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ACTIONS OF PROSTAGLANDINS E_1, E_2 AND E_3 ON THE CENTRAL NERVOUS SYSTEM

BY

E. W. HORTON

From the Miles-Ames Research Laboratories, Stoke Poges, Bucks.

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Prostaglandins E_1, E_2 and E_3, injected into the cerebral ventricles of unanaesthetized cats, produced sedation, stupor and signs of catatonia. The threshold dose was 3 μg/kg. Slight sedation was also observed following an intravenous injection, but a dose of 20 μg/kg was required. In chicks, intravenous injections of prostaglandins (10 to 400 μg/kg) caused respiratory depression, profound sedation, loss of normal posture and, with the higher doses, loss of the righting reflex.

Brain extracts contain biologically active lipid-soluble substances (Ambache & Reynolds, 1960, 1961 ; Kirschner & Vogt, 1961 ; Toh, 1963), most of which stimulate smooth muscle. The chemical structure of many of these substances is unknown but their biological and physicochemical properties somewhat resemble those of the prostaglandins (see Horton & Main, 1963, for references to early history and formulae of these substances). It was therefore of interest to know whether prostaglandins have any actions on the central nervous system. In the present experiments prostaglandins of the E series produced stupor and prolonged sedation when injected into the cerebral ventricles of cats and sedation when injected intravenously into chicks. The prostaglandins of the E series have been isolated and their structure elucidated in Bergström's laboratory in Stockholm (Bergström & Sjövall, 1960; Bergström, Dressler, Ryhage, Samuelsson & Sjövall, 1962 ; Bergström, Ryhage, Samuelsson & Sjövall, 1962 ; Samuelsson, 1963).

METHODS

Injections into the cerebral ventricles of cats. Collison cannulae (C. F. Palmer, Ltd.) were implanted with sterile conditions into the lateral ventricles of six female adult cats, weighing 2.5 to 3 kg and anaesthetized with pentobarbitone sodium (40 mg/kg), as described by Feldberg & Sherwood (1953). After an interval of not less than 1 week, injections were made through the cannula without anaesthesia. Prostaglandin E_1 was dissolved in sterile 0.9% saline by the addition of solid sodium bicarbonate. Neutral solutions warmed to 37° C were injected slowly under aseptic conditions in volumes of 0.1 or 0.2 ml. and washed in with 0.1 ml. of 0.9% saline. The cats were observed continuously for 2 to 8 hr and intermittently for 48 to 72 hr.

In four cats weighing 1.8 to 3.3 kg, prostaglandin E_1 was injected intravenously without anaesthesia through the superficial vein of the foreleg.

Intravenous injections into chicks. Two- to five-day-old chicks weighing 40 to 50 g were used and the injections were made into the right external jugular vein in volumes of not less than 0.1 ml. and not more than 0.5 ml.

RESULTS

Injections into the cerebral ventricles of cats. The intraventricular injection of 7 to 20 μg/kg of prostaglandin E_1 was followed within 5 to 20 min by sedation and stupor. Spontaneous movement decreased and the cat would sit in a corner of its cage or, if allowed its freedom, would seek out a dark recess usually under a bench, where it would continue to sit for hours, if undisturbed. The cat assumed a characteristic posture with head forward and slightly lowered ; the eyes were closed. The cat showed little interest in its surroundings, it did not resent being picked up and it showed no signs of affection. When taken up and set free, it tended to retire quickly to its former sheltered position. Its movements were not impaired but rapid and fully co-ordinated.

The cat failed to respond to a sudden loud noise or to a bright flash of light. On the other hand, when pressure was applied to a foot-pad the limb was rapidly withdrawn but there was no vocalization, indeed the cats were invariably silent. To a few stimuli, there was a sluggish response ; for example on the introduction of another cat into the room, the eyes slowly opened, the ears pricked up and the head moved in the appropriate direction.

Sometimes there were definite signs of catatonia. This was a late feature which occurred after a latency of at least 40 min and developed gradually. When fully developed, the cat could be placed across the rungs of an inverted stool and would remain in such an unnatural position without moving for periods up to 90 min. In contrast, uninjected cats could not be induced to adopt such a position at all. The catatonic signs lasted up to 4 hr, sedation and stupor up to 24 hr, and even at 48 hr there was sometimes reduced spontaneous activity. The threshold dose which produced sedation and stupor was approximately 3 μg/kg and the effect lasted 4 to 8 hr.

Another effect of the injection of prostaglandin E_1 was moderate dilatation of the pupils lasting 3 to 4 hr ; the pupillary reflexes were, however, normal. There was no evidence of any loss of function of any cranial or spinal nerves. There was no obvious change in respiratory or cardiac rates ; no salivation, lachrymation, vomiting, defaecation or micturition occurred. There was no hyperphagia, indeed cats which had been starved for 24 hr before the injection showed no interest in food during the stupor due to prostaglandin. The injection caused no scratching or other movements.

In one cat prostaglandin E_2 (12 μg/kg) and in another cat prostaglandin E_3 (12 μg/kg) were injected intraventricularly. Sedation, stupor and catatonia developed and the effects resembled those seen following an intraventricular injection of 7 μg/kg of prostaglandin E_1.

In control experiments intraventricular injections of neutral 0.9% saline were followed by transient slight diminution in spontaneous activity.

Intravenous injections into cats. When injected intravenously into unanaesthetized cats in doses up to 10 μg/kg, no effects were detected with prostaglandin E_1. In doses of 20 μg/kg the only effect was a reduction in spontaneous activity lasting about 2 hr. The effect was less than that following an intraventricular injection of 3 μg/kg of prostaglandin E_1.

Intravenous injections into chicks. Immediately following an intravenous injection of prostaglandin E_1, E_2 or E_3 in doses from 10 to 400 μg/kg there was a great reduction

in respiratory rate—sometimes the rate decreased from 60 to 15 breaths/min. In addition there was profound sedation but no signs of catatonia. The chick lay on its side and, with the higher doses (50 to 200 μg/kg of prostaglandin E_1), the righting reflex was lost. There was little spontaneous movement, but in a few chicks during the first 3 min after the injection short-lasting convulsive movements of the legs and wings occurred. The duration of sedation depended upon the dose injected. When sedation subsided the chick slowly resumed its normal posture. The righting reflex was first restored, the chick remaining in a squatting position with its eyes closed. The respiratory rate had by then returned to normal. Gradually the chick resumed the standing posture and finally it would begin to chirp and move about the cage.

During the period of sedation the chicks were invariably silent even when pressure was applied to a toe, although this produced immediate withdrawal of the limb. There was no loss of the corneal reflex and, when the standing posture had been regained, there was no abnormality of gait or lack of co-ordination. Control injections of 0.5 ml. of 0.9% saline produced no detectable changes.

With prostaglandin E_1 the effects of 10 μg/kg lasted about 5 min and those of 200 μg/kg about 75 min. When an estimate of the relative activities of the three prostaglandins was made by measuring the time between injection and the recovery or normal posture, prostaglandin E_1 was 1.5-times more active than E_2 and 4-times more active than E_3.

DISCUSSION

The effects following an intraventricular injection of the prostaglandins E resemble the late effects of intraventricular injection of physostigmine, dyflos, acetylcholine or bulbocapnine seen by Feldberg & Sherwood (1954, 1955). These authors describe the posture of a cat after intraventricular physostigmine as sitting "hunched up without movement ; its eyes half shut or shut and its head slightly inclined forward" ; this description could be used equally for cats injected with prostaglandin. The catatonic stupor produced by the four drugs used by Feldberg & Sherwood, however, was preceded by signs of pronounced excitation—vigorous scratching, licking and washing movements followed by reflex hyperexcitability and tremor. None of these excitatory effects was observed with the prostaglandins.

The effects of intraventricular prostaglandin could be mimicked, but to a small degree only, by intravenous injection of a relatively large dose. Such a dose injected intravenously into anaesthetized cats would cause a substantial fall in blood pressure (Holmes, Horton & Main, 1963), and therefore the possibility cannot be excluded that part of the short-lived sedative effect seen on intravenous injection is secondary to this fall of blood pressure. The effects following intraventricular injection, however, cannot be explained in this way, since by the intraventricular route much smaller doses were effective than on intravenous injection, and the effects were not only sedation but also stupor and catatonia.

As the effects of intravenous prostaglandins in the 2- to 5-day-old chick somewhat resemble those seen in cats on intraventricular injection and are not typical signs of circulatory failure, they also appear to be central nervous effects. Prostaglandins will reach the brain from the blood stream as, in these young chicks, the blood-brain

barrier has not yet developed. It is of interest to note that the relative central depressant activities of the three prostaglandins in chicks were similar to those found in smooth muscle preparations (Horton & Main, 1963).

Ambache & Reynolds (1960, 1961) found a smooth muscle stimulating substance in rabbit brain which they were unable to distinguish from irin, a hydroxy unsaturated fatty acid extracted from the iris. Kirschner & Vogt (1961) prepared three biologically active fractions from horse, rabbit and guinea-pig brains ; two were identified as lysophosphatidic acid and ganglioside respectively, but the third fraction was believed to consist of unsaturated fatty acids. Similarly, Toh (1963) separated three fractions from cat and dog brain extracts ; the third fraction (Toh's substance C) behaved like an unsaturated fatty acid. Ramwell & Shaw (1963) have found an oxytocic ether-soluble acid in brain superfusates. Whether any of these biologically active fatty acids are prostaglandins is unknown. It is significant, however, that Bergström and his colleagues (Bergström, Dressler, Krabisch, Ryhage & Sjövall, 1962) were unable to detect any prostaglandin in sheep brain whereas other sheep tissues which they extracted all contained either prostaglandin or prostaglandin-like material. The demonstration of the central actions of prostaglandin described in this paper perhaps justifies a renewed search for it in the central nervous system.

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