clearance (CL_R) are altered significantly. The terminal half-life ($t\frac{1}{2}$) of ceftriaxone was shortened slightly but not significantly by coadministration of caffeine.

In conclusion, caffeine did not affect the plasma protein binding of ceftriaxone in-vitro. Caffeine elevated rabbit plasma concentrations of ceftriaxone and increased the volume of distribution of the central compartment (V_1). Caffeine decreased the volume of distribution of ceftriaxone of the peripheral compartment (V_2) and the rate of transfer to the peripheral compartment (k_{12}) in the rabbit. The mechanism for these pharmacokinetic changes by caffeine may be by its effect on drug distribution to organs and peripheral tissue.

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Lack of effect of BW755c on glucose-induced insulin secretion in the rat in-vivo

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Glucose-induced elevations in plasma immunoreactive insulin (IRI) were examined in anaesthetized rats pretreated with BW755c, sodium meclofenamate or vehicle. Neither drug influenced the glucose-induced hyperinsulinaemia or the glucose disappearance rate. The results do not support a physiological role for arachidonic acid metabolites in the regulation of glucose-induced insulin secretion.

It has been suggested that certain metabolites of arachidonic acid produced by the lipoxygenase pathway may act as second or third messengers in coupling the glucose stimulus to the secretion of insulin (Metz et al 1984). These suggestions have been made in light of the ability of certain lipoxygenase products to stimulate insulin secretion and of lipoxygenase inhibitors to prevent secretion of insulin in response to glucose in-vitro (Yamamoto et al 1982; Metz et al 1983). We have examined the effect of the dual lipoxygenase-cyclooxygenase inhibitor, BW755c (Higgs et al 1979) on glucose-induced elevations in the plasma insulin concentration in the rat. This drug was compared with sodium meclofenamate, a potent cyclooxygenase inhibitor, as inhibition of cyclooxygenase has been reported to enhance glucose-induced insulin secretion (MacAdams et al 1984).

Method

Male Sprague-Dawley rats (190–350 g) were fasted for 18 h and anaesthetized with pentobarbitone sodium

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(60 mg kg^{-1} i.p.). The trachea was cannulated and the animal ventilated with 100% O_2 (1 ml/100 g; 53 strokes min^{-1} to maintain arterial pH at 7·34 ± 0·027 and P_{CO_2} at 38·0 ± 1·7 mmHg). Rectal temperature was maintained at 37 °C. Cannulae were placed in the aortic arch via the right common carotid artery (blood sampling) and the femoral vein (drug injection). Blood samples (0·1 ml) were removed before and at 5 min intervals after glucose injection (0·5 g kg^{-1} i.v.) and centrifuged immediately (Beckman microfuge). Plasma glucose was measured using a Beckman Glucose Analyser and 25 μl plasma frozen for subsequent insulin assay (Hales & Randle 1963).

Pretreatment with BW755c (3-amino-1-[(*m*-trifluoromethyl)phenyl]-2-pyrazoline, 50 mg kg^{-1} p.o. 1 h before anaesthesia) or sodium meclofenamate (10 mg kg^{-1} i.v. 30 min before glucose injection) had no effect on fasting plasma insulin concentrations or glucose-induced hyperinsulinaemia (Table 1). Fasting plasma glucose concentrations, peak plasma glucose concentrations after the glucose injection and glucose disappearance constants were not significantly different from the control values of 4·7 ± 0·3 mmol $litre^{-1}$, 13·6 ± 0·5 mmol $litre^{-1}$ and 3·9 ± 0·4% min^{-1}, respectively. Neither drug influenced glucose-induced elevations in the plasma immunoreactive insulin (IRI) concentration when a lower dose of glucose (0·25 g kg^{-1}) (results not shown) was injected during an arachidonic acid infusion. This lower dose of glucose produced a smaller increase in plasma IRI (peak value 5·3 ± 1·4 ng ml^{-1}).

Table 1. Plasma immunoreactive insulin concentrations (ng ml^{-1}) in the fasting state (−5 min) and at various times after the injection of glucose (0·5 g kg^{-1} i.v.). Each value is the mean ± s.e. mean of 7 observations. Analysis of variance shows no difference among the three groups.

Treatment	Time after glucose injection (min) −5	5	15	30
Control	2·0 ± 0·4	11·5 ± 1·8	5·6 ± 0·8	3·3 ± 0·6
Sodium meclofenamate (10 mg kg^{-1})	1·9 ± 0·21	9·2 ± 1·7	6·9 ± 0·7	3·2 ± 0·9
BW755c (50 mg kg^{-1})	2·8 ± 0·33	12·7 ± 2·7	7·1 ± 1·3	3·5 ± 0·6

Discussion

These results, obtained using intact animals, do not support the suggestion, made on the basis of in-vitro findings, that arachidonic acid metabolism along the lipoxygenase pathway mediates glucose-induced insulin release. The dose of BW755c was considerably in excess of that found to inhibit leukocyte migration into inflammatory exudate over a 24 h period (Eakins et al 1980), an effect probably related to inhibition of lipoxygenase. Moreover, this dosage regimen completely prevents the massive increase in plasma prostanoids produced by bacterial lipopolysaccharide (McKechnie et al 1985). Thus we have reason to believe, but no proof, that the dose of BW755c is adequate. The failure of sodium meclofenamate (in a dose adequate to inhibit cyclooxygenase) to modify glucose-induced hyperinsulinaemia again argues against the negative modulatory physiological role in glucose-induced insulin secretion postulated for cyclooxygenase metabolites (Metz et al 1981). The explanation for the discrepancy between the present in-vivo results and published in-vitro results is unknown. However, results obtained using islets in-vitro may, in this context, correspond more to a pathological situation with enhanced phospholipase A_2 activity and arachidonic acid metabolism. Moreover the possibility must be considered that, in the high concentrations used in-vitro, drugs such as BW755c may have actions additional to lipoxygenase inhibition. In view of the potential use of compounds such as BW755c as anti-inflammatory agents (Higgs et al 1979), it is necessary to establish if they inhibit glucose-induced insulin in man in therapeutic doses. The present work suggests this to be unlikely.

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