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SYNTHETIC OXYTOCIN AS AN ANTAGONIST OF EXPERIMENTAL CARDIAC ANOXIC CHANGES IN RABBITS

BY

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Synthetic oxytocin (Syntocinon) can be shown to reduce or abolish ST-T changes induced experimentally by hypoxaemia alone, by hypoxaemia and ergometrine, by vasopressin, and by a new procedure involving injection of small doses of picrotoxin into the lateral cerebral ventricle. Ventricular fibrillation induced by picrotoxin can also be reversed by oxytocin. These effects suggest a probable metabolic action of oxytocin against cardiac anoxic changes, and its possible therapeutic usefulness as an antagonist of myocardial ischaemia. It is speculated that this might be a physiological action of the hormone.

Rinzler, Travell, Karp & Charleson (1956) have reported that ergometrine (ergonovine) produces transient ST segment depression in rabbits with experimental coronary atherosclerosis. Stein (1949) has also employed these ST changes as a diagnostic procedure in patients with angina pectoris. In connexion with other studies from this laboratory (Varma & Melville, 1961a) it was observed that ergometrine intensified ST-T depression in the electrocardiogram associated with hypoxaemia in rabbits with experimental coronary atherosclerosis, but not in normal rabbits. Since ergometrine and oxytocin are both primarily uterine stimulants, it was of interest to test the effects of synthetic oxytocin (Syntocinon) upon the changes in the electrocardiogram induced by hypoxaemia. It was immediately observed that oxytocin strikingly antagonized these changes.

It had previously been reported (Melville, 1936) that, in unanaesthetized dogs, pressor pituitary preparations induced a fall in blood pressure which is abolished by simultaneous injections of large doses of oxytocic preparations. It is also well known that vasopressin induces experimentally coronary constriction and T-wave changes (Melville, 1939). It was therefore of interest also to investigate the effects of synthetic oxytocin upon these latter changes.

Finally, it has recently been observed (Share & Melville, 1961) that sustained ST-T depression (suggesting myocardial hypoxia) and various types of ventricular arrhythmias, including fibrillation, can be produced experimentally by injections of small doses of picrotoxin into the lateral cerebral ventricle of cats. While the exact mechanism of production of these cardiac changes is still uncertain, preliminary studies (Varma, Share & Melville, 1961) suggest that they might be due

to central sympathetic stimulation. As an additional method it was nevertheless of interest to study the effects of oxytocin upon the cardiovascular changes induced by this procedure.

METHODS

Albino rabbits (males and females, 2.5 to 3.5 kg) anaesthetized with intravenous pentobarbitone sodium (20 to 40 mg/kg) were used in these experiments. Coronary atherosclerosis was induced in male rabbits by prolonged (5 to 9 months) feeding with a diet containing 2% cholesterol and 6% corn oil in Purina Chow, as described by Melville & Shister (1959). Electrocardiograms (leads II and V) and femoral arterial blood pressure (using a Sanborn pressure transducer) were recorded concurrently. For the experiments with hypoxia the animals were placed in a large box (100 l. capacity) and a mixture of 10% oxygen and 90% nitrogen was blown through a flowmeter into the box at a rate of approximately 10 l./min, so that the air is completely displaced within 10 min. The effects of synthetic oxytocin (Syntocinon) were studied after both hypoxia (10 to 20 min) alone and hypoxia combined with an injection of 0.05 mg/kg of ergometrine maleate (Ergotrate maleate). In the experiments with vasopressin, Pitressin was used. After the cardiovascular responses to a dose of 1.0 i.u./kg of vasopressin were established, the injection was repeated 90 min later immediately following oxytocin, and a third similar injection of vasopressin alone tested after a further period of 90 min. This was necessary since the responses to repeated vasopressin were somewhat reduced even after 90 min. In the experiments with picrotoxin the effects of oxytocin were studied both during the period of ST-T depression in some experiments, and immediately following the occurrence of ventricular fibrillation in other experiments. All injections (except picrotoxin) were given intravenously through a polythene cannula attached to a needle inserted into the marginal ear vein of the rabbit.

RESULTS

Fig. 1 shows examples of the electrocardiogram and blood pressure changes recorded following injections of oxytocin, either during hypoxia alone (A) or during hypoxia combined with ergometrine (B). Similar results were observed in 10 atherosclerotic rabbits. As can be seen during either hypoxia alone or hypoxia with ergometrine, when marked ST-T depression was evident, intravenous injection

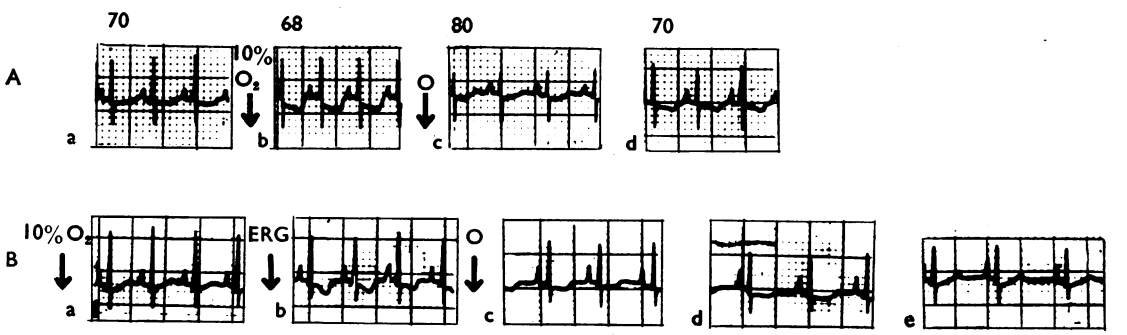

Fig. 1. Effects of oxytocin (1.0 i.u./kg intravenously) on electrocardiogram (lead V) changes induced by ergometrine and/or hypoxaemia in atherosclerotic rabbits under pentobarbitone sodium anaesthesia. A: Male 3.5 kg rabbit (fat-cholesterol diet for 8 months); a, control; b, after 10 min of hypoxia; oxytocin (O) injected after b and hypoxia continued ; c, 1 min, and d, 10 min, after oxytocin. B: Male 3.5 kg rabbit (fat-cholesterol diet for 9 months); a, after 15 min of hypoxia; ergometrine (Erg.) 0.05 mg/kg injected after a; b, 3 min after ergometrine; oxytocin then injected; c, 10 sec, d, 1 min, and e, 2 min, after oxytocin.

of oxytocin (1.0 to 2.0 i.u./kg) led to prompt temporary reversal of the ST-T changes. This effect occurred within 30 sec, reaching its peak in 1 to 3 min, but with continued hypoxia ST-T depression gradually reappeared in 5 to 10 min. Oxytocin also induced a transient bradycardia and a variable slight rise in blood pressure.

In other experiments reported elsewhere (Varma & Melville, 1961b) it was observed that coronary dilator drugs, including glyceryl trinitrate, do not antagonize the ST-T changes induced by this type of hypoxaemia. Indeed, all the agents studied either exerted no effect or enhanced the ST-T depression observed. It would therefore appear that this antagonistic action of oxytocin is probably not due to coronary dilatation.

In the next series of experiments, the effects of oxytocin upon the cardiovascular changes induced by vasopressin were studied in 8 normal rabbits. Fig. 2 shows a typical example of the results obtained in all these experiments. Thus, after the

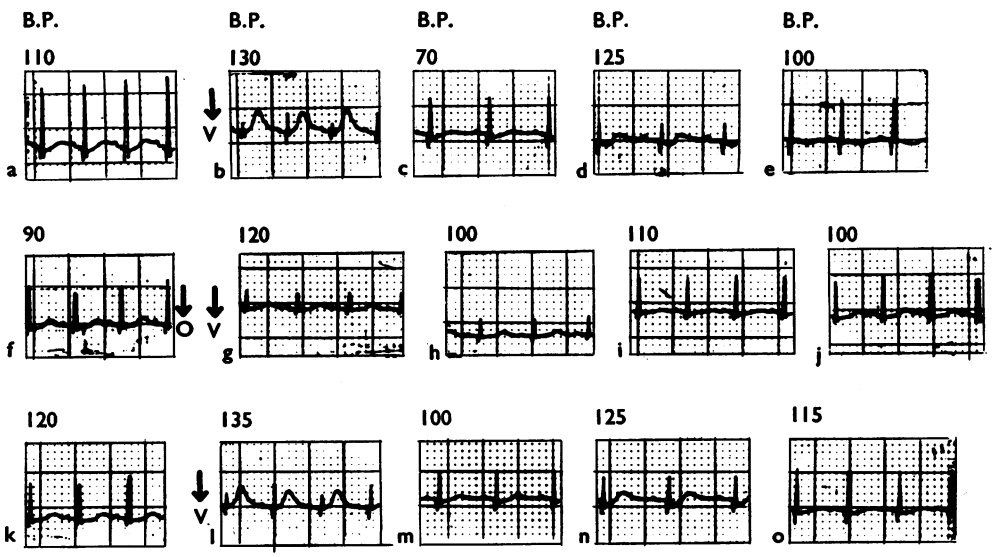

Fig. 2. Effect of oxytocin (5 i.u./kg intravenously) on the electrocardiogram (lead V) and mean arterial pressure (B.P. mm of Hg) changes induced by vasopressin (V)—1 i.u./kg—in a normal 3 kg male rabbit under pentobarbitone sodium anaesthesia. a, Control; vasopressin injected after a; b, 10 sec, c, 30 sec, d, 5 min, e, 15 min, and f, 90 min, after vasopressin; between f and g, oxytocin (O) was injected followed immediately by vasopressin (V); g, 10 sec, h, 30 sec, i, 5 min, j, 15 min, and k, 90 min, after oxytocin and vasopressin; between k and l, third injection of vasopressin; l, 10 sec, m, 30 sec, n, 5 min, and o, 15 min, after vasopressin.

initial dose of 1 i.u./kg of vasopressin, there was a prompt rise in blood pressure followed by a temporary sharp fall (lasting for 1 to 1.5 min) and a secondary rise (lasting for 7 to 10 min). Both ST-T changes and bradycardia also occurred. After 90 min, when a similar dose of vasopressin was injected immediately following oxytocin (5 i.u./kg), both the depressor response and the ST-T changes were reduced or abolished. However, the bradycardia and pressor response were unaffected or

only slightly reduced. The third injection of vasopressin produced more marked ST-T changes than the second although less than the first. In other experiments oxytocin (5 i.u./kg) alone led to a rise in blood pressure, although Woodbury & Abreu (1944) have reported only a depressor effect with oxytocin in morphinized rabbits. It is, however, evident that oxytocin can antagonize the ST changes induced by vasopressin.

In the third series of experiments, picrotoxin (0.1 mg) was injected into a lateral cerebral ventricle in 10 normal rabbits. The animals were previously anaesthetized with pentobarbitone sodium, maintained on artificial respiration, vagotomized, and 3 to 5 mg/kg of gallamine triethiodide injected in order to prevent convulsions. Examples of the effects of oxytocin upon both the ST-T changes (A) and ventricular fibrillation (B) induced by picrotoxin are shown in Fig. 3. Following picrotoxin

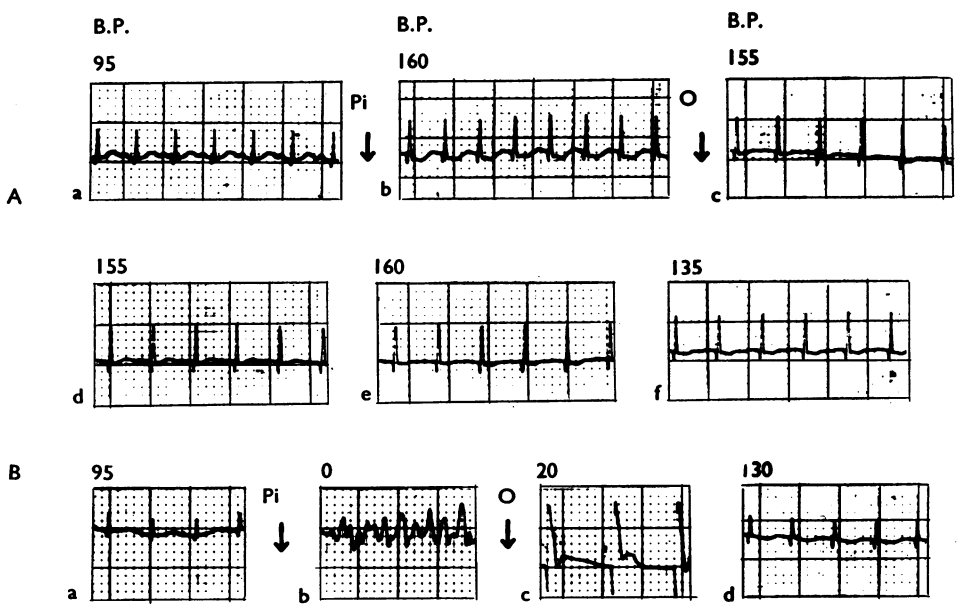

Fig. 3. Effect of oxytocin (2 i.u./kg) on the ST segment depression and ventricular fibrillation (electrocardiogram lead II) produced by injection of picrotoxin into the lateral cerebral ventricle of anaesthetized vagotomized, male rabbits paralysed with gallamine. Artificial respiration. Mean arterial blood pressure (B.P.) mm of Hg. A: 2.5 kg; a, control; b, 10 min after picrotoxin (Pi); oxytocin (O) injected after b; c, 10 sec, d, 30 sec, e, 5 min, and f, 10 min, after oxytocin. B: 3.0 kg.; a, control; b, 4 min after picrotoxin (Pi) showing ventricular fibrillation; after 3 min of fibrillation, oxytocin injected and washed with 7.0 ml. of 0.9% saline; c, 10 sec, and d, 15 min, after oxytocin.

injection, in every experiment there was a marked immediate rise in blood pressure, associated consistently with marked ST-T depression and varying degrees of cardiac arrhythmias, including sinus arrhythmia, bradycardia, tachycardia, ventricular ectopic beats and even ventricular fibrillation in different experiments. When fibrillation did not ensue early, ST-T changes with regular rhythm generally

persisted for 30 to 60 min with gradual restoration to normal. In 5 such experiments, injection of oxytocin (2.0 i.u./kg) promptly reduced the existing ST-T depression. The records of one experiment are reproduced in Fig. 3A. In these experiments ST-T depression was still absent or markedly reduced 30 min after the oxytocin.

In another group of 9 rabbits, after the onset of ventricular fibrillation, oxytocin (2.0 i.u./kg) was injected intravenously (1 to 3 min later) and rapidly washed in with 7 ml. of physiological saline. In 6 of 9 rabbits this procedure led to prompt reversal of the fibrillation with restoration of normal cardiac rhythm and blood pressure. An example of this dramatic response is shown in Fig. 3B. In the 3 unsuccessful experiments, despite injections of oxytocin fibrillation could not be reversed. It is, however, clear that oxytocin can antagonize both ST-T changes and even ventricular fibrillation under these conditions. Further studies on the anti-fibrillatory action of oxytocin under other conditions are now in progress.

DISCUSSION

The mechanism by which oxytocin exerts the above actions is still uncertain. As already pointed out, the fall in blood pressure observed following injection of pressor pituitary preparations in unanaesthetized dogs can be abolished by simultaneous injection of large quantities of oxytocin preparations. Since vasopressin is known to lead to coronary constriction, it might be assumed that the antagonistic action of oxytocin is due to a coronary vasodilator effect. Coon (1939) and Woodbury & Abreu (1944) have also reported that oxytocin exerts a coronary dilator effect in the isolated chicken heart. However, since ST-T depression under hypoxia is enhanced by coronary dilator drugs (Varma & Melville, 1961b), the antagonism of the two hormones as observed in those experiments might not involve changes in the coronary flow *per se*. Moreover, the ST-T changes induced by hypoxaemia are readily reversed by adequate oxygenation. Geiling, DeLawder & Rosenfeld (1931) and Geiling & DeLawder (1932) have observed an increase in tissue metabolism and oxygen consumption with oxytocic preparations in unanaesthetized dogs, and have also reported that vasopressin and oxytocin have opposite metabolic effects. Fraser (1937) and Brooks & Pickford (1958) have shown that oxytocic preparations can antagonize the antidiuretic effect of the pressor hormone in rats and dogs. It is therefore postulated that the protective cardiac action of oxytocin observed in these experiments might be due to a metabolic action rather than to coronary dilatation. It is conceivable that this action might enable the heart to utilize oxygen more effectively.

In connexion with the above observations the question arises whether or not this is a physiological or pharmacological action of the hormone. Relatively high doses (of 2.0 i.u./kg) are necessary to reverse ventricular fibrillation in the rabbit, but the minimal quantities required to overcome the anoxic changes under other conditions have not been determined. Assuming that the oxytocic hormone is a physiological antagonist of myocardial ischaemia, it is tempting to speculate that this might possibly be a factor in the lower incidence of coronary ischaemic attacks in women. These preliminary observations also suggest possible therapeutic usefulness of oxytocin as an antagonist of myocardial ischaemia in coronary diseases and possibly

also in preventing and reversing ventricular arrhythmias in man. It is, however, obvious that a great deal of study would be required before definite conclusions of these questions can be drawn.

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