. Bottom record: (a to e) from a 2.7 kg cat; (f) from a 2.5 kg cat. The arrows indicate in the top and middle record, injections of 0.5 ml into the cisterna magna and in the bottom record injections of 0.3 ml into the left lateral ventricle except at (f) when the volume was 0.2 ml. For all three records the injections were: (a) 0.15 M NaCl; (b) 0.51 M NaCl; (c) 1.02 M glucose and (d) 0.05 M NaCl. The last two injections (e and f) were distilled water and 0.51 M NaCl for the top, 0.05 M NaCl and 0.1 M glucose for the middle, and distilled water and 0.5 M $NaHCO_3$ for the bottom record. The figures at the sides of the arrows indicate heart rate per min before and after the injections. (For details see text).

are shown in the bottom record of Figure 1. They illustrate that a pressor response with tachycardia was produced by the hypertonic NaCl and $NaHCO_3$ (b and f), but not by the hypertonic glucose (c), the isotonic NaCl (a), the hypotonic NaCl solution (d) nor by the distilled water (e).

## Discussion

The pressor responses and tachycardias obtained with the various solutions injected either into the cisterna magna or into a lateral ventricle were central in origin and mediated by the sympathetic because they were not obtained on intravenous injection, and were obtained after bilateral vagotomy. But here the parallelism ends, and the responses obtained with the cisternal and ventricular injections have to be considered separately even when the effects were the same. A hypertonic NaCl solution produced a rise in blood pressure with tachycardia whether injected into the cisterna magna or into a lateral ventricle, with the aqueduct cannulated so as to prevent the injected solution from entering the subarachnoid

space. Yet not only the site and structures affected but also the stimuli which initiated the sympathetic discharge were different. On cisternal injection the structures affected were reached from the subarachnoid space; on ventricular injection they lay in the ventricular walls, probably in the hypothalamus. On cisternal injection the effective stimulus appeared to be the osmolarity because a hypertonic glucose or sucrose solution of equal osmolarity produced a similar pressor response with tachycardia. But these hypertonic solutions were inactive when injected ventricularly. This suggests that a hypertonic NaCl solution, when acting on structures in the walls of the ventricles acts by virtue of its sodium ions. This conclusion is supported by the finding that a hypertonic $NaHCO_3$ solution was also effective on ventricular injection.

The results obtained with hypotonic solutions illustrate a further difference in that they initiated a sympathetic discharge when acting from the subarachnoid space but not when acting from the cerebral ventricles. But they proved to be weaker stimuli than hypertonic solutions. On cisternal injection the strongest hypotonic solution, i.e. distilled water, produced a pressor response with tachycardia which was at most equal to that produced by a 0.51 M NaCl or a 1.03 M glucose solution, whereas stronger effects were obtained with stronger molar concentrations of NaCl and glucose injected cisternally.

In recent years, methods of injecting drugs into different parts of the liquor space in order to analyze their central effects have become more and more common. Our findings illustrate that a vehicle used for dissolving drugs, though innocuous on intravenous injection, may have pronounced effects when injected into the liquor space. This possibility has to be kept in mind when applying drugs by the cisternal or ventricular route.

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