THE CORONARY VASODILATOR ACTION OF THE CRYSTALLINE PRINCIPLES OF *AMMI VISNAGA* LINN.

By M. M. Bagouri

From the Physiological Department, Medical Faculty of Abbasia, Cairo

Received June 30, 1948

The two main crystalline principles of the fruit of *Ammi Visnaga*, khellin and khellol glycoside, have been extracted by Mustafa,[1] Malosse,[2] Fantl and Salem,[3] Fahmy and El-Keiy,[4] and Samaan.[5] The chemical structure of the two compounds was determined by Späth and Gruber.[6,7] Samaan claims that khellin (named by him visammin) causes a relaxation of visceral plain muscle, while the glycoside (named by him khellinin) conspicuously dilates the coronary blood vessels of the perfused rabbit's heart.[8,9] The latter observation stands in direct contradiction with that of Anrep, Barsoum, Kenawy and Riad,[10] who find, in the heart-lung preparation on dogs, that the glycoside has no effect on the coronary circulation and that the relaxation of plain muscle, as well as the coronary vasodilation are both due to khellin. The question arises whether possibly both substances, khellin as well as the glycoside, have a coronary vasodilator action, the difference in the results being due to the difference in the species of animals used or to the fact that Samaan worked on isolated hearts perfused with Ringer-Locke's solution, while the experiments of Anrep *et al.* were performed on hearts supplied with blood.

The object of the experiments described in this communication was to compare the action of khellin and of the glycoside on the coronary circulation in the isolated perfused rabbit's heart. I should like to thank Prof. Fahmy and Dr. Haddad, of the Pharmacognosy Department, for the supply of the two substances. Some of the experiments were made with the khellin and the glycoside prepared in the Physiological Laboratory or obtained from pharmaceutical firms. These samples will not be described separately, since no difference in their action could be detected.

Comparative Action of khellin and of khellol glycoside on the Coronary Circulation of the Isolated Perfused Rabbit's Heart

The administration of the different substances was made by changing the fluid perfusing the isolated heart from oxygenated Ringer-Locke's solution to the same solution in which the one or the other of the two substances had been dissolved. A modified form of Langendorff's method was used for the perfusion. The coronary outflow was recorded by collecting the fluid in a measuring cylinder at intervals of 30 seconds. The perfusion pressure was kept at 100 to 120 mm. Hg. A few examples representing the average results obtained are given in Table I.

Khellin in such a large concentration as used in the above experiment, caused a diminution in the amplitude of the heart beat, which was in

EXPERIMENTS WITH KHELLIN

TABLE I

PERFUSION OF THE ISOLATED RABBIT'S HEART. KHELLIN CONCENTRATION 40 mg./l.

Perfusion Fluid	Coronary outflow in ml./minute measured at intervals of 30 seconds
1—Ringer Locke's solution	9, 9, 8·6, 9, 9, 9·2, 9, 9
2— „ „ with Khellin ...	12, 19, 24, 28, 35, 36, 38, 37·5, 38, 39
3— „ „ solution	35, 33, 28, 24, 22, 17, 16·5, 11, 11, 9, 9·5, 9, 9, 9·5, 9
4— „ „ with Khellin ...	12, 16, 19, 22, 28, 36, 38, 40, 39, 40, 39
5—7 minutes later	35, 36, 38, 35, 37, etc.
6—Ringer Locke's solution	33, 30, 26, 22, 20, 18, 14, 13, 10, 8·5, 8, 8

most cases of a temporary nature. It is unnecessary to give a detailed description of each experiment, instead, a summary, showing the initial coronary outflow and the maximum increase obtained with different concentrations of khellin, is given in Table II.

TABLE II

INITIAL CORONARY OUTFLOW AND THE MAXIMUM INCREASE OBTAINED WITH DIFFERENT CONCENTRATIONS OF KHELLIN

Average initial coronary outflow in ml./minute	Concentration of khellin mg./l.	Maximal coronary outflow during perfusion with khellin ml./minute	Increase per cent.
9·0	40·0	39·0	333
9·0	40·0	40·0	334
4·5	10·0	12·0	167
4·2	10·0	10·8	157
10·2	4·0	15·5	52
9·2	4·0	14·5	58

Concentration of 2 to 10 mg./l. caused no detectable effect on the heart beat. As regards the coronary circulation, the minimum effective concentration of khellin, for the rabbit's heart perfused with Ringer's solution, is somewhat below 2 mg/l., i.e., about double that given by Anrep, Barsoum, Kenawy and Misrahy[11] for the heart lung preparation.

In several experiments, solutions of 1:40,000 or 1:50,000 of barium chloride were used to induce an artificial spasm of the coronary blood vessels before perfusion with khellin. No special advantage was, however, gained by this procedure. In the presence of barium chloride, larger concentrations of khellin had to be used to cause an appreciable increase of the ordinary outflow. The coronary vasodilator action of khellin can be demonstrated on the normally beating heart as well as on the fibrillating heart.

EXPERIMENTS WITH KHELLOL GLYCOSIDE

The observations with the glycoside were carried out with the same technique as those with khellin. The results obtained in some of the typical experiments are summarised in Table III.

Every observation was made on a different heart. In all the above experiments, administration of khellin caused the usual coronary dilata-

TABLE III

EFFECT OF KHELLOL GLYCOSIDE ON CORONARY OUTFLOW

Average initial coronary outflow ml./minute	Concentration of the glycoside mg./l.	Average coronary outflow during perfusion with the glycoside ml./minute
11·0	4·0	10·5
6·5	4·0	6·8
10·8	20·0	11·2
8·8	20·0	8·8
12·0	20·0	11·5
7·4	40·0	5·2
5·8	40·0	4·4
4·7	100·0	4·5
5·9	100·0	5·2

tion. Attempts to demonstrate the coronary vasodilator action of the glycoside after inducing a coronary spasm by means of barium chloride were unsuccessful. In fact, in many experiments, administration of large doses of the glycoside caused some diminution of the coronary outflow, but never an increase. The diminished outflow does not necessarily indicate a vaso-constriction, since it may be accounted for by the mechanical effects accompanying the slight increase in the strength of the heart beat, which is usually observed on administration of large doses of the glycoside.

COMPARATIVE ACTION OF KHELLIN AND OF THE KHELLOL GLYCOSIDE ON THE ISOLATED CORONARY AND SYSTEMIC ARTERIES

The study of the action of drugs on isolated arterial rings was first made by Langendorff. A detailed description of the results obtained by this method was given by Cruickshank and Subba Raw.[12] These authors observed some fundamental difference in the reaction of coronary and systemic arterial rings to changes in temperature and to different drugs. Kountz,[13] working in this laboratory, confirmed the results of the previous workers and applied the method to human arterial rings. The same method was used for the study of the action of khellin and of the glycoside.

Intramuscular branches of the coronary arteries of the water buffalo were dissected and several rings, about 2 mm. thick, were joined together by means of silver wire, 3-4 rings in a chain. The rings were mounted in a 50-ml. bath containing oxygenated Ringer-Locke's solution at 37° C. The contractions of the rings were recorded by a light lever allowing a magnification of about 30 to 40 times. The drugs were administered directly into the bath.

Khellin, in doses of 0·5 mg., caused a definite relaxation of the rings. After replacing the khellin-containing solution with fresh Ringer-Locke's fluid the rings showed a partial recovery, never, however, completely regaining their original tone. Both the relaxation and the recovery were very slow. The difference between the action of khellin and of the glycoside was quite obvious. The latter caused no relaxation of the coronary rings, even though the doses were increased to about 10 times above those of khellin.

As regards the action of khellin upon rings of systemic arteries, I found that doses up to 2 mg. caused no relaxation. Evidently the systemic arteries are much less sensitive to the drug than the coronary arteries.

In order to gain further knowledge about the action of khellin and of the glycoside on systemic blood vessels, I made use of Pissemsky's method[14] of the perfused rabbit's ear. This method presents the advantage that the perfusing fluid need not be oxygenated or warmed.

Samaan found that the flow of fluid through the perfused toad may be as much as doubled by khellin in a concentration of 1 : 5,000. Such high concentrations present no therapeutic interest. My own observations confirm the statement of Anrep, Barsoum, Kenawy and Misrahy,[11] that khellin in concentrations which cause a conspicuous dilatation of coronary blood vessels has no effect on the systemic blood vessels, the latter being less sensitive. Khellin as well as the khellol glycoside, in concentrations up to 40 mg./l., caused no increase in the flow of the Ringer-Locke's solution through the perfused rabbit's ear.

Conclusion

1. Khellin causes a conspicuous increase in the coronary outflow in the isolated perfused rabbit's heart, the minimum effective concentration being about 2 mg./l.

2. The khellol glycoside causes no increase in the coronary outflow, even when administered in concentrations as high as 100 mg./l.

3. Isolated coronary rings are relaxed by khellin and are not affected by the glycoside.

4. The systemic blood vessels are considerably less sensitive to khellin than the coronary blood vessels.

References

1. Mustafa, *C. R. Acad. Sci., Paris.*, 1879, **89**, 442.
2. Malosse, *Thesis, University of Montpellier*, 1881.
3. Fantl and Salem, *Biochem. Z.*, 1930, **226**, 166.
4. Fahmy and El-Keiy, *Rep. pharm. Soc., Egypt*, 1931, **3**, 36.
5. Samaan, *Quart. J. Pharm. Pharmacol*, 1931, **4**, 14.
6. Späth and Gruber, *Ber. dtsch. chem. Ges.*, 1938, **71**, 106.
7. Späth and Gruber, *ibid.*, 1941, **74**, 1549.
8. Samaan, *ibid*, 1946, **19**, 135.
9. Samaan, Hussein and El-Ridi, *ibid*, 1947, **20**, 502.
10. Anrep, Barsoum, Kenawy and Riad, *Gaz. Fac. Med., Cairo*, 1947, **14**, 1.
11. Anrep, Barsoum, Kenawy and Misrahy, *Brit. Heart J.*, 1946, **8**, 171.
12. Cruickshank and Subba Raw, *Physiol, J.*, 1927, **64**, 65.
13. Kountz, *J. Pharmacol*, 1932, **45**, 65.
14. Pissemsky, *Russky Vrach*, 1912, **11**, 264.