Reactivity to Pressor Agents in Hypertension

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The pressor responses to intravenous injections of angiotonin and s-methyl iso-thiourea have been studied in 50 hypertensive subjects and 20 normotensive controls. The rises of blood pressure in the two groups were similar, being but slightly greater in the hypertensives. After the blood pressure has been reduced with hexamethonium, however, the pressor responses to angiotonin, s-methyl iso-thiourea and noradrenaline are much greater in hypertensives than normotensive subjects. The responses under these conditions to all three pressor agents run parallel to each other, suggesting that there is no specific increase in reactivity in hypertensive subjects, either to angiotonin or noradrenaline. It has been concluded that there is evidence of increased reactivity to pressor substances in hypertensive subjects but that this is not demonstrable until the blood pressure control mechanisms have been inactivated by hexamethonium.

It is generally agreed that in human hypertension the blood pressure rise is due to an abnormally high peripheral resistance, the result of constriction of the arterioles. While some workers believe that the arteriolar constriction is predominantly due to an overaction of the sympathetic nervous system, others hold the view that it is the result of the presence of a circulatory pressor substance.

The demonstration by Goldblatt1 that experimental renal ischemia leads to hypertension was followed by the isolation of a pressor substance which was named angiotonin by Page and Helmer2 and hypertensin by Braun-Menendez and associates.3 Angiotonin produces vascular constriction by a direct action on the muscle of blood vessels,4 and would seem to be a substance capable of producing a rise of blood pressure like that which occurs in human hypertension.

Direct evidence that angiotonin is responsible for some of the blood pressure rise in hypertension depends on the demonstration that the substance is present in the blood of hypertensive subjects. Kahn and his co-workers5 have reported that the concentrations of angiotonin in the blood of patients with malignant hypertension are approximately 20 times as great as in the blood of normal control subjects. The same workers found that in non-malignant essential hypertension the angiotonin concentration, although slightly greater than in the controls, was too small to allow conclusions to be drawn as to its effectiveness in producing the vasoconstriction in these patients.

The further possibility remains, however, that hypertensive subjects might react more vigorously than normals to this substance. If this were so, a normal or slightly raised amount of circulating angiotonin might produce a larger rise of blood pressure in the hypertensive than in the normotensive subject. The action of angiotonin in normotensive man has been described by Bradley and Parker6 and Wilkins and Duncan7 but except for the report of Gregory and his colleagues,8 who studied the effects of angiotonin in hypertensive subjects after spinal anesthesia, we have found no reference to its administration to hypertensive patients.

The possibility, moreover, that the blood vessels of hypertensive subjects are unusually sensitive to many pressor stimuli has been extensively studied in man and in animals, using both chemical and nervous stimulation. In man, the cold pressor test was found by Hines and Brown9 to produce larger responses in hypertensive subjects and in subjects susceptible to hypertension, than in normotensive subjects. Reports of other workers, however, have conflicted with these findings. Alam and Smirk10 found that while large pressor responses to cold and to the reflex from voluntary muscle were more common in cases of essential hypertension than in normal subjects, yet in many cases of hypertension the response was no

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greater than in some normal subjects. Russek and Zohman\textsuperscript{11} reported similar results with the cold pressor test, but Pickering and Kissin\textsuperscript{12} could find no difference in the responses to cold in the hypertensive and normotensive groups.

The responses to chemical stimuli have also been extensively examined. Clough\textsuperscript{13} found that in hypertensive subjects the rises of blood pressure produced by adrenaline were much greater than those in normal subjects. Lian, Stoicesco and Vidrasco\textsuperscript{14} found that the vascular reactions produced by adrenaline, and other stimuli, were greater in hypertensives than in normals. Goldenberg and his co-workers\textsuperscript{15} reported that hypertensive patients had similarly exaggerated pressor responses to noradrenaline, whilst Raab\textsuperscript{16} has reported that a much greater rise in blood pressure occurs in hypertensive subjects than in normals after the inhalation of carbon dioxide. In contrast to these findings, however, many workers have reported similar pressor responses in hypertensive and normotensive subjects. Fatheree and Hines\textsuperscript{17} noted no distinct difference in the response of hypertensive and normotensive subjects to adrenaline and similar results were reported by Gordon and Levitt\textsuperscript{18} and by Judson and associates.\textsuperscript{19, 20} Page\textsuperscript{21} has reported that angiotonin produces similar rises of blood pressure in renal hypertensive dogs and in normal dogs.

It seems that the evidence concerning the pressor reactivity in hypertensive and normotensive subjects is conflicting; while some have found exaggerated pressor responses in hypertensives, many others have found similar responses in the two groups. This may be due to the fact that the investigation of this problem is complicated by the fact that the different starting levels of the blood pressure may themselves determine differences in the degree to which hypertensives and normotensives respond to various stimuli. In addition, the extent to which the homeostatic regulatory mechanisms oppose rises of pressure from pressor stimuli may not have precisely the same effects in hypertensives as they have in normotensives.

We report here a comparison of the pressor effects of angiotonin in hypertensive and normotensive subjects. A comparison of the pressor effects of angiotonin and the effects of noradrenaline and the synthetic pressor agent s-methyl iso-thiourea has also been made in the two groups. The observations have been made under standard conditions, and also after ganglionic blockade with hexamethonium. The preliminary administration of hexamethonium has the advantage that it not only renders the starting levels of the blood pressure more nearly comparable, but it also minimises interference from the homeostatic blood pressure control mechanisms. Some observations have also been made after the blood pressure had been reduced by veratrum alkaloids.

**Methods**

Blood pressures were recorded by the auscultatory method, in accordance with the recommendations of the Committee for the Standardization of Blood Pressure Readings of the American Heart Association and the British Cardiac Society (1939). The subjects were recumbent in a quiet room. The blood pressure was measured every 30 seconds by one of us. After a preliminary period of about 10 minutes, a needle was introduced into the median basilic vein in the other arm, and a slow infusion of 5 per cent glucose was commenced. After this, injections were made through a three-way tap. These were given without the patient's knowledge of the nature of the injection. Occasional dummy injections of 5 per cent glucose were given to exclude pressor responses other than those attributable to the pressor agent being studied.

In the experiments in which hexamethonium was used 20 mg. of hexamethonium was injected every three minutes, until two successive doses produced no further fall in blood pressure. When the veratrum alkaloids were used 0.5 mg. of Veriloid (Riker) was given at two-minute intervals until premonitory toxic symptoms were reported, or until the blood pressure had reached a near normal level.

The doses used were: angiotonin 5 units, noradrenaline 2 μg. and s-methyl iso-thiourea 30 mg.

**Selection of patients:** The hypertensive subjects were selected from those attending the hypertensive clinic. All had casual blood pressures consistently higher than 180/100 mm. Hg. A normotensive group of similar age was selected from surgical patients awaiting operation, or from healthy normotensive volunteers. In this group the casual blood pressures were consistently below 150/90 mm. Hg.
Results

(1) Effects of Angiotonin in Hypertensive and Normotensive subjects

The rises of blood pressure produced by angiotonin were examined in 50 hypertensive subjects and in 20 normotensive controls (fig. 1). Repeated injections of the same dose to individual patients on the same day and on different days produced similar rises of blood pressure. The average rise of blood pressure in the hypertensive group was 26/20 mm. Hg; the average rise in the control group was 20/16 mm. Hg.

The duration of the pressor effect was substantially the same in the two groups, the average duration being five minutes in each group.

In agreement with the findings of most other workers, the pulse slowed in most of the normotensive group, the slowing on occasion being pronounced. There was, however, no striking alteration in the pulse rate in the hypertensive group.

Most of the hypertensive subjects had essential hypertension. Four had hypertension associated with manifest renal disease, 8 had hypertension which was thought to have followed a pre-eclamptic toxemia of pregnancy and one had coarctation of the aorta. No striking differences were noted either in the size of the blood pressure rise or in the duration of the response in these various groups of patients.

(2) Effects of S-Methyl Iso-Thiourea in Normotensive and Hypertensive Subjects

Ten of the subjects who had been tested with angiotonin were subsequently given injections of s-methyl iso-thiourea. Of the subjects examined, five were hypertensive and five normotensive. The subjects were selected because they had shown extreme variation in the pressor response to angiotonin. Although the effects of 50 mg. of s-methyl iso-thiourea were usually greater than the effects of 5 units of angiotonin, the responses of the individual patients to the two drugs were otherwise similar, in the sense that those who exhibited large rises of blood pressure with one substance also had large rises of blood pressure with the other, whilst those in whom the pressor effects of one were slight similarly showed smaller responses to the other drug.

(3) Effects of Angiotonin in Hypertensive and Normotensive Subjects after Ganglionic Block with Hexamethonium

Seventeen hypertensive subjects and 17 normotensive subjects were tested with angiotonin after the blood pressure had been reduced by large intravenous doses of hexamethonium. Repeated doses of hexamethonium were given, and when an apparently stable level of blood pressure had been reached, the angiotonin was injected. The results are shown in figure 2. The pressor response was now much greater in the hypertensive group than in the normotensive group. The average rise of blood pressure in the hypertensive subjects was 45/32 mm. Hg as compared with 22/18 mm. Hg for the control group under the same conditions. The responses in the hypertensive group were almost doubled by ganglionic block, whereas in the control group the augmentation of the pressor response produced by hexamethonium was usually much smaller. The extent to which the blood pressure of the hypertensive subjects fell after hexamethonium did
not seem to be an important factor in determining the degree to which the pressor response was augmented, for both those with large falls of blood pressure with hexamethonium and those with small falls had similarly augmented pressor responses. There was less individual variation in the response to angiotonin after ganglionic block than under control conditions, but some variation in the response was still found.

(4) Comparison of the Effects of Angiotonin, Noradrenaline and S-Methyl Iso-Thiourea after Ganglionic Block

The pressor responses to angiotonin, noradrenaline and the synthetic pressor agent, s-methyl iso-thiourea, were compared in 20 subjects, 13 hypertensive and 7 normotensive, after hexamethonium had been given. The subjects were selected because of the wide variation in their previous responses to angiotonin under similar conditions. The results are shown in figures 3 and 4. It is clear that the sensitivity to the three substances runs parallel, for those with large responses to angiotonin also had large responses to the other substances tested. It is also clear that the pressor responses to all three substances are consistently greater in the hypertensive group than in the normotensive.

(5) Effect of Angiotonin after Administration of Veratrum in Hypertensive Subjects

In 10 hypertensive subjects, the blood pressure was reduced to near normal levels by the intravenous administration of Veriloid, an alkaloidal extract of veratrum viride. After the blood pressure had been so reduced, the pressor response to angiotonin was studied. The responses were similar to those obtained after hexamethonium, the average response being 51/31 mm. Hg. The pressor responses
were greater in all the patients after the blood pressure had been lowered than they were under resting conditions.

**Discussion**

The three pressor agents which have been studied in this work have similar sites of action but are otherwise widely dissimilar. Two of them, angiotonin and noradrenaline, although unrelated chemically are both substances which occur naturally, but s-methyl iso-thiourea is a synthetic substance. The cardiac output in man is reduced by angiotonin, and by noradrenaline and it seems likely that it is not raised by s-methyl iso-thiourea. All three drugs produce rises of blood pressure primarily by a direct action on the blood vessels.

It cannot be assumed, however, that the rises of blood pressure which follow the administration of any pressor substance under ordinary test conditions give any precise indication of the degree of vascular constriction which the substance has caused; for there is evidence that rises or falls of blood pressure produced in a variety of ways may be buffered by regulatory mechanisms, which tend to maintain the blood pressure at a constant level. It seems probable that the rise of blood pressure which follows the administration of a pressor substance represents the resultant of the vascular constriction produced by the pressor stimulus and the modification of this produced by reflex homeostatic regulatory mechanisms.

The rises in blood pressure produced by the intravenous administration of angiotonin and s-methyl iso-thiourea are usually a little larger in hypertensives than in normotensives. But, following ganglionic blockade with large doses of hexamethonium, the rises of blood pressure in the hypertensives are considerably larger than in the normotensives. The extensive degree of blockade by hexamethonium which occurs with intravenous doses of the order of 1 to 2 mg. per kilogram, such as we used, undoubtedly severely limits and may even abolish the capacity of the reflex homeostatic regulatory mechanisms to counter changes in blood pressure. The profound postural hypotension which occurs with the doses we have used suggests that this is so. The average pressor responses to angiotonin and to s-methyl iso-thiourea under these conditions are about twice as large in hypertensives as in normotensive subjects.

A possible interpretation of this result is that pressor reactivity is greater in hypertension than in normotension and that, when this is not manifest under ordinary circumstances, it is because the activity of the regulatory mechanisms limits the rises of blood pressure to a greater extent in the hypertensive than in the normotensive.

An alternative explanation is that the rises of blood pressure produced by pressor agents are greater from the lower levels of blood pressure which result from methonium administration. We have insufficient evidence to comment on this possibility.

The changes in the responses of the blood pressure to various pressor agents may involve adjustments throughout the cardiovascular system. Certainly, on the evidence presented, it cannot be assumed that such changes are confined to alterations in the state of contraction of blood vessels. Some of our observations, however, seem to warrant further discussion.

In the absence of ganglionic blockage, the magnitudes of the blood pressure rises, in response to a standard dose of angiotonin, vary from one person to another. This statement applies both to normotensives and to hypertensives. The differences in the pressor responses are considerable. A less reactive person may have a rise of 5/0 mm. Hg from 5 units of angiotonin, whereas a more reactive person may have a rise of 50/30 mm. Hg. These variations, however, are not fortuitous because when angiotonin is compared with the synthetic substance s-methyl iso-thiourea and with noradrenaline, it is found that the patients who give big rises with angiotonin also give big rises with noradrenaline and s-methyl iso-thiourea; likewise, small responses to angiotonin are associated with small responses to noradrenaline and s-methyl iso-thiourea. Therefore, we may conclude that large and small responses to angiotonin reflect changes in the
reactivity to pressor agents in general, rather than a specific sensitivity to angiotonin.

A further conclusion may be drawn, namely, that if circulating pressor agents play a part in maintaining the blood pressure level in hypertension or in normotension, then the extent to which they influence the blood pressure level depends to an important degree upon the patient's responsiveness to the pressor agent. Amounts of angiotonin or of certain other pressor agents which cause substantial blood pressure increases in reactive patients, have very little action in unreactive patients. Hence, the presence or absence of hypertension could depend as much upon the reactivity of the patient to a stimulus as on the magnitude of the stimulus.

The fact that increased pressor activity can be demonstrated, not only in essential hypertension but also in renal hypertension, and post-toxemic hypertension, is favorable to the conclusion that the increased reactivity may be a result of continued blood pressure elevation and possibly due to cardiovascular hypertrophy.

If increase of cardiovascular reactivity is an effect of continued hypertension, then the development of abnormal sensitivity to pressor stimuli is probably one of the mechanisms which lead to the perpetuation of the hypertensive state, irrespective of the initiating cause.25

SUMMARY AND CONCLUSIONS

Under standard conditions, hypertensives have slightly greater pressor responses to angiotonin and to s-methyl iso-thiourea.

After ganglionic blockade with hexamethonium, these substances and also noradrenaline induce much larger pressor responses in hypertensives than in normotensives.

The increased pressor response following ganglionic blockade is present in essential, renal and post-toxemic hypertension.

Some patients react strongly to all three substances, and other patients give but small rises of blood pressure. In almost all instances high or low reactivity to angiotonin is associated with reactivity of corresponding magnitude to the administration of the other pressor substances.

There seems to be good evidence that there are variations in the reactivity of the circulatory system as a whole to pressor stimuli; this variation from one person to another is likely to be an important factor in determining the effect of any humoral pressor agents on the blood pressure level.

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SUMMARY IN INTERLINGUA

Le responsas pressorial a injectiones intra-venose de angiotonina e s-methyl-iso-thiourea esseva studiate in 50 individuos hypertensive e 20 individuos normotensive de controlo. Le augmento del pression sanguinee esseva simile in le duo gruppos; in le individuos hypertensive illo esseva levemente plus grande. Del altere latere, si le pression sanguinee esseva primo reducette per medio de hexamethonium, le responsas pressorial a angiotonina, s-methyliso-thiourea, e noradrenalina, le responsas pressorial esseva multo plus grande in le gruppo hypertensive que in le gruppo normotensive. Sub iste conditiones le responsas al tres mentionate agentes se manifesta in formas parallel. Isto pare significar que individuos hypertensive non es characterisate per un augmento specific de reactivitate a angiotonina o a noradrenalina. Le conclusion a derivar ab iste constatationes es que in individuos hypertensive il ha un augmentate reactivitate a substantias pressorial sed que iste augmento non es demonstrabile usque le mechanismos regulatori del pression sanguinee es inactivate per hexamethonium.

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