Effect of diazepam (Valium®) on chronic stress-induced hypertension in the rat

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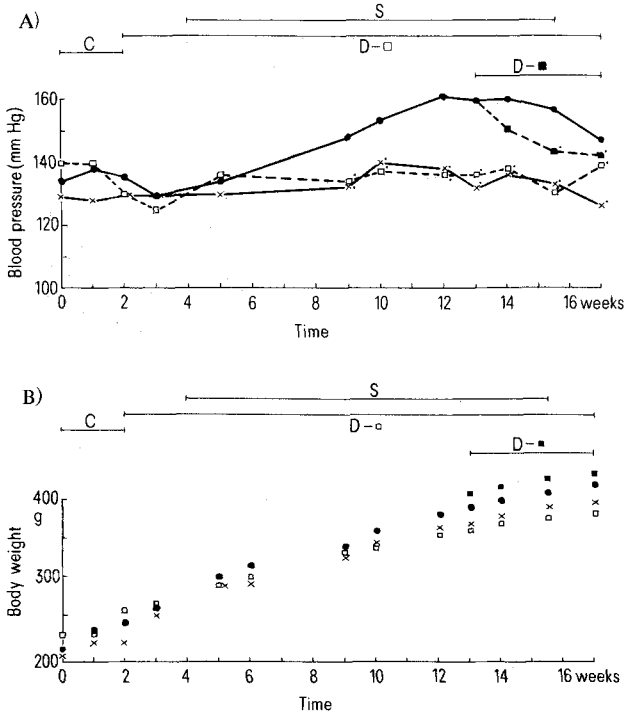
Summary. Chronic treatment with diazepam was effective in preventing chronic stress-induced hypertension in rats. It also prevented the stressful stimuli from maintaining a hypertensive level in animals previously made hypertensive by chronic stress.

Diazepam has long been used for its psychotherapeutic (anti-anxiety), anticonvulsant and muscle relaxant properties[1] and, despite the numerous reports that it lowers blood pressure[2-4] by either a central [5] or a direct peripheral vasodilator mechanism[6,7], 'Medical Letter'[8] has negated its use as an antihypertensive agent or as an adjunct in the treatment of hypertension. Although there are some reports that diazepam is effective in stressful conditions in both animals[9] and man[10], no data exist on its effect in chronic stress-induced hypertension in either animals or man. This report describes the effect of diazepam in an animal model of chronic stress-induced hypertension.

Method. The method used for chronically inducing hypertension in rats was that of Perhach et al.[11], as modified by Segal and Edelstein[12]. In summary, the method and experimental design were as follows.

40 adult male Sabra rats (strain of the Hebrew University of Jerusalem), with an initial b.wt of slightly more than 200 g, were used in this study. Immediately upon their arrival in the laboratory, the rats were divided into 4 groups of 10 each (with no more than 4 rats being placed together in 1 cage). 3 of these groups were then placed into the stress chamber where they were allowed to acclimatize for 2 weeks: the 4th group was maintained outside the stress chamber and served as the 'out of stress chamber' controls for the duration of the experiment. Standard laboratory chow and water were allowed ad libitum. Following the 2-week acclimatization period, the rats' blood pressures were measured twice at weekly intervals by a modification of the tail-cuff method (as also previously reported[12]) to obtain control, base-line, values. At the end of the 2-week control period, 1 of the 3 groups in the stress chamber recieved diazepam[13] (1 mg/kg) in the daily food: the other 2 groups served as 'in chamber' controls. Blood pressure measurements were continued at weekly intervals for another 2 weeks and then the stress schedule was started (alternating 5-min periods of flashing light and buzzing sound for 4 h per day at 3 days per week, selected on a random schedule). After 9 weeks in the stress period, 1 of the 2 control groups within the stress chamber recieved diazepam (1 mg/kg) in the daily food and the stress schedule continued for another 2 weeks. Medication was terminated 10 days after the end of the stress period. Blood pressure measurements were continued at weekly intervals until the end of the experiment. All drug administrations, based upon daily food intake, were as previously reported[12]: the amount of drug administered was calculated on the basis of an average daily intake of 20 g of food per rat and the diazepam regimen was freshly prepared each day. Significance determinations ($p < 0.01$) were according to the Student's t-test.



A Blood pressure and *B* body weight during each phase of the experimental design. ●——●, Controls maintained within the stress chamber; x-x, controls maintained outside of the stress chamber for the duration of the experiment; D - □ and □——□, diazepam (1 mg/kg) in the daily food from weeks 2 to 17; D - ■ and ■——■, diazepam (1 mg/kg) in the daily food from weeks 13 to 17: C - control period; D - □ and D - ■, drug treatment periods; S - stress schedule duration. All values indicated by small black dots at the upper right of symbols are significantly ($p < 0.01$) lower than the control hypertensive group's pressure for that period.

Results and discussion. The results are outlined in the figure, A (blood pressure) and B (body weight). As can be seen in A, the control blood pressures averaged from 135 mm Hg at the beginning of the experiment and rose to an average of 160 mm Hg by the 8th week of stress, maintainig this average until the stress was terminated. On the other hand, after 5 weeks of stress, the diazepam-treated group's blood pressure was significantly lower than that of the hypertensive controls. This significant difference remained until the end of the experiment, with blood pressures being maintained within the range of the untreated 'out of stress chamber' controls, i.e., approximately 130 mm Hg.

The administration of diazepam to the 2nd non-treated group of rats maintained within the stress chamber (9 weeks after stress), and now also in hypertensive stress with an average blood pressure of 158 mm Hg, produced a fall in blood pressure to 152 mm Hg within 1 week (not significantly lower than the hypertensive controls) and a further fall to 145 mm Hg within 2 weeks of drug administration (significantly lower than the hypertensive controls). After the termination of stress, the blood pressure average of the remaining hypertensive control group decreased over a 2-week period from 157 mm Hg to approximately 150 mm Hg.

This is contrary to what we observed in an earlier study[14], when we administered para-methoxyphenylethylamine (PMPEA) to a group of 10 rats in chronic hypertensive stress. In that study[14], the blood pressure fell within 1 week from its maximum to a value of 133 mm Hg and then further to 122 mm Hg within the following week. Contrary to this type of immediate, and probably direct effect of PMPEA upon some central cardiovascular mechanism, diazepam appeared indirectly to prevent the stress from maintaining the blood pressure at the hypertensive level by a central filtering of the stressful stimuli. Since diazepam did hinder stressful stimuli from maintaining an elevated blood pressure in addition to preventing chronic stress-induced hypertension, it can be assumed that its effect upon blood pressure is most probably mediated centrally, as suggested originally by Chai and Wang[5], and not by some vasodilator mechanism[6,7]. The observed effects of diazepam were independent of any action that this agent may have had upon the growth pattern of the experimental animal (figure, B).

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Structure and antiarrhythmic activity of three ketophosphonium salts[1]

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Summary. Three alicyclic organic phosphonium salts with an oxo and a morpholino group were found to exhibit a substantial antiarrhythmic action. The different activity levels were tentatively related to the structural modifications that they could induce in the cardiac cell membrane.

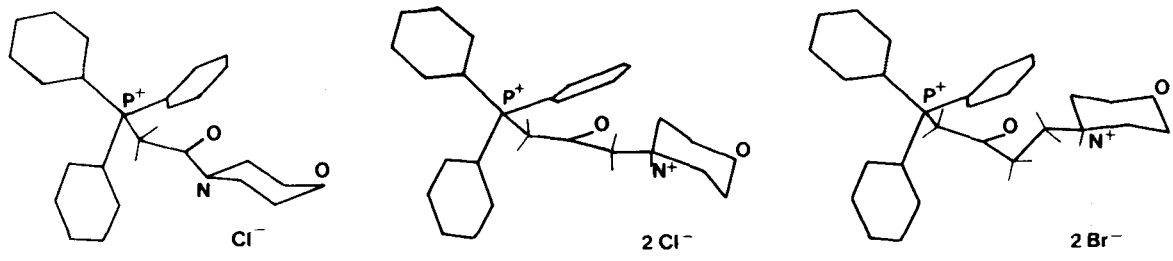
The 2 broad classes of agents used to correct arrhythmias[2,3] are specific drugs. β-adrenergic blockers such as propranolol, and non-specific ones such as quinidine which act as membrane-stabilizing agents[4]. Attempts to correlate the mode of action of 'quinidine-like' drugs with their molecular size revealed no simple relationships[5,6] when one considers the variety of their chemical classes.

However, the molecular structure of most non specific antiarrhythmic drugs consists of an aromatic portion connected with a basic amino group by way of an ester, ether or amide group. We present here the antiarrhythmic activity of 3 compounds possessing such structural requirements but where the ammonium electropositive site has been replaced by a phosphonium group, and we report their geometric characteristics to delineate possible structure-activity relationships (figure 1).

Material and methods. Synthesis of ketophosphonium salts. (2-oxo-2-morpholino) ethyltriphenylphosphonium chloride (OMETP) was prepared by treatment of chloroacetyl chloride with morpholine in 1,2-dichloroethane at -10 °C and further condensation of the thus-formed N-chloroacetylmorpholine (b.p. 106 °C/0.01 mm) with triphenylphosphine in dry benzene, refluxing under nitrogen for 5 h. The isolated precipitate was recrystallized from isopropanol (m.p. 225 °C).

(2-oxo-3-morpholino) propyltriphenylphosphonium chloride hydrochloride (OMPTP) was obtained by reacting (2-oxo-3-chloropropyltriphenylphosphonium chloride[7] with morpholine hydrochloride in the presence of sodium in ethanol under reflux for 3 h. Sodium chloride was filtered, ethanolic hydrochloric acid added to the filtrate and solvent evaporated. The crude product was recrystallized from ethanol (m.p. 165 °C).

(2-oxo-4-morpholino)butyltriphenylphosphonium bromide hydrobromide (OMBTP) was synthesized in anhydrous chloroform, by refluxing under nitrogen for 12 h, from



OMEPT OMPTP OMBTP

Fig. 1. Perspective drawn views of the 3 antiarrhythmic ketophosphonium salts.