THE SPASMOLYTIC ACTION OF FLAVONE

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Jongebreur[1] has recently compared the spasmolytic action of 42 synthetically prepared pyrone derivatives with that of khellin. His observations were made on the rectal cæcum of the fowl and on the coronary blood vessels of the isolated heart of the rat and of the cat. The action of 5 compounds was found to be either equal to, or even about 100 per cent. stronger than, that of khellin. The remaining 37 compounds were considerably inferior to khellin.

7 of the 42 compounds synthesised by Jongebreur had been already prepared and tested, previously to his publication, by Schönberg and Sina.[2] Jongebreur and the two earlier observers agree in regard to the spasmolytic action of 6 of these compounds finding them much weaker than khellin. There is no such agreement in the case of the seventh compound and the difference in the results of the two investigations exceeds any possible experimental error. This compound is the 2-phenylchromone or flavone.

While Schönberg and Sina report that flavone, when tested on the rectal cæcum, had only 15 per cent. of the activity of khellin, Jongebreur found it to be 100 per cent. stronger than khellin. No observations on coronary blood vessels have been made by Schönberg and Sina while the results of Jongbreur's experiments are contradictory. In one series of observations flavone had only 3 per cent. of the coronary vasodilator action of khellin while in another series it was 100 per cent. stronger than khellin. Such a large difference in the results cannot be accepted without further verification.

The samples of pure flavone and khellin used in the present investigation were prepared in the Department of Chemistry. As required for the pure substances the respective melting points of the samples were found to be 97° C. for the flavone and 154° C. for the khellin. Flavone was prepared according to the method of Löwenbein[3] and khellin by extraction from the fruit of *Ammi visnaga* and repeated crystallisation from methanol. The biological assays of the two substances were made in the Department of Physiology.

Observations on the rectal cæcum of the fowl. This preparation has been first used for the assay of khellin by Anrep, Kenawy, Barsoum and Fahmy[4] who found it sensitive to khellin concentrations of 0·2 μg./ml. and accurate to about 10 per cent. For the present investigation the cæcum was suspended in a bath 6 ml. in capacity in ærated Tyrode solution at 35° C. An example of a comparative assay of flavone and khellin is given in Table 1 from which it can be seen that the equivalent amounts of the two substances were 5μg. of khellin and 30 μg. of flavone.

The spasmolytic action of flavone was, therefore, approximately 15 per cent. of that of khellin. With different preparations of the cæcum this relation varied within the narrow limits of 15 and 20 per cent.

TABLE I

COMPARATIVE ASSAY OF THE SPASMOLYTIC ACTION OF FLAVONE AND KHELLIN ON THE RECTAL CAECUM OF THE FOWL

Khellin and flavone were administered alternately at intervals of 4 minutes. No corrections for lever magnification have been made.

Khellin		Flavone	
Amount administered μg.	Relaxation of cæcum in mm.	Amount administered μg.	Relaxation of cæcum in mm.
5	36	5	6
,,	34	10	14
,,	39	15	20
,,	37	20	26
,,	37	25	31
,,	36	30	37

Observations on the coronary blood flow. These were made on 10 standard heart-lung preparations on dogs. The coronary blood flow was recorded from the coronary sinus. 5 preparations were used after the end of some other experiments and 5 were specially made for the assay; in these no other substance had been administered besides flavone and khellin. Flavone, in 1 or 2 doses, was always administered first and khellin, last. The administrations of the 2 substances were made at intervals of not less than 10 minutes and never before the outflow of blood from the coronary sinus had reached a steady level. The results obtained in the 5 experiments specially made for the assay are given in Table II.

TABLE II

COMPARISON OF THE CORONARY VASODILATOR ACTION OF FLAVONE AND OF KHELLIN ON THE HEART-LUNG PREPARATION

The amount of blood in circulation in each of the 5 experiments was about 600 ml.

Substance administered	Total amount administered mg.	Outflow of blood from coronary sinus ml./minute				
		Exp. 1	Exp. 2	Exp. 3	Exp. 4	Exp. 5
Initial blood flow ..	None	40	46	74	55	60
Flavone	10	—	52	82	—	—
,, ...	20	50	—	—	68	—
,, ...	40	—	65	110	—	—
,, ...	50	65	—	—	—	90
Khellin	10	—	120	—	—	—
,, ...	15	—	—	250	165	190
,, ...	20	175	—	—	—	—

It can be seen from these experiments that the coronary vasodilator action of khellin was considerably greater than that of flavone. Because of the prolonged action of the 2 substances it becomes difficult to express their relative activity in a numerical way. The action of flavone, although much inferior to that of khellin, continues for a long time. Therefore khellin had to be administered before the coronary blood flow returned

to its initial value. But even so, the difference between the action of the two substances is obvious. Doses of flavone as high as 50 mg. increased the coronary blood flow by only about 50 per cent. while doses of 15 mg. of khellin caused a further increase by more than 100 per cent.

Summary

1. Contrary to the observations of Jongebreur the spasmolytic action of khellin was found to be considerably superior to that of flavone.

2. When tested on the rectal cæcum of the fowl the activity of flavone was only 15 to 20 per cent. of that of khellin.

3. In heart-lung preparations khellin in doses of 15 mg. caused a considerably greater increase of the coronary blood flow than doses of 50 mg. of flavone.

References

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2. Schönberg and Sina, *J. Amer.chem. Soc.*, 1950, **72**, 1611.
3. Löwenbein, *Ber. dtsch. chem. Ges.*, 1924, **57**, 1515.
4. Anrep, Kenawy, Barsoum and Fahmy, *Gazette of the Cairo Medical Faculty*, 1947, **14**, 1.