THE CHOLINERGIC ACTION OF OESTRIN

WHEN oestrin is injected into ovariectomized rabbits, a maximal hyperemia develops in the uterine tissues within thirty to sixty or more minutes.[1,2] As a result of this, changes in the distribution of fluid in the uterus take place within the next six hours,[3,4] as metabolic processes in the uterus are stimulated.[5,6] After ten or more hours, intermittent contractions commence in the myometrium.[5,6,7]

The little-known fact that the initial hyperemia can be temporarily inhibited in unanesthetized rabbits by the injection of atropine[2] suggests that the primary agent which initiates this series of changes, particularly the vasodilatation, may be acetylcholine which increases in amount under the influence of oestrin. In order to test this hypothesis, assays of the acetylcholine content of the uteri of ovariectomized rabbits, some of which were untreated and others of which received oestrone, were made. The latter group includes one rabbit in which the uterus, minus the cervix containing the uterine cervical ganglia, was transplanted to the anterior abdominal wall. The rabbits were ovariectomized for seventeen to twenty-eight days, except one which had been operated only two weeks, and one that was castrated longer than two months. Extraction of the uterus was carried out by the method recommended by Chang and Gaddum.[8] The extracts so obtained were assayed as recommended by these authors, using the rectus abdominis muscle of the frog. The confirmatory tests include potentiation of the action of the extracts by eserinizing the frog muscle; inhibition of responses by atropine; inactivation of the extracts by sodium hydroxide and inactivation by blood. The quantity of extract obtained was too small to permit testing of the stability of the active material by boiling.

Of twenty-eight ovariectomized rabbits used thus far, fifteen were untreated and yielded extracts giving the following results: six tests on the uneserinized frog rectus were negative, two showed an activity equivalent in one case to 0.2 gamma of acetylcholine per gram of uterus, the other, unaccountably, showed an activity of 5 gamma per gram of uterus. This could not be confirmed with a larger amount of extract on the eserinized preparation. All fifteen extracts were tested on the eserinized rectus preparation. Ten of these showed no activity, and five showed an activity equivalent to 0.06 to 0.13 gamma of acetylcholine per gram of uterus. In no case was sufficient extract available for any of the confirmatory tests.

Thirteen uteri extracted one hour after the injection of one hundred international units of oestrone (Amniotin, Squibb) per kilogram of body weight gave the following results: eight tests on the uneserinized rectus were made, six of which were positive, showing an activity equivalent to 0.5 to 2.0 gamma (in one case, 4 gamma) per gram of fresh uterus, and two of which were inactive. Twelve of the thirteen extracts were tested on eserinized rectus preparations. Two were inactive and one showed only a trace of activity. In the nine remaining cases positive responses were obtained. Seven of these which had been tested previously on the uneserinized muscle showed potentiation of the responses. Atropine inhibition was attempted with five extracts (including the one from the transplanted tissue), and in each case inhibition was observed. Three attempts to inactivate the active agent in extracts with sodium hydroxide were successful, including inactivation of a sample from the transplant. Two attempts to inactivate this substance by mixing it with blood for about one minute were made. One, with human blood was successful, the other, with rabbit blood showed a diminution of about two thirds in the magnitude of the response.

Recent experiments indicate that twelve hours after injection of oestrin no acetylcholine-like substance can be extracted from the uterus.

These results show unmistakably that the acetylcholine content of the uterus is significantly increased within one hour after the injection of oestrin. Since the effect occurred in a transplanted uterus, connection with the central nervous system is not essential, although in this experiment, time for complete degeneration of the nerves had not elapsed.

In the sense therefore that certain nerve effects upon effector organs are mediated by local liberation of acetylcholine and accordingly are said to be "cholinergic," it is clear that oestrin, under the conditions of this work, is similarly "cholinergic." Hence this term must be broadened to include possible hormonic effects which are mediated peripherally by acetylcholine. In this way, the maximal hyperemia which occurs in uterine transplants in which no nerves have been demonstrated[1] may be explained, and so, perhaps, may the high oestrin content and the high acetylcholine content of human placenta[8] be explained, in the complete absence of nerves in this tissue.[9]

SAMUEL R. M. REYNOLDS,
Fellow, John Simon Guggenheim Memorial Foundation
DEPARTMENT OF ANATOMY,
THE UNIVERSITY OF ROCHESTER
SCHOOL OF MEDICINE AND DENTISTRY

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