Release of prostaglandins and incapacitation after injection of endotoxin in the knee joint of the dog.

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Ferreira, Moncada & Vane (1974) suggested that incapacitation during inflammation in the knee joint of the dog is due to sensitization of pain receptors by locally released prostaglandins. Since injection of endotoxin into the knee joint cavity induces incapacitation (Morgan & Bennett, 1947; Van Arman, Carlson, Kling, Allen & Bondi, 1974) and since endotoxin releases prostaglandins (Collier, Herman & Vane, 1973; Herman & Vane, 1974), we decided to study the time course of this inflammatory process, the release of prostaglandins during its development and the effect of local treatment with indomethacin.

Mongrel dogs of either sex were anaesthetized with thiopentone (10 mg/kg intravenously). Endotoxin (*E. coli* Difco 0111B4,) 25 ng/kg in 0.5 ml of sterile saline, was injected in one of the knee joint cavities and sterile saline (0.5 ml) was injected in the contralateral joint. Symptoms of incapacitation ranging from limping, occasional 3-legged gait to complete 3-legged gait were scored. One hour to 1½ h after the injection, symptoms started to develop and were most pronounced from the 3rd to the 5th or 6th hour. In the next 3 to 4 h a gradual recovery occurred. The symptoms had disappeared completely within 24 hours.

At different times after the injection of endotoxin, synovial fluid was sampled from both joints under light thiopentone anaesthesia and the cavities washed twice with 2 ml of sterile saline. Total samples were extracted and bioassayed for PG-like activity (Gilmore, Vane & Wyllie, 1968). The results show a close relationship between the prostaglandin content of the samples and incapacitation: synovial fluid obtained before injection of endotoxin had no PG-like activity; the mean PG-like activity of the samples collected just before limping started and during maximal symptoms was respectively 43 (range: 0-191; 10 experiments) and 123.5 (range: 11-141; 7 experiments) ng PG E_2-equivalents. Only in 1 out of 10 dogs PG-like activity could be detected in synovial fluid obtained after 24 h when symptoms had disappeared. No PG-like activity was found in the saline treated joints.

In 9 dogs endotoxin was injected together with indomethacin (200 μg/kg dissolved in phosphate buffer 0.1 M, pH 8.9). In 7 of these dogs no symptoms developed up to 7 h after the injection. In 2 of them, mild symptoms appeared. No PG-like activity was found in the dogs treated with indomethacin in which no symptoms developed; in 2 dogs with symptoms, small amounts of PG-like activity could be detected.

These experiments show that endotoxin injected in the cavity of the knee joint produces incapacitation which is closely related to the appearance of prostaglandins in the joint fluid and which is susceptible to local treatment with indomethacin. These findings are consistent with the hypothesis (Ferreira, 1972; Ferreira, *et al.*, 1973, 1974) that prostaglandins are important in the development of pain (possibly by sensitizing the pain receptors) and that aspirin-like drugs exert their analgesic action by the abolition of the sensitization of the pain receptors caused by the local release of prostaglandins.

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