THE EFFECT OF ADRENERGIC BLOCKING AGENTS AND OF CHLORPROMAZINE ON BLOOD PRESSURE INCREASE BY VASOPRESSIN AND ANGIOTENSIN

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The influence of the adrenergic blocking agents hydergine, dibenamine and tolazoline and of chlorpromazine on the mean arterial pressure response to vasopressin, angiotensin and barium chloride in anaesthetised dogs was investigated. Adrenergic blocking agents potentiate significantly the pressure response to vasopressin while leaving the responses to angiotensin and barium chloride unaltered. Chloropromazine potentiates the responses to both vasopressin and angiotensin. This potentiation is not due to blood pressure lowering produced by adrenergic blockade or by chlorpromazine.

THE experimental data on the influence of adrenergic blocking agents or of chlorpromazine on hypertensive effects of substances not belonging to the sympathomimetic drugs, are partly incomplete and partly contradictory. Nickerson, Bullock and Nomaguchi (1948) explained the potentiation of angiotensin after dibenamine as a result of a decrease of blood pressure caused by this adrenolytic drug. De Vleeschhouwer (1947) found an insignificant alteration of the effect of pituitrin after dibenamine. Youmans and Rankin (1947) could not demonstrate any influence of dibenamine on arterial pressure response of pitressin and angiotensin. According to Bianchi, De Schaepdryver, De Vleeschhouwer and Preziosi (1960) phentolamine does not change the pressor effect of synthetic angiotensin. We have made a controlled series of experiments to investigate the influence of adrenolytic drugs and of chlorpromazine on the hypertensive effect of vasopressin and angiotensin. Some of the results have already been briefly reported (Supek, Uroić, Gjuriš and Kečkeš, 1959).

METHODS

Mongrel dogs were anaesthetised with chloralose (70 mg./kg.) dissolved in 25 per cent urethane solution (urethane solution 6·0 ml./100 mg. chloralose) and rabbits with urethane (1·25 g./kg.). Arterial blood pressure was taken through a cannula inserted into the carotid artery and recorded by a mercury manometer. The drugs studied were: vasopressin (Tonephin, Hoechst, 5 I.U./ml), angiotensin (2 Edman U./mg), barium chloride (analytical reagent), *NN*-dibenzyl-β-chloroethylamine chloride (Dibenamine, S.K.F.), tolazoline (Benizol, Krka), Hydergine (Sandoz), chlorpromazine (Largactil, Specia). Blood pressure was recorded before and after application of adrenolytic drugs or chlorpromazine.

In preliminary experiments no interference between the three vasopressor substances was found. Therefore all three substances were tested in the same experiment. The difference between the mean of blood

TABLE I

THE MEAN VALUES OF BLOOD PRESSURE INCREASE IN MM. HG OF VASOPRESSIN, ANGIOTENSIN AND BARIUM CHLORIDE BEFORE AND AFTER HYDERGINE, DIBENAMINE, TOLAZOLINE OR CHLORPROMAZINE IN ANAESTHETISED DOGS

	Number of dogs	Hydergine 0·3–0·9 mg./kg. i.v.			Number of dogs	Dibenamine 25 mg./kg. i.v.			Number of dogs	Tolazoline 20–40 mg./kg. i.v.			Number of dogs	Chlorpromazine 2–5 mg./kg. i.v.		
		Before	After			Before	After			Before	After			Before	After	
Vasopressin 0·1 I.U./kg. i.v.	14	8·9±1·1*	18·4±2·7	P<0·01	8	15·9±2·8	33·1±4·0	P<0·01	8	14·0±2·0	27·9±2·6	P<0·01	22	8·8±0·7	21·1±1·5	P<0·01
Angiotensin 0·07 mg./kg. i.v.	12	9·4±1·3	10·0±1·4	P>0·1	8	9·4±0·8	10·9±1·5	P>0·1	8	6·3±0·5	7·7±1·1	P>0·1	11	8·2±0·7	13·4±1·3	P<0·01
Barium chloride 0·5–1·0 mg./kg. i.v.	14	10·8±1·6	14·0±1·5	P>0·1	8	9·7±1·3	5·2±0·6	P<0·01	8	8·5±0·9	8·9±1·1	P>0·1	24	7·9±0·9	8·4±0·7	P>0·5

* Standard error of the mean.

TABLE II

1. THE CORRELATION OF BLOOD PRESSURE LEVEL AFTER HYDERGINE, DIBENAMINE, TOLAZOLINE OR CHLORPROMAZINE AND PRESSOR EFFECT OF VASOPRESSIN, ANGIOTENSIN AND BARIUM CHLORIDE

2. THE CORRELATION OF PERCENTAGE FALL OF BLOOD PRESSURE CAUSED BY THESE ADRENOLYTICS OR CHLORPROMAZINE AND PRESSOR EFFECT OF VASOPRESSIN, ANGIOTENSIN AND BARIUM CHLORIDE

	1. Blood pressure after adrenolytics and chlorpromazine				2. Percentual fall of blood pressure after adrenolytics and chlorpromazine			
	Hydergine	Dibenamine	Tolazoline	Chlorpromazine	Hydergine	Dibenamine	Tolazoline	Chlorpromazine
Vasopressin	n = 13 r = −0·486 P > 0·05	n = 6 r = −0·366 P > 0·1	n = 6 r = −0·585 P > 0·1	n = 18 r = −0·162 P > 0·1	n = 13 r = −0·422 P > 0·1	n = 6 r = −0·368 P > 0·1	n = 6 r = −0·695 P > 0·05	n = 18 r = −0·316 P > 0·1
Angiotensin	n = 10 r = −0·501 P > 0·05	n = 6 r = 0·906 P < 0·01	n = 6 r = −0·792 P < 0·02	n = 8 r = 0·376 P > 0·1	n = 10 r = −0·378 P > 0·1	n = 6 r = 0·941 P < 0·01	n = 6 r = −0·917 P < 0·01	n = 8 r = 0·251 P > 0·1
Barium chloride	n = 12 r = −0·195 P > 0·1	n = 6 r = 0·603 P > 0·05	n = 6 r = −0·535 P > 0·1	n = 22 r = 0·615 P < 0·01	n = 12 r = −0·276 P > 0·1	n = 6 r = 0·613 P > 0·1	n = 6 r = 0·531 P > 0·1	n = 22 r = 0·311 P > 0·1

pressure effects before and after tested substances was compared by a "t" test. The correlation coefficients were calculated according to Fisher (1950).

Results

The results summarised in Table I show that the blood pressure increase produced by vasopressin is significantly potentiated by all the drugs. Moreover chlorpromazine also potentiates the pressor effect of angiotensin. Barium chloride used as an unspecific vasopressor control agent showed no potentiation. Correlations of blood pressure level, before and after adrenergic blockade or chlorpromazine, and blood pressure effect of investigated substances are presented in Tables II and III.

TABLE III

THE CORRELATIONS OF HYPERTENSIVE EFFECT OF VASOPRESSIN, ANGIOTENSIN AND BARIUM CHLORIDE AND INITIAL BLOOD PRESSURE LEVEL BEFORE AND AFTER HYDERGINE, DIBENAMINE, TOLAZOLINE OR CHLORPROMAZINE

	Before adrenolytics and chlorpromazine	After adrenolytics and chlorpromazine			
		Hydergine	Dibenamine	Tolazoline	Chlorpromazine
Vasopressin	n = 50 r = −0·160 P > 0·1	n = 13 r = −0·053 P > 0·1	n = 6 r = −0·006 P > 0·1	n = 6 r = 0·233 P > 0·1	n = 18 r = 0·145 P > 0·1
Angiotensin	n = 36 r = −0·325 P < 0·05	n = 9 r = −0·246 P > 0·1	n = 6 r = 0·179 P > 0·1	n = 6 r = 0·427 P > 0·1	n = 9 r = 0·457 P > 0·1
Barium chloride	n = 28 r = −0·307 P > 0·1	n = 12 r = 0·518 P > 0·05	n = 6 r = −0·229 P > 0·1	n = 6 r = 0·147 P > 0·1	n = 22 r = 0·336 P > 0·05

Initial blood pressure level, blood pressure after adrenolytics or chlorpromazine, as well as blood pressure fall caused by these agents are not related to the above described phenomenon. Between the hypertensive effect of angiotensin and the initial blood pressure level there is a significant negative correlation ($P<0·05$; Table III).

Discussion

Braun-Menendez, Fasciolo, Leloir and Munoz (1940) found that the pressor effects of angiotensin were inhibited by previous administration of vasopressin. Our experiments did not confirm this finding.

Page and Taylor (1949) could not show any relationship between blood pressure level and pressor effect of angiotensin in anaesthetised dogs. Our results showed a statistically significant negative relation between these two values.

The most interesting finding in our experiments is the potentiation of vasopressin and angiotensin by chlorpromazine and the potentiation of vasopressin by three different adrenergic blocking agents. It is well known that chlorpromazine is a very potent adrenolytic drug. Therefore it is likely that the potentiation of vasopressin is related to the adrenergic blocking properties of the drugs investigated. The additional potentiation

of angiotensin by chlorpromazine seem to be ascribable to other pharmacological activities of this drug which are, as it is well known, numerous. The described potentiations are neither correlated with blood pressure level (before and after blockade) nor with the blood pressure decrease caused by the investigated blocking agents. This is evident from our correlation data.

Up to now we have no satisfactory explanation for the described effect. The mechanisms of this phenomenon are under investigation. Preliminary experiments showed that pure synthetic substances (isoleucin^5-angiotensin octapeptide and lysin^8-vasopressin) behave identically to the crude preparations.

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