MEIOSIS: A PROSTAGLANDIN RESPONSE THAT IS NOT INHIBITED BY ASPIRIN

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Antidromic stimulation of the sensory nerve to the rabbit eye produces pupillary meiosis, supposedly by release of prostaglandins into the aqueous humour. The analogy between this phenomenon and neurogenic inflammation is drawn. It is shown that aspirin and indomethacin, known blockers of prostaglandin synthesis and release, fail to block the meiosis thus produced.

Introduction The role of the peripheral nervous system, and more particularly the axon reflex mechanism, in the inflammatory process has been studied by Janscó and co-workers (Janscó, 1966; Janscó, Janscó-Gábor & Szolcsanyi, 1967; Janscó, Janscó-Gábor & Szolcsanyi, 1968). They showed that the vasodilatation, increased capillary permeability and oedema typical of an inflamed tissue could be mediated solely by antidromic stimulation of peripheral sensory neurones such as can occur locally in the physiological axon reflex response. Further, using an unique pharmacological tool, they showed that blocking of the peripheral nerves greatly modified the inflammation produced locally by various noxious stimuli, which clearly implies that the nervous system does play a part in the inflammatory response under physiological conditions.

In the rabbit eye, the vascular inflammatory signs produced by antidromic stimulation of the sensory ophthalmic nerve were shown by Perkins (1957) to be manifest as increased permeability of ocular capillaries, increased intraocular pressure (equivalent to oedema), and pupillary meiosis, the latter being a smooth muscle effect probably mediated by capillary dilatation (Langworthy & Ortega, 1943). Similar effects in the eye are produced physiologically by a local axon reflex (Duke-Elder & Duke-Elder, 1932). There is good evidence to support the theory that the antidromically-induced effects in the eye are produced by release of prostaglandins into the aqueous humour (Ängård & Samuelsson, 1964; Ambache, Kavanagh & Whiting, 1965).

As there is now evidence linking prostaglandins with several inflammatory mechanisms (Ambache, 1966; Greaves, Sondergaard & McDonald-Gibson, 1971; Vane, 1971), and evidence implicating several anti-inflammatory drugs with synthesis and/or release of prostaglandins (Ferreira, Moncada & Vane, 1971; Smith & Willis, 1971; Vane, 1971) it was decided to ascertain whether aspirin (acetyl salicylic acid) or indomethacin would also modify the iris response to antidromic nerve stimulation.

Methods Six male albino rabbits (2.5-3.5 kg) were anaesthetized with urethane (1.5 g/kg, intravenously), blood pressure was monitored via a cannula in a common carotid artery, and body temperature maintained at a normal level with a water blanket. The animals were decerebrated to expose the trigeminal nerves and ganglia, and the dura overlying the ganglia was carefully removed. The ophthalmic nerves were cut on both sides peripheral to the ganglion.

After recovery from the ensuing meiosis (about 0.5 h), an intense unilateral pupillary constriction could be obtained by stroking the peripheral end of the cut ophthalmic nerve. The intensity and time course of recovery of this antidromically induced response was determined by measurement of the diameter of both pupils with a vernier caliber, at 5 min intervals.

The pupillary changes were followed in this manner for two control stimulations. Acetyl salicylic acid (200 mg/kg) in buffered solution (Cooke & Goulston, 1969) was then infused into the external jugular vein, and the mechanical stimulation of the nerve repeated at 30 and 60 min post infusion. Changes in pupillary diameter and the time course of recovery were noted as before. In 2 animals, up to 400 mg/kg of acetyl salicylic acid were given.

This protocol was also undertaken in an additional 4 rabbits substituting indomethacin (Merck, Sharpe & Dohme; 25 mg/kg) in buffered solution (Hucker, Zacchei, Cox, Brodie & Cantwell, 1966) for the acetyl salicylic acid infusate. A further 2 rabbits were pretreated with indomethacin (20 mg/kg, i.v.) at 24, 12 and 1 h before the decerebration and stimulation procedure.

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Results In every instance, mechanical stimulation, found by Perkins (1957) to give a more consistent response than electrical stimulation of the cut peripheral end of the ophthalmic nerve, resulted in an intense constriction of the pupil of the ipsilateral eye.

The pupil returned to its prestimulus size in 10-30 minutes. No change in the diameter of the contralateral pupil was observable during or after the stimulation in any animal.

Intravenous administration of acetyl salicylic acid solution had no appreciable effect in modifying the intensity or duration of any subsequent antidromically induced meiosis. This was true also for the rabbits which were acutely infused with indomethacin.

In the two animals which were pretreated with large doses of indomethacin, the response to antidromic stimulation of the cut trigeminal nerve was essentially the same as in untreated control rabbits, in intensity and duration.

Discussion It has been reported that meiosis can be produced by an axon reflex in the rabbit eye (Duke-Elder & Duke-Elder, 1932); hence antidromically mediated meiosis in the eye can be looked upon as the smooth muscle analogue of antidromically induced (or axon reflex produced) vascular inflammatory responses in other tissues. The results obtained in these experiments suggest that aspirin may not prevent all the nerve-dependent inflammatory signs in the eye. That is, if indeed it is the release of prostaglandins into the aqueous which initiates meiosis under these conditions, then this component of the inflammatory process is not totally inhibited by some known prostaglandin blockers. This observation is in good agreement with those of Neufeld, Jampol & Sears (1972), who found that, although aspirin will inhibit protein exudation into the aqueous humour induced by such insults to the eye as paracentesis or laser burns to the iris, the meiosis component of the inflammatory reaction is not prevented. It is particularly interesting in the light of Janscó's experiments (Janscó, 1966; Janscó *et al.*, 1967; Janscó *et al.*, 1968) with the neurogenic aspects of chemically induced inflammation, that Neufeld *et al.* (1972) also found that it is the inflammatory response to a chemical insult to the eye that is not blocked by aspirin. It is likely, therefore, that the nervous component is more significant in inflammation produced in response to a chemical stimulus, than to other types of stimulus.

The preliminary results from the indomethacin-treated rabbits must be assessed guardedly. There are no data on the accessibility of the aqueous to circulating indomethacin, although it is known to diffuse sparingly into the cerebrospinal fluid (Hucker *et al.*, 1966). Aspirin, on the other hand, appears to enter the aqueous in significant amounts (Neufeld *et al.*, 1972).

These data are interesting in that they suggest a model in which aspirin apparently does not totally prevent the release of prostaglandins which is subsequent to a given stimulus, although it is known to block prostaglandin release in several other preparations (Smith & Willis, 1971; Ferreira *et al.*, 1971).

An incidental observation of some interest was that, when constriction was produced in one pupil by stimulation of the cut ipsilateral ophthalmic nerve, no consensual changes in pupil diameter could be seen in the contralateral eye (with or without drug pretreatment), nor were blood pressure changes noted. This is not consistent with the hypothesis of Chiang & Thomas (1972) that the release (or injection, as in their experiments) of prostaglandins into the anterior chamber of one eye leads to consensual pressure changes in the contralateral eye, supposedly by way of prostaglandins released into the circulation. This may be explicable, however, on the grounds of type and dosage of drugs that were used in their injection experiments.

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