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ANORECTIC ACTIVITY OF PROSTAGLANDIN PRECURSORS

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1 Intraperitoneal and intragastric (i.g.) administration of prostaglandin precursors arachidonic (2 mg, 15 mg/kg, i.p.; 30 mg/kg, i.g.), linolenic (100 mg/kg, i.p.; 200 mg/kg, i.g.) and linoleic (15, 100 mg/kg, i.p.; 100 mg/kg, i.g.) acids to 22 h food-deprived rats inhibits food intake.

2 This anorexia is similar to that induced by prostaglandin $F_{2\alpha}$ (1 mg/kg, i.p.).

3 At anorectic doses these fatty acids do not cause pyrexia, in fact arachidonic acid causes hypothermia.

4 Prior treatment with indomethacin (15 mg/kg) and paracetamol (50 mg/kg) specifically reverses the anorexia and the behavioural satiety induced by the three fatty acids, while not affecting prostaglandin $F_{2\alpha}$-induced suppression of food intake.

5 Results of the present experiments suggest that both physiological and pharmacological modification of appetite could be brought about through an effect on prostaglandin generating systems.

Introduction

Prostaglandins are of ubiquitous distribution within the body and are synthesized from essential fatty acid precursors by various tissues including the brain (Bergström, Danielsson, Klenberg & Samuelsson, 1964; Bergström, Danielsson & Samuelsson, 1964). Since the first report (Horton, 1964), their possible involvement in the regulation of the hunger–satiety phenomenon has been studied by a number of workers (for references see Doggett & Jawaharlal, 1977). It has been shown that in man, fasting is associated with lower prostaglandin levels in the blood as compared with post-prandial samples (Greaves, McDonald-Gibson & McDonald-Gibson, 1972). Apart from this, insulin has been shown to play an important role in the hunger–satiety phenomenon (Mayer, 1955) and is closely associated with the formation of polyunsaturated fatty acids, which are prostaglandin precursors. For example, desaturation of fatty acids is markedly depressed in the liver of diabetic animals in a similar way to that produced by fasting (Benjamin & Gellhorn, 1964), an effect which in both cases can be reversed by insulin (Mercuri, Peluffo & Brenner, 1966). Furthermore diabetes mellitus, an insulin deficient state, is characterized by 'hyperphagia'. Earlier studies on the possible role of fatty acids as a satiety signal have not yielded any information as to their possible role in appetite regulation, although their role has been emphasized (Kennedy, 1966). Intravenous infusion of neutral fat emulsions has no effect on the electrical activity of the lateral or ventromedial hypothalamus, both of which play an important part in appetite regulation (Anand, Dua & Singh, 1961). An inverse correlation between non-esterified free fatty acid concentrations and glucose utilization exists which is thus related to hunger–satiety (Mayer, 1963). In rats deprived of food for 1 h, it has been shown that oleic acid produces latent anorexia after intragastric administration (Booth, 1972). A number of esters of saturated fatty acids, like palmitic acid, on feeding for 30 days to rats have recently been shown to increase food intake, feed efficiency and weight gain when they provided 36% of dietary energy (Caster, Resurreccion, Cody, Andrews & Bargmann, 1975). The anorexigenic activity of oleic acid, the monoenoic fatty acid, is very interesting in view of the opposite effect of palmitic acid, since both these fatty acids together constitute approximately 70% of free fatty acids in the rat blood (Oomura, Sugimori, Nakamura & Yamada, 1975). In view of the anorexigenic activity of the prostaglandins, a study of the possible role of their precursor polyunsaturated fatty acids in this homeostatic mechanism is warranted: this is the subject of the present paper.

Methods

Measurement of food intake

Male albino rats weighing between 200–250 g were housed singly in cages with wire grid bottoms in which they were allowed to acclimatize for 3 days with free access to food and water. During experiment water was available *ad libitum* throughout, but the animals were deprived of all food for 22 h before presentation of 100 g 41B pellets. Since rats eat mainly at night (Richter, 1927; Hemmingsen & Krarup, 1937), all experiments were performed in darkness between 18 h 00 min and 24 h 00 min, the artificial lighting being extinguished 1 h before the start. Accurate values of food intake were obtained by adding the spillage collected on the papers placed underneath the cages during experiments to the leftover food while reweighing. Food intake was measured at 15 min intervals up to 2 h and expressed as the mean weight eaten per 100 g body weight. At least 7 days elapsed between consecutive experiments in the same animal. The significance of any observed differences between the group means was determined by Student's t test.

Intragastric administration

Intragastric administration was accomplished with a stainless steel hypodermic needle beaded at the end and curved to facilitate easy oesophageal insertion. The procedure was repeated 2 or 3 times before the actual experiment in order to accustom the rat to the procedure.

Measurement of the body temperature

The rectal temperature was measured by the method described previously (Lomax, 1966). The thermistor probe was lubricated with liquid paraffin, and inserted into the rectum to a depth of at least 6 cm.

Drugs and solutions

The following substances were used: arachidonic acid sodium salt, linoleic acid sodium salt, linolenic acid ethylester, indomethacin and paracetamol.

Prostaglandin $F_{2\alpha}$ as tromethamine salt (supplied by Dr J.E. Pike, Upjohn Co., U.S.A. and Professor B. Samuelsson, Karolinska Institute, Stockholm,

Table 1 Effect of intraperitoneal administration of fatty acids on food intake in 22 h fasted rats

No.	Fatty acid	Dose (mg/kg, i.p.)	Time of administration of fatty acid before presentation of food	Food intake (g/100 g body wt.) 0–30 min	0–60 min
I	Tween-80-saline		5 min		2.64 ± 0.44
(a)	Arachidonic acid	15	5 min		0.66 ± 0.22 ($P < 0.01$)
(b)	Tween-80-saline		15 min		4.88 ± 0.91
	Arachidonic acid	15	15 min		0.62 ± 0.24 ($P < 0.01$)
(c)	Tween-80-saline		30 min	3.14 ± 0.30	3.95 ± 0.57
	Arachidonic acid	15	30 min	1.21 ± 0.34 ($P < 0.01$)	2.84 ± 0.57 (NS)
II	Tween-80-saline		5 min		3.02 ± 0.31
(a)	Linoleic acid	100	5 min		1.42 ± 0.06 ($P < 0.01$)
(b)	Tween-80-saline		15 min		4.88 ± 0.91
	Linoleic acid	100	15 min		1.52 ± 0.31 ($P < 0.05$)
(c)	Tween-80-saline		30 min		2.60 ± 0.40
	Linoleic acid	100	30 min		–
III	Arachis oil		30 min	1.66 ± 0.23	2.60 ± 0.30
(a)	Linolenic acid	100	30 min	0.45 ± 0.30 ($P < 0.01$)	2.08 ± 0.47 (NS)

Values are mean ± s.e. mean. n = at least 4.

Sweden) was prepared freshly from a stock ethanolic solution (10 mg/ml) with pyrogen-free saline (0.9% w/v NaCl solution) containing 0.02% sodium carbonate. Arachidonic and linoleic acids were dissolved in a solution of 0.5% Tween 80 in saline, while linolenic acid was dissolved in arachis oil. Paracetamol was prepared in hot saline containing 20% propylene glycol as described by Milton & Wendlandt (1971). Indomethacin was suspended in 0.5% methylcellulose in water.

Indomethacin was given subcutaneously; all other substances were administered intraperitoneally or intragastrically. The volume of injection was 1 ml/kg in all cases except for paracetamol which was 2 ml/kg. In order to study the effect of prostaglandin biosynthesis blockers on hunger, both indomethacin and paracetamol were administered 1 h before each of the fatty acids. Food was presented 5 min after the administration of fatty acids.

Results

Anorectic activity of prostaglandin precursors

Table 1 summarizes the effect of the three fatty acids administered intraperitoneally on food intake in rats deprived of food for 22 hours. The onset of anorexia after both arachidonic acid and linoleic acid occurred within a few minutes of administration. Anorectic activity of arachidonic acid appears to last for at least 60 min. With linoleic acid, reduction of food intake occurred 30 min after administration of the fatty acid. The fact that linoleic acid has to be further converted to arachidonic or linolenic acid, while linolenic acid and arachidonic acid are the immediate precursors of prostaglandins, could account for this. Intragastric administration (Table 2) of the three fatty acids also caused anorexia. All the three fatty acids produced a statistically significant decrease in food intake in the next hour when food was presented 30 min after fatty acid treatment, while only arachidonic acid still caused a statistically significant reduction in intake of food offered 60 min after treatment.

Prostaglandin synthesis blockers on anorectic activity of fatty acids and prostaglandin $F_{2\alpha}$

In Figure 1, the effect of prostaglandin synthetase inhibitors or vehicle alone on arachidonic acid (2 mg/kg)-induced suppression of food intake is depicted. In vehicle pretreated rats, arachidonic acid caused complete suppression of food intake for the first 15 min after presentation of food. Indomethacin

Table 2 Effect of intragastric administration of fatty acids on food intake in 22 h fasted rats

	Fatty acid	*Dose*	*Time of administration of fatty acid before presentation of food*	*Food intake (g/100 g body wt.)* 0–30 min	0–60 min
I	Control (Tween-80-saline)	1 ml/kg			4.64 ± 0.58
	Arachidonic acid	30 mg/kg	30 min		1.90 ± 0.67 ($P < 0.02$)
	Arachidonic acid	30 mg/kg	60 min		1.47 ± 0.70 ($P < 0.01$)
II	Control (Tween-80-saline)	1 ml/kg		2.79 ± 0.36	4.88 ± 0.74
	Linoleic acid	100 mg/kg	15 min	0.24 ± 0.24 ($P < 0.01$)	1.47 ± 0.28 ($P < 0.01$)
	Linoleic acid	100 mg/kg	30 min	0.67 ± 0.36 ($P < 0.01$)	2.71 ± 0.50 ($P < 0.05$)
	Linoleic acid	100 mg/kg	60 min	1.89 ± 0.06 ($P < 0.05$)	4.70 ± 0.38 ($P < 0.1$)
III	Control (Arachis oil)	1 mg/kg		2.20 ± 0.42	3.50 ± 0.61
	Linolenic acid	200 mg/kg	30 min	0.21 ± 0.21 ($P < 0.01$)	1.49 ± 0.77 ($P < 0.05$)
	Linolenic acid	200 mg/kg	60 min	1.09 ± 0.34 ($P < 0.05$)	2.96 ± 0.58 ($P < 0.1$)

Values are mean ± s.e. mean. n = at least 4.

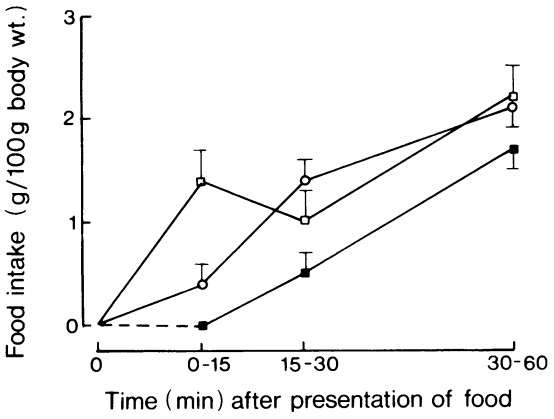

Figure 1 Effect of 1 h pre-treatment with vehicle (■), indomethacin (□, 15 mg/kg s.c.), and paracetamol (○, 50 mg/kg, i.p.) on suppression of food intake induced by arachidonic acid (2 mg/kg, i.p.) in 22 h food-deprived rats. Food was presented 5 min after administration of fatty acid. Each point represents the mean of results from at least 4 rats. Vertical lines show s.e. mean.

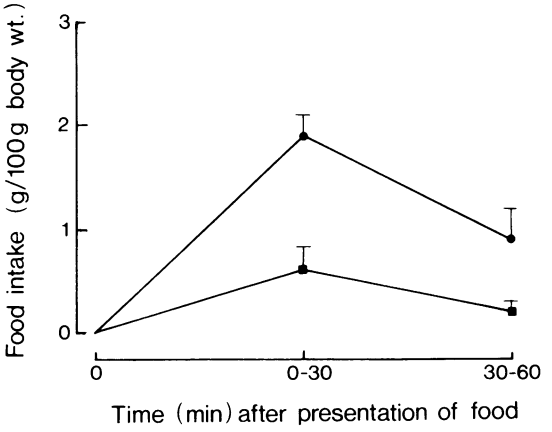

Figure 2 Effect of 1 h pre-treatment with vehicle (■), and paracetamol (●, 50 mg/kg, i.p.) on suppression of food intake induced by linoleic acid (15 mg/kg, i.p.) in 22 h food-deprived rats. Food was presented 5 min after administration of fatty acid. Each point represents the mean of results from at least 4 rats. Vertical lines show s.e. mean.

(15 mg/kg) completely reversed this anorectic activity, immediately after presentation of food. The effect of paracetamol in the first 15 min was weak, but its activity then became much more evident. At the end of the 1 h feeding period those rats treated with indomethacin and paracetamol ate significantly more ($P < 0.01$) than the vehicle-treated rats. Although there was an initial latent period in the paracetamol-treated animals in antagonizing the effect of arachidonic acid, such a latency was not seen when linoleic acid (15 mg/kg)-induced anorexia was reversed (Figure 2). None of the blockers antagonized the anorexia caused by prostaglandin $F_{2\alpha}$ (Table 3). Since administration of either blocker alone had no significant effect on food intake compared to vehicle or non-injected rats, the results are not included.

Table 3 Effect of administration of prostaglandin biosynthesis blockers, indomethacin (subcutaneously) and paracetamol (intraperitoneally) on food intake of 22 h fasted rats

	Drugs	*Dose/route*	*Time of administration of the drug before injection of $PGF_{2\alpha}$*	*Food intake (g/100 g body wt.)* 0–30 min	0–60 min
I					
(a)	Vehicle (methyl cellulose 0.5%)	1 ml/kg s.c.	1 h	0	1.32 ± 0.23
(b)	Indomethacin	15 mg/kg s.c.	1 h	0	1.20 ± 0.19 (NS)
II					
(a)	Vehicle (propylene-glycol-saline)	2 ml/kg i.p.	1 h	0	1.36 ± 0.44
(b)	Paracetamol	50 mg/kg i.p.	1 h	0	1.24 ± 0.34 (NS)

Values are mean ± s.e. mean. n = at least 4.
NS = not significantly different ($P < 0.1$) from controls.

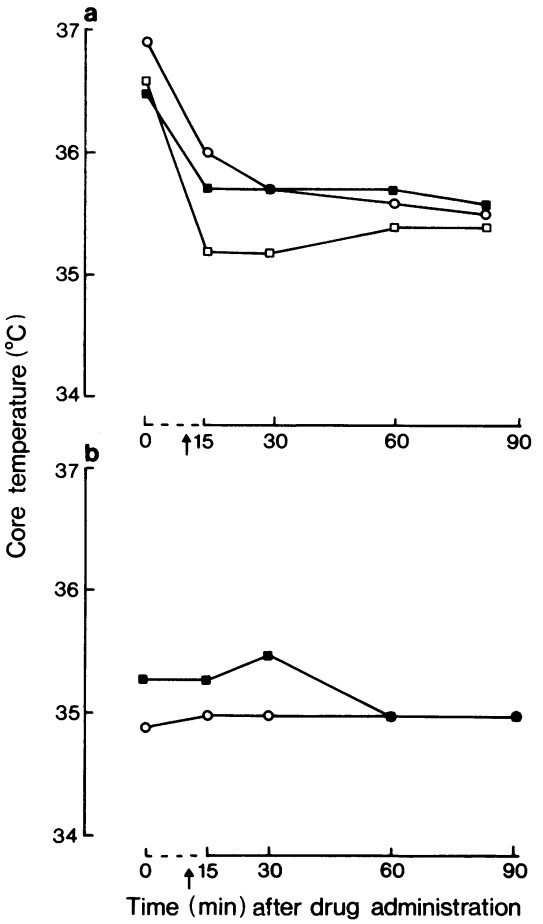

Figure 3 (a) Effect of intraperitoneal administration of vehicle (■), arachidonic acid (□, 15 mg/kg, i.p.) and linoleic acid (○, 100 mg/kg, i.p.) on the rectal temperature in 22 h food-deprived rats. Each point represents the mean of results from 6 animals. (b) Effect of intraperitoneal administration of arachis oil (■, 1 ml/kg) and linolenic acid (○, 100 mg/kg) on the rectal temperature in 22 h food-deprived rats. Each point represents the mean of results from 6 animals.

Behavioural effects of fatty acids, prostaglandin $F_{2\alpha}$ and prostaglandin biosynthesis inhibitors

All three fatty acids, like prostaglandin $F_{2\alpha}$, at doses which have been shown to cause anorexia, did not produce any central nervous depression nor did they affect locomotor activity. They all caused the typical behavioural tranquillization that is seen after food intake in a food-deprived animal and the animals showed no interest in food. No other behavioural effects were seen. Indomethacin and paracetamol by themselves did not cause any observable behavioural effects. However, they did antagonize the behavioural tranquillization seen after fatty acid administration, and they restored the animals' desire to eat in a similar way to that seen in food-deprived rats.

Effect of fatty acids on core temperature

Measurement of rectal temperature in 22 h food-deprived rats at the highest doses of fatty acids used in this present study indicate complete absence of any pyrogenic activity. In fact, contrary to its hyperthermic effect after intracerebroventricular administration (Splawinski, Gorka, Sudar & Kaluza, 1975), arachidonic acid caused a slight fall in rectal temperature (Figure 3a,b).

Discussion

The results of the experiments described here clearly indicate that, like prostaglandins, all the three precursor fatty acids possess anorectic activity in food-deprived rats, when given either intraperitoneally or intragastrically before presentation of food. This anorectic activity is blocked by two prostaglandin synthetase inhibitors, indomethacin and paracetamol. Since these fatty acids produce pain (abdominal constrictions) when given intraperitoneally and this pain can be blocked by prostaglandin synthetase inhibitors (Vane, 1973), it is possible that inhibition of the anorectic activity of precursor fatty acids by these drugs is only secondary to their antagonism of such pain. However, this possibility can be excluded since they also cause anorexia by other routes of administration, e.g. intragastric. Furthermore, induction of similar pain with acetic acid does not affect food intake (Doggett & Jawaharlal, 1977). Since these fatty acids do not cause pyrexia an elevation of body temperature can also be excluded as a cause of anorexia. The food-deprived and fatty acid-treated rats and satiated non-treated animals both showed similar behavioural tranquillization.

The specific inhibition by prostaglandin synthetase inhibitors of the anorectic activity of the fatty acids, in the absence of any effect on prostaglandin $F_{2\alpha}$ itself, suggests that the fatty acids themselves do not cause anorexia; rather they have to be converted to prostaglandins. If such an endogenous prostaglandin formation exists and affects food intake, then drugs which inhibit such a formation might be expected to increase food intake, and it was surprising that the two prostaglandin synthetase inhibitors had no effect on food intake when given alone. To this extent our hypothesis is not supported by our findings. However, there are several possible explanations for this lack of

effect, including the use of wrong doses of synthetase inhibitors or wrong locations and time. Alternatively, since it has already been shown that prostaglandin formation is low in hungry rats (Greaves *et al.*, 1972), a finding which itself supports the involvement of a prostaglandin generating system in the regulation of the hunger–satiety phenomenon, it could be that in our food-deprived animals endogenous prostaglandin formation was already so low as to be incapable of further reduction. It has also been shown that indomethacin and aspirin, apart from their actions on prostaglandin synthetase (Vane, 1971), inhibit prostaglandin dehydrogenase (Flower, 1974) thereby inhibiting prostaglandin catabolism and contributing to the anorexia often reported as one of the effects of intoxication of these antipyretic analgesics (Woodbury, 1970). However, drugs which specifically inhibit prostaglandin biosynthesis without inhibiting prostaglandin catabolism, for example the acetylenic analogue of arachidonic acid, eicosa 5,8,11,14-tetraynoic acid, should increase food intake. Support for the involvement of a prostaglandin generating system in hunger–satiety can also be cited from the literature. For example, gold thioglucose (Brecher & Waxler, 1949) and bipiperidyl mustard (Rutman, Lewis & Bloomer, 1966) have been shown to cause hyperphagia resulting in obesity in experimental animals, an effect which can be antagonized by prior treatment with indomethacin (Caffyn, 1972). In addition, a wide variety of clinically used drugs, for example psychotropics (Bainbridge, 1968), local anaesthetics (Epstein, 1960), Δ^8-tetrahydrocannabinol (Rating, Broerman, Honecker, Kluwe & Coper, 1972) have been shown to increase food intake; although they are chemically diverse, all inhibit prostaglandin biosynthesis *in vitro* (Bradley, Samuels & Shaw, 1969; Burstein & Raz, 1972; Kunze, Bohn, Kurz & Vogt, 1973; Kunze, Bohn & Bahrke, 1975). Similarly, the anorectic activity of oleic acid (Booth, 1972) and methylxanthines (Fajardo, 1974) can possibly be explained by their *in vitro* inhibitory action on prostaglandin dehydrogenase (Flower, 1974). However, it is difficult to establish a direct causal relationship.

Regarding the site of such a hypothetical prostaglandin generating system one can only speculate. In view of the short latency of anorectic activity it is possible that there are peripheral sites of action, particularly since labelled linoleic acid has been shown to accumulate in liver and adipose tissue (Panksepp, 1975), areas which have been shown to contain receptors that participate in the regulation of the hunger–satiety phenomenon (Russek, 1971). Evidence for a prostaglandin generating system at the hypothalamic level is that the precursor fatty acids cross the blood brain barrier (Alfin-Slater & Aftergood, 1968) and that hypothalamic centres concerned with regulation of food intake have been demonstrated to accumulate labelled linoleic acid when given intragastrically (Panksepp, 1975). Since paracetamol is a specific inhibitor of brain prostaglandin synthetase (Flower & Vane, 1972), the longer time lag in reversing anorectic activity of arachidonic acid shown in this study (Figure 1) can be explained easily.

The present results suggest why Anand, Dua & Singh (1961) failed to find any meaningful correlation when they infused neutral fat emulsions intravenously. It is not the total non-esterified fatty acids that are important, but the individual fatty acid fractions that might determine the formation of prostaglandins at any given time. It has been suggested that one of the factors that regulate biosynthesis of prostaglandins is the presence or absence of other fatty acids that compete for the same enzyme system (Lands, Letellier, Rome & Vanderhoek, 1973).

Is there any pathological state where there is derangement of prostaglandin generating systems and resultant hyperphagia? Although no direct evidence is available, one condition where such possibility appears to be more likely is diabetes mellitus. In this condition there is depression of desaturation of fatty acids due to lack of insulin (Benjamin & Gellhorn, 1964) and consequently a lack of availability of precursors which might limit the formation of prostaglandins. In this condition, administration of exogenous arachidonic acid has been shown to correct the atrophy of the seminal vesicles and testes (Brenner, Peluffo, Mercuri & Restelli, 1968). It would be of interest to know whether the hyperphagia associated with this condition can be controlled by the addition of polyunsaturated fatty acids to the diet of such patients.

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