Prostaglandins are not essential in experimental fever of rats

J. FRENS, A.S.J.P.A.M. VAN MIERT & C.TH.M. VAN DUIN
(introduced by E. SCHÖNBAUM)

Institute of Veterinary Pharmacology and Toxicology, Utrecht University, Biltstraat 172, Utrecht, The Netherlands

Milton & Wendlandt (1970) hypothesised that prostaglandins (PG's) may act as mediators in the development of fever. It is difficult to evaluate this hypothesis, because not only PG's but also other biologically active metabolites from essential fatty acids (EFA) may be involved. To assess the importance of PG's and other EFA derivatives in the fever reaction, EFA deficient rats were treated with yeast and their response compared to normal controls of the same strain. Bonta, Bult, Vincent & Zijlstra (1977) described the characteristics of these EFA deficient rats. They were markedly deficient in bishomo-γ-lineoleic and arachidonic acids. Fever was produced by subcutaneous injection of activated yeast (Niemegeers, Leneaerts & Janssen, 1975) and body temperature was measured every half hour for 6 hours, at an ambient temperature of 27 ± 1°C.

EFA deficient rats as well as controls showed a complex temperature response to yeast (Fig. 1), but control and EFA deficient rats responded identically. The changes in body temperature 2 and 6 h after injection were different from saline controls ($P < 0.005$). It seems that a marked deficiency of prostaglandins or their precursors does not impair the fever reaction. The results described need corroboration from results in other animal species. The rat had to be used as it is the only animal species at present that has been made fatty acid deficient. However in order to confirm this hypothesis it will be necessary to demonstrate that prostaglandins do not occur in the CNS of the EFA deficient rats.

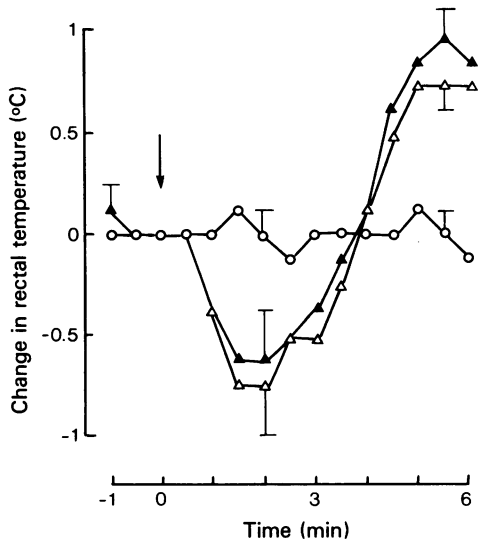

Figure 1 Effect of s.c. injection of saline or yeast on rectal temperature. (○) saline in EFA deficient rats (n = 6), (△) yeast in EFA deficient rats (n = 14). (▲) yeast in normal rats (n = 13). Vertical lines are the standard error.

References

BONTA, I.L., BULT, H., VINCENT, J.E. & ZIJLSTRA, F.J. (1977). Acute anti-inflammatory effects of aspirin and dexamethasone in rats deprived of endogenous prostaglandin precursors. *J. Pharm. Pharmac.*, **29**, 1–7.

MILTON, A.S. & WENDLANDT, S. (1970). A possible role for prostaglandin E, as a modulator for temperature regulation in the central nervous system of the cat. *J. Physiol. (Lond.)*, **207**, 76–77P.

NIEMEGEERS, C.J.E., LENEAERTS, F.M. & JANSSEN, P.A.J. (1975). The antipyretic effect of suprofen in rats with yeast-induced fever. *Arzneimittel. Forsch.*, **25**, 1519–1524.

Effects of prostaglandin synthetase inhibition on natriuresis induced by diuretics and sodium loading in the rat

M.J. COOLING & M.F. SIM

Research Department, The Boots Co. Ltd., Nottingham NG2 3AA

Olsen (1975) suggested that prostaglandins have a role in the natriuretic response to high efficacy diuretics since indomethacin reduced the effect of bumetanide in dogs. Indomethacin pretreatment also reduced frusemide-induced natriuresis in anaesthetised rabbits (Oliw, Kövér, Larsson & Änggård, 1976) and in normal and hypertensive man (Patak, Mookerjee, Bentzel, Hysert, Babej & Lee, 1975). We have extended these investigations by studying the effects of oral pretreatment with indomethacin on the responses to four types of diuretic and to oral sodium loads in female conscious rats.

The effect of indomethacin (5 mg/kg) pretreatment on natriuretic and kaliuretic responses is shown in Table 1. These results are apparently due to prostaglandin synthetase inhibition since flurbiprofen, another potent but chemically unrelated inhibitor of prostaglandin synthetase, had a similar action (results not shown).

Natriuresis induced by frusemide, acetazolamide, amiloride or bendrofluazide was significantly reduced by indomethacin, but kaliuresis was almost identical with or without indomethacin pretreatment.

Sodium loading-induced natriuresis was also reduced after indomethacin and the maximal reduction was approximately 2 mmol/kg despite the very high natriuresis achieved. Again kaliuresis was not significantly affected.

The diuretics used are thought to act at sites proximal to or at the sodium/potassium exchange site in the distal nephron. Prostaglandin synthetase inhibition significantly reduced natriuresis without affecting kaliuresis suggesting an effect distal to the exchange site. There is evidence that the collecting duct participates in sodium regulation (Stein & Reineck, 1974) and that its cells are rich in prostaglandin synthetase (Janszen & Nugteren, 1973).

Our results are consistent with the view that in rats part of the natriuretic effect of highly and moderately efficacious diuretics and sodium loading is dependent on the presence of renal prostaglandins and is effected at the level of the collecting duct.

References

JANSZEN, F.H.A. & NUGTEREN, D.H. (1973). A histochemical study of the prostaglandin biosynthesis in the urinary system of rabbit, guinea-pig, gold-hamster and rat. *Adv. Biosci.*, **9**, 287–292.

OLIW, E., KÖVÉR, G., LARSSON, C. & ÄNGGÅRD, E. (1976). Reduction by indomethacin of furosemide effects in the rabbit. *Eur. J. Pharmac.*, **38**, 95–100.

OLSEN, U.B. (1975). Indomethacin inhibition of bumetanide diuresis in dogs. *Acta pharmac. tox.*, **37**, 65–78.

PATAK, R.V., MOOKERJEE, B.K., BENTZEL, C.J., HYSERT, P.E., BABEJ, M. & LEE, J.B. (1975). Antagonism of the effects of furosemide by indomethacin in normal and hypertensive man. *Prostaglandins*, **10**, 649–659.

STEIN, J.H. & REINECK, H.J. (1974). The role of the collecting duct in the regulation of excretion of sodium and other electrolytes. *Kidney Int.*, **6**, 1–9.

Table 1 Effect of indomethacin pretreatment on natriuresis and kaliuresis in rats

Treatment†	n	Na^+ excretion (mmol/kg) Control	Na^+ excretion (mmol/kg) Indomethacin‡ (5 mg/kg)	K^+ excretion (mmol/kg) Control	K^+ excretion (mmol/kg) Indomethacin‡ (5 mg/kg)
0.25% cellosize in glass distilled water	6	0.22 ± 0.06	0.11 ± 0.02	0.50 ± 0.07	0.33 ± 0.04*
Frusemide (10 mg/kg)	6	1.32 ± 0.24	0.79 ± 0.20	0.93 ± 0.07	0.90 ± 0.05
Frusemide (30 mg/kg)	6	4.44 ± 0.19	3.24 ± 0.15***	1.65 ± 0.06	1.63 ± 0.02
Frusemide (90 mg/kg)	6	6.22 ± 0.21	5.04 ± 0.16***	2.19 ± 0.06	2.12 ± 0.05
0.25% cellosize in glass distilled water	4	0.17 ± 0.04	0.07 ± 0.03	0.58 ± 0.08	0.33 ± 0.01
Acetazolamide (10 mg/kg)	4	2.19 ± 0.22	1.50 ± 0.08*	2.06 ± 0.06	1.93 ± 0.18
Amiloride (10 mg/kg)	4	2.36 ± 0.18	1.16 ± 0.10***	0.11 ± 0.00	0.12 ± 0.02
Bendrofluazide (10 mg/kg)	4	1.65 ± 0.18	0.81 ± 0.12**	0.97 ± 0.09	0.98 ± 0.12
Glass distilled water	6	0.25 ± 0.08	0.18 ± 0.05	0.37 ± 0.03	0.47 ± 0.08
0.9% w/v NaCl solution	6	0.92 ± 0.05	0.43 ± 0.03***	0.48 ± 0.03	0.40 ± 0.06
1.8% w/v NaCl solution	6	4.45 ± 0.45	3.55 ± 0.24	1.04 ± 0.09	1.23 ± 0.06
3.6% w/v NaCl solution	6	13.89 ± 0.32	12.04 ± 0.35**	2.00 ± 0.05	2.12 ± 0.10

Results are mean electrolyte excretion ± s.e. mean for n groups of 5 female Boots Wistar rats weighing 80 to 100 g. *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$ for difference between control pretreatment and indomethacin pretreatment; all other differences were not significant at the 5% level using Student's t-test.

‡ Pretreated orally 1 h before administration of diuretics or sodium load with indomethacin (5 mg/kg) in 0.25% cellosize in glass distilled water (10 ml/kg) or vehicle alone (10 ml/kg).

† Administered orally (30 ml/kg); the diuretics were given in 0.25% cellosize in glass distilled water; urine was collected for 3 h.