PHYTOPHARMACOLOGICAL EXAMINATION OF EPINEPHRINE AND EPHEDRINE.

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INTRODUCTION.

The alkaloid ephedrine bears so many points of resemblance to the alkaloid epinephrine, especially in regard to its vaso-constricting properties, that it has been styled by some practising physicians and by the laity as "vegetable adrenalin." This resemblance between the two drugs is not altogether a superficial one because the pharmacological action of the two is also, in many respects, similar, so that the earlier workers with ephedrine believed that its pharmacodynamics was identical with that of epinephrine. Thus Chen (1) and Kreitmair (2) assumed that ephedrine, like epinephrine, stimulated the myoneural junctions (commonly spoken of as nerve endings) of the true sympathetic nervous system, and in that way produced its characteristic pharmacological effects. On the other hand, other investigators have found certain points of difference in the actions of the two alkaloids and have questioned, for that reason, the exact mechanism of ephedrine action as being identical with that of epinephrine. Thus, for instance, Nagel (3) has failed to obtain any inhibition of the intestinal movements after ephedrine, which some of the earlier writers claimed produced a relaxation of the same. The sympatico-mimetic action of ephedrine has also been called in question by De Eds and Butt (4), Gradinesco (5), and very recently, by Halsey (6). The present writer has also called attention to the interesting difference between ephedrine and epinephrine in their action on the bladder, which is described elsewhere (7). In the present paper the author wishes to call attention to the very interesting striking difference in pharmacological action between ephedrine and epinephrine on plant protoplasm.

PHYTOPHARMACOLOGICAL.

The author and his collaborators have been engaged for many years in a comparative study of the reactions to drugs on animal and plant protoplasm. It was found, as set forth in various publications, that certain drugs were more poisonous for living animal preparations than for living plant tissues and, vice versa, other drugs were more toxic for living plant protoplasm than for living animal protoplasm. It was further demonstrated that in many cases living animal test objects were more sensitive to poisons derived from the plant world than to poisons of animal origin, on the one hand, and on the other hand, living plant preparations were extremely sensitive to certain poisons produced by animals and were not at all so sensitive to small doses of drugs or poisons derived from the vegetable kingdom. Thus it was found that whereas cocaine was very toxic for living animal tissues, it was comparatively little toxic for living plants (8). Such differences in reaction between animal and plant preparations have led to the discovery of certain animal toxins which were hitherto undemonstrable. Thus Macht and his co-workers have shown the presence of a toxin in the blood of menstruating women (9). Again by phytopharmacological methods, the presence of a toxin in the blood of pernicious anemia could be absolutely demonstrated and methods for differentiation between pernicious anemia and other anemia states have thus been developed which are of clinical importance (10), (11), (12).

In the present investigation, the author examined the action of epinephrine and ephedrine on living plants. The methods employed were exactly the same as those employed in other studies published by Macht and his co-workers elsewhere (13). Living seedlings of *Lupinus albus* were grown in nutrient plant physiological solutions and the increment of the single, straight, well-demarcated roots was measured. In this way the rate of growth of the Lupinus roots for a series of seedlings was studied in normal physiological solution, on the one hand, and the growth of another similar series of Lupinus seedlings from the same batch of plants was studied at the same time in physiological saline solution to which different quantities of the drugs to be examined were added. It was found that the action of small quantities of epinephrine and ephedrine hydrochlorides did not change the hydrogen-ion concentration of the solutions, as compared with the normal physiological solution, to any appreciable extent, and certainly not at all sufficiently to produce a change in the rate of growth.

On comparing the effects of ephedrine and epinephrine on the growth of the seedlings, marked differences between the two were noted. It was found that ephedrine was very little toxic for the Lupinus seedlings, whereas epinephrine was very toxic for such seedlings. Some of the results thus obtained are exhibited in the subjoined table.

TABLE I.—TOXICITY FOR GROWTH OF LUPINUS ALBUS.

Preparation.	Concentration.	Phytotoxic index.	Preparation.	Concentration.	Phytotoxic index.
Epinephrine A	1: 5,000	7%	Ephedrine A	1: 1,500	75%
Epinephrine A	1:10,000	16%	Ephedrine A	1: 3,000	80%
Epinephrine B	1:10,000	14%	Ephedrine A	1: 5,000	84%
Epinephrine C	1:10,000	13%	Ephedrine A	1:10,000	88%
Epinephrine A	1:15,000	19%	Ephedrine A	1:10,000	86%
Epinephrine A	1:20,000	35%			
Epinephrine A	1:30,000	38%			
Epinephrine A	1:40,000	73%			

It will be seen, on examining the data, that a solution of epinephrine, 1:5000 almost completely inhibited the growth of the plants. Concentrations of 1:10,000 and 1:15,000 were also very markedly toxic, and even solutions of 1:40,000 produced a distinct inhibition as indicated by the phytotoxic index. On the other hand, solutions of ephedrine, 1:10,000, produced much less inhibition than epinephrine, 1:40,000, and even concentrations of ephedrine, 1:1500, gave a better growth than epinephrine, 1:40,000.

The writer has examined different specimens of epinephrine solutions and also prepared a solution of epinephrine of the highest purity, obtained from Professor John J. Abel, and the toxicity for *Lupinus albus* was noted with all of them. Some of the solutions examined contained chloretone as a preservative and in examining such preparations, proper controls were made with Shive solution, containing the same percentage of chloretone as the epinephrine solutions used. In addition to the experiments performed with the ordinary levo-rotatory epinephrine, the writer made a few experiments with a solution of racemic or *DL*-epinephrine, a small quantity of which he had in his possession. It was found that the racemic form was less active than the levo-rotatory form of epinephrine. An examination of the various commercial solutions of epinephrine, revealed the interesting fact that out of four

different makes which were examined, three were of very nearly the same potency. A fourth specimen, however, showed much less toxicity for the plants.

DISCUSSION.

A comparative study of solutions of epinephrine and ephedrine hydrochlorides on the growth of *Lupinus albus* by the author's phytopharmacological methods, reveals a very interesting fact. The epinephrine was found to be very much more toxic than ephedrine which, in many respects, has a very similar action to that of epinephrine when tested by ordinary zoöpharmacological methods. These findings are of special interest when examined in connection with data obtained by the present author in regard to the action on plants of certain other drugs of animal origin, on the one hand, and of plant origin, on the other. Thus, for instance, the author has found that the powerful heart drug or poison, bufagin, isolated by Abel and Macht from the secretions of the tropical toad, *Bufo Agua* (14), is chemically and pharmacologically very similar to digitoxin, the active principle of digitalis. When, however, a solution of bufagin was compared with a solution of digitoxin on living plant tissues, it was found that the former was much more toxic (15). Again, the author has recently shown in a comparative study of cantharidin and ricin on plant protoplasm that cantharidin is extremely toxic for plants, whereas ricin, one of the most powerful poisons for animals known, is practically non-toxic for the same plants (16). In the present work, we find again that epinephrine, the drug of animal origin, is much more toxic for plants than the similar drug, ephedrine, which is derived from plants.

SUMMARY.

1. A comparative study of epinephrine and ephedrine by phytopharmacological methods shows that epinephrine is much more toxic for plants than ephedrine.

2. Examination of various samples of epinephrine by the phytopharmacological method affords, in experienced hands, a method of not only distinguishing this alkaloid from ephedrine but also of evaluating the activity of different samples of epinephrine.

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