

THE NATURE OF UTERINE AND INTESTINAL SYMPATHIN

BY

MONICA MANN AND G. B. WEST

*From the Pharmacological Laboratories, School of Pharmacy, University of London,
and Medical School, University of St. Andrews, Dundee*

(Received October 18, 1950)

Evidence is accumulating to show that a substance with the physiological properties of synthetic *l*-noradrenaline is liberated together with adrenaline into the blood stream when certain adrenergic nerves in the cat are stimulated. Bülbring and Burn (1949) found that splanchnic nerve stimulation in spinal cats resulted in the liberation of varying proportions of *noradrenaline* and *adrenaline*; their results were obtained in single animals by comparing the height of contraction of the denervated nictitating membrane with that of the normal membrane. Gaddum and Lembeck (1949) tested the blood from the suprarenal vein (after stimulation of the splanchnic nerve) on the rat's uterus and colon and confirmed this result. West (1950) injected the blood immediately after withdrawal from the suprarenal vein of one cat into the arteries supplying the nictitating membrane and non-pregnant uterus of a second cat under chloralose and cocaine, and obtained a similar result.

In a study of the nature of splenic sympathin, Peart (1949) tested the blood from the splenic vein after nerve stimulation on the rat's uterus and colon, the perfused rabbit's ear and cat's spleen, and nictitating membrane or lower lid of the cat. All the evidence supported the view that the active material was *noradrenaline* in a concentration of 50 to 500 m μ g./ml., although smaller amounts of *adrenaline* were sometimes liberated. Mann and West (1950) estimated the concentrations of the two amines in the blood from the splenic and hepatic veins after stimulation of the respective nerves and showed that the main active constituent was *noradrenaline* in both types of blood; this was present in the blood of the hepatic veins in a mean concentration of 0.48 μ g./ml., and in the blood of the splenic veins in a mean concentration of 0.13 μ g./ml. Smaller amounts of *adrenaline* were sometimes also liberated. Using a similar method, we have estimated the concentrations of the two amines in the plasma after stimulation of the hypogastric and inferior mesenteric nerves, utilizing the formula developed by Bülbring (1949).

METHODS

Collection of uterine blood.—Cats anaesthetized with chloralose were used. The left hypogastric nerve was dissected free from peritoneum and divided centrally just below the inferior mesenteric ganglion. Blood from the left ovarian vein was led through a cannula and reservoir to the femoral vein. When blood samples were required, the reservoir was replaced by a graduated centrifuge tube standing in ice. Heparin or chlorazol fast pink was used as the anticoagulant, and plasma samples were obtained by rapid centrifugation. In about half the experiments the adrenals were excluded from the circulation by ligatures.

Stimulation of the nerve was through platinum electrodes with an ordinary coil (Faradic stimulation at 7.5 cm. on 4 V.) and usually lasted a total time of one minute. It was found that a good yield of sympathin was obtained with four alternate periods of 15 sec. stimulation and 30 sec. rest. During this time and for the next two minutes the volume of blood collected was usually 3–4 ml. In some experiments a bulldog clip was attached to the left uterine vein after stimulation had occurred in an effort to increase the yield of sympathin in the ovarian vein. The control plasma was obtained by bulking samples secured before, and 15 min. after, stimulation.

Collection of intestinal blood.—Cats anaesthetized with chloralose were used. The inferior mesenteric nerve was dissected free from the artery and divided centrally. Blood in the inferior mesenteric vein was led through a cannula and small reservoir to the femoral vein. The remainder of the method was similar to that described above. The adrenals were excluded from the circulation in all these collections. A better yield of sympathin was sometimes obtained with four alternate periods of 5 sec. stimulation and 55 sec. rest; with this intermittent stimulation, about 3 ml. of blood was collected in 5 min.

Assay methods.—These were essentially the same as those used in a previous study (Mann and West, 1950). The pharmacological tests were the isolated uterus from a non-pregnant rat in dioestrus, the isolated rectum of a week-old chick, and the chronically denervated nictitating membrane of a cat under chloralose. As originally stated, as little as 4 per cent of one of the amines could be accurately measured in a mixture of the two.

RESULTS

Parallel quantitative assays by different methods were carried out on the plasma obtained in each experiment. The estimates were taken in pairs and values for adrenaline and *noradrenaline* calculated by Bülbring's formula. In a series of 13 experiments (Table I), estimates of the uterine sympathin gave a mean value of 0.037 μ g. *l-noradrenaline* per ml. plasma. Small amounts of adrenaline were present in all

TABLE I
CONCENTRATION OF UTERINE SYMPATHIN IN POST-STIMULUS SAMPLES OF PLASMA

| Exp. | μ g./ml. plasma | | Exp. | μ g./ml. plasma | |
|------|------------------------|---------------------|------|------------------------|---------------------|
| | <i>l-noradrenaline</i> | <i>l-adrenaline</i> | | <i>l-noradrenaline</i> | <i>l-adrenaline</i> |
| 1 | 0.035 | 0.004 | 8* | 0.008 | 0.003 |
| 2 | 0.001 | 0.003 | 9* | 0.100 | 0.010 |
| 3 | 0.064 | 0.002 | 10* | 0.095 | 0.005 |
| 4 | 0.050 | 0.001 | 11* | 0.078 | 0.005 |
| 5* | 0.005 | 0.005 | 12 | 0.024 | 0.002 |
| 6* | 0 | 0.005 | 13 | 0.020 | 0.009 |
| 7* | 0 | 0.010 | | | |

* Adrenal vessels open in these experiments; tied in all other experiments.

samples, the mean value being 0.005 μ g. per ml. plasma, but *noradrenaline* was absent from two specimens (Nos. 6 and 7). In Experiments 3, 10, and 11, the "post-stimulus" samples and *noradrenaline* stimulated the isolated uterus from a non-pregnant rat in early oestrus, thereby supplying additional evidence that the main active material in these cases was *noradrenaline*. It is clear that a mixture of the two amines is liberated when the hypogastric nerve in the non-pregnant cat is

TABLE II
CONCENTRATION OF INTESTINAL SYMPATHIN IN POST-STIMULUS SAMPLES OF PLASMA

| Exp. | $\mu\text{g./ml. plasma}$ | | Exp. | $\mu\text{g./ml. plasma}$ | |
|------|---------------------------|---------------------|------|---------------------------|---------------------|
| | <i>l-noradrenaline</i> | <i>l-adrenaline</i> | | <i>l-noradrenaline</i> | <i>l-adrenaline</i> |
| 1 | 0.138 | 0.001 | 10 | 0.012 | 0.050 |
| 2 | 0.045 | 0.001 | 11 | 0.031 | 0.019 |
| 3 | 0.013 | 0.025 | 12 | 0.009 | 0.005 |
| 4 | 0.020 | 0.009 | 13 | 0.096 | 0.002 |
| 5 | 0.020 | 0.020 | 14 | 0.144 | 0.006 |
| 6 | 0.008 | 0.002 | 15 | 0.090 | 0.010 |
| 7 | 0.008 | 0.002 | 16 | 0.036 | 0.004 |
| 8 | 0.015 | 0.010 | 17 | 0.044 | 0.006 |
| 9 | 0.050 | 0.050 | 18 | 0.017 | 0.008 |

stimulated, and usually *noradrenaline* predominates. It is hoped to identify the sympathin liberated in pregnant cats by this technique.

In a series of 18 experiments (Table II), estimates of the intestinal sympathin gave mean values of 0.044 $\mu\text{g. l-noradrenaline}$ and 0.013 $\mu\text{g. l-adrenaline}$ per ml. plasma. In this series, as in the uterine one, adrenaline was found in all samples.

DISCUSSION

Noradrenaline was detected by Euler (1948) in the sympathomimetic extracts of various mammalian organs including the uterus and intestine. Results reported here confirm his observations. Bacq and Fischer (1947) were the first workers to suggest that the mediator in the cat uterus might be *noradrenaline* and not adrenaline, although they compared the results of intravenous doses of the amines with those of nerve stimulation. By reinjection of the uterine blood, West (1950) failed to reach any conclusion as to the possible nature of uterine sympathin. Probably his test objects were not sensitive enough since the amounts liberated are much smaller than those found in the hepatic and splenic veins. The inhibitory activity of *noradrenaline* on the non-pregnant uterus of the cat is about one-eighth that of adrenaline, and on intestinal loops both cause dilatation (Burn and Hutcheon, 1949), adrenaline being slightly the more active of the two. Our results indicate, therefore, that physiologically equiactive amounts of the amines are liberated in the uterus and intestine. These results also add weight to the findings of Blaschko (1942) that *noradrenaline* is the probable precursor of adrenaline in the body.

SUMMARY

1. Stimulation of the hypogastric and inferior mesenteric nerves in cats resulted in the appearance of *noradrenaline* and adrenaline in the plasma.

2. Parallel quantitative assays showed that *noradrenaline* was present in the blood of the ovarian vein in a mean concentration of 0.037 $\mu\text{g./ml.}$ (13 experiments), with 0.005 $\mu\text{g. adrenaline}$ per ml. plasma: in the blood of the inferior mesenteric vein, *noradrenaline* was present in a mean concentration of 0.044 $\mu\text{g./ml.}$ (18 experiments) with 0.013 $\mu\text{g. adrenaline}$ per ml. plasma.

REFERENCES

- Bacq, Z. M., and Fischer, P. (1947). *Arch. int. Physiol.*, **55**, 73.
Blaschko, H. (1942). *J. Physiol.*, **101**, 337.
Bülbring, E. (1949). *Brit. J. Pharmacol.*, **4**, 234.
Bülbring, E., and Burn, J. H. (1949). *Brit. J. Pharmacol.*, **4**, 202.
Burn, J. H., and Hutcheon, D. E. (1949). *Brit. J. Pharmacol.*, **4**, 375.
Euler, U. S. v. (1948). *Acta physiol. scand.*, **16**, 63.
Gaddum, J. H., and Lembeck, F. (1949). *Brit. J. Pharmacol.*, **4**, 401.
Mann, M., and West, G. B. (1950). *Brit. J. Pharmacol.*, **5**, 173.
Peart, W. S. (1949). *J. Physiol.*, **108**, 491.
West, G. B. (1950). *Brit. J. Pharmacol.*, **5**, 165.