Br. J. Pharmac. (1977), **60**, 409–415

SOME OBSERVATIONS ON THE ANORECTIC ACTIVITY OF PROSTAGLANDIN $F_{2\alpha}$

N.S. DOGGETT & K. JAWAHARLAL

Department of Applied Pharmacology, Welsh School of Pharmacy, University of Wales Institute of Science and Technology, Cardiff

1 Intracerebroventricular injection of prostanglandin $F_{2\alpha}$ (10–40 μg) decreases food intake in a dose-dependent manner in rats trained to consume their daily total food intake in a 2 h period.

2 This anorexia is also observed in satiated rats, which had *ad libitum* access to food.

3 The anorectic activity of prostaglandin $F_{2\alpha}$ is not modified by changes in the internal environment of the body after food intake, such as increased blood glucose and insulin levels and decreased fatty acid levels, or by the presence or absence of food in the stomach, as is evident from the anorectic activity of prostaglandin $F_{2\alpha}$ in partially satiated rats.

4 The anorexia is not due to pain or irritative properties of prostaglandin $F_{2\alpha}$ since induction of comparable pain with 3% acetic acid does not affect food intake in rats deprived of food for 22 hours.

5 Anorectic doses of prostaglandin $F_{2\alpha}$ when injected intraperitoneally cause hypothermia.

6 The results suggest that the inhibitory activity of prostaglandin $F_{2\alpha}$ on food intake is at both peripheral and central sites.

7 Prostaglandin $F_{2\alpha}$-induced anorexia is associated with the behavioural tranquillization that is seen after the ingestion of food.

Introduction

Horton (1964) was the first to introduce prostaglandins into the field of appetite regulation. While studying the effect of prostaglandins E_1, E_2 and E_3 on injection into the cerebral ventricles of cats, he observed that they did not cause hyperphagia, but in cats starved for 24 h before injection a disinterest in food was observed. Later experiments with rats trained to press a bar for food demonstrated that various prostaglandins (E_1, E_2, $F_{1\alpha}$, $F_{2\alpha}$, A_1, B_1) when given subcutaneously decrease feeding (Scaramuzzi, Baile & Mayer, 1971). Further studies on the possible site of action have shown that injection of prostaglandin E_1 into the lateral hypothalamic, anterior commissure, perifornical and ventromedial hypothalamic areas reduced food intake in rats, while prostaglandin B_1 injections had no effect (Baile, Bean, Simpson & Jacobs, 1971; Baile, Simpson, Bean, McLaughlin & Jacobs, 1973). These workers also reported that there were no behavioural depressant effects nor was there any change in water intake. Since prostaglandins are interrelated with fatty acids and adipose tissue and since they depress feeding when injected into areas of the hypothalamus concerned with regulation of food intake, they suggested that prostaglandins might be acting as intermediaries between fat depots and the hypothalamus and may be involved in energy balance regulation. Studies involving sheep have revealed a dual action of prostaglandin E_1 on food intake. When injected into loci in the medial and anterior hypothalamus where (–)-noradrenaline injections elicited feeding (α-adrenoceptor loci), prostaglandin E_1 reduced feeding, while injections of prostaglandin E_1 into loci in the lateral anterior hypothalamus (which are β-adrenoceptor sensitive) elicited feeding. These effects were specific for prostaglandin E_1 since prostaglandin E_2 did not have any effect when injected into those loci. Injection of a prostaglandin antagonist into the α-adrenoceptor loci increased feeding when given alone and antagonized the hypophagia induced by prostaglandin E_1 on prior injection (Martin, Baile, Webb & Kingsbury, 1972; Baile & Martin, 1973; Baile, Martin, Forbes, Webb & Kingsbury, 1974). Most of the studies mentioned above were concerned with injection of E or B prostaglandins and no detailed studies have been reported with prostaglandin $F_{2\alpha}$ on food intake when injected into the central nervous system. Prostaglandin $F_{2\alpha}$ effects are more relevant in an understanding of the possible physiological role of prostaglandins in this important component of energy balance because prostaglandin $F_{2\alpha}$ is a natural constituent of all the mammalian brains studied (Holmes & Horton, 1968), and furthermore F prostaglandins are the only ones that can be synthesized by

rat brain (Feldberg, 1974). A preliminary investigation on food intake when prostaglandin $F_{2\alpha}$ was injected into the cerebroventricular system has been reported earlier (Doggett & Jawaharlal, 1975). The present paper is an extension of our earlier study.

Methods

Animals

Male albino rats weighing 200–250 g were used in these experiments.

(a) Hungry rats: The method employed in this type of study is the one described earlier (Hollifield & Parson, 1962). Rats were trained to eat all their food in 2 h per day (between 14 h 00 min–16 h 00 min). After 15 days of training when the animals had adapted to the 2 h food regimen as indicated by their positive weight gain, the animals were used for experiment. Rats not adapting to this regimen and showing no weight gain were discarded. Water was allowed *ad libitum.*

(b) Satiated rats: The method is based on that of an earlier study (Grossman, 1962). All the experiments were done at 12 h 00 min, the time when the food intake was found to be minimal in all animals. In this experiment both food and water were allowed *ad libitum.*

Laboratory conditions

All the rats were housed in a room maintained at 25 ± 1°C with a 12 h light/dark cycle, all experiments being performed in the light. Animals were maintained on a conventional 41B cube diet (Spilsburys, Birmingham).

Estimation of food intake

The rats were housed singly in cages with wire grid bottoms. In order to collect the spillage during experiments, paper was placed under the cages and an accurate measure of the amount of food eaten was obtained by reweighing the left-over food together with the spillage. The food intake was measured at regular intervals of 15, 30, 60, 90 and 120 min for rats under 2 h feeding tests and after 1 h for satiated rats. In experiments with satiated rats, in order to ensure satiety conditions the rats were given fresh food 30 min before the experiment started. However, no attempt was made to get super satiety by forced feeding. Three types of controls were maintained: (1) no injection; (2) the needle was inserted into the cannula and removed without injection; (3) injection of vehicle.

The food intake is expressed as the amount eaten in g/100 g body weight in the case of experiments with hungry rats and the total amount consumed per rat in experiments with satiated animals because of the very small quantity of food eaten by these animals. The significance of any observed differences between the group means was determined by Student's *t* test.

Implantation of cannula and injection techniques

The construction of the intracerebroventricular cannula and its implantation was as described by Sparkes & Spencer (1971). At least a week was allowed to elapse between implantation and the start of injections. All injections were made into the left lateral ventricle in a volume of 10 to 20 µl. There was an interval of at least two or three days between any two injections. Prostaglandin solutions were always given alternately with an injection of vehicle in any one animal.

In order to minimize the effect of stress caused by handling and by cerebroventricular injections, the animals were repeatedly handled and mock injections were done many times in order to familiarize the animals with the procedure before actual experiments started.

Measurement of body temperature

The rectal temperature was measured as 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

Prostaglandin $F_{2\alpha}$ as tromethamine salt used in this experiment was supplied by Dr J.E. Pike, Upjohn Company, Kalamazoo, Michigan and Professor B. Samuelsson, of Karolinska Institute, Stockholm, Sweden. The stock solutions were prepared in 95% ethanol in concentration of 10 mg/ml and were kept frozen until used. All the prostaglandin solutions were prepared fresh before experiments by diluting with pyrogen-free saline (0.9% w/v NaCl solution) containing 0.2 mg/ml of sodium carbonate. This procedure brought the pH range of injected solution in the present experiments to 6.5 to 7.5. All the doses of prostaglandin $F_{2\alpha}$ given refer to the salt.

Results

Hungry rats

Intracerebroventricular injections of 10–40 µg prostaglandin $F_{2\alpha}$ immediately before access to food in rats trained to consume their total 24 h food intake over a 2 h period, suppressed food intake in a dose-dependent manner compared to those animals which

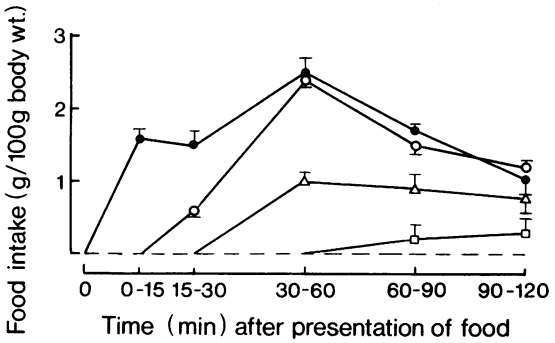

Figure 1 Effect of intracerebroventricular injection of vehicle (control) (●), 10 μg (○), 20 μg (△) or 40 μg prostaglandin $F_{2\alpha}$ (□) on food intake over a 2 h period in the rat. Each point represents the mean of results from 40 rats for control group and 15 rats for groups receiving prostaglandin $F_{2\alpha}$. Vertical lines show s.e. mean. Broken lines indicate complete suppression of food intake.

were injected with vehicle alone or non-injected controls. Since no differences in food intake were observed between vehicle and non-injected groups the results of these were pooled and used as a combined control for comparison with prostaglandin $F_{2\alpha}$-treated rats (Figure 1). Prostaglandin $F_{2\alpha}$ (1 and 5 μg) did not cause any detectable anorexia in the present experimental situation. When a dose of 10 μg was injected it suppressed food intake for only the initial 15 min period of the 2 h feeding session. It was often observed at this dose, that at a later part of the feeding session there was a tendency to compensate for the initial depression, and when bodyweights were

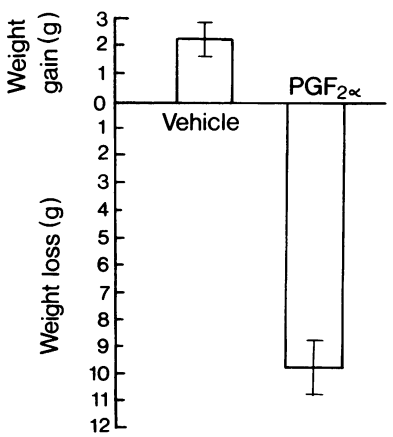

Figure 2 Effect of intracerebroventricular injection of vehicle or prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) 20 μg to rats feeding for 2 h period on 24 h body weight. Each column is the mean of results from 15 rats; vertical lines show s.e. mean.

measured after 24 h there was no statistically significant difference between the controls and treated group ($P<0.1$). However, a dose of 20 μg which suppressed food intake completely for the first 30 min of the feeding period, and whose anorectic activity was still evident in the latter part of the feeding period, produced a fall in the 24 h bodyweights, when compared to the vehicle-treated group which registered a slight positive gain in weight (Figure 2). The highest dose (40 μg) of prostaglandin $F_{2\alpha}$ used in the present study produced marked anorexia; it completely suppressed food intake for the first hour and even in the final 60 min of the feeding period only a small food intake occurred. Individual variations were observed between rats both in control food intake and its suppression by prostaglandin $F_{2\alpha}$. In some animals there was a quicker recovery from the suppressant activity, while a few exhibited prolonged anorexia. Injection of these doses subcutaneously did not cause anorexia.

Partially satiated rats

A number of factors can influence the effect of substances on food intake. Changes in the internal environment brought about by a meal, for example increased glucose and insulin levels, have been correlated with food intake (Steffens, 1969; 1970). Furthermore, recent studies have shown that there are differences in the mode of action of the well known anorectic drugs amphetamine and fenfluramine, the former acting upon hunger but the latter on satiety. The consumption of a certain amount of food is required for the inhibitory action of fenfluramine to occur, but this is not so for amphetamine (Blundell, Latham & Lesham, 1976). In the present experiments the effect of these factors were examined on prostaglandin $F_{2\alpha}$-induced anorexia in partially satiated rats. Food was presented to one group of rats for 30 min and to a second group for 60 min of the 2 h feeding period. Injection of prostaglandin $F_{2\alpha}$ (20 μg) intracerebroventricularly suppressed food intake for at least 30 min in both groups (Figure 3), an effect similar to that seen when it was injected before presentation of any food (Figure 1). Since injection of vehicle at these two periods did not affect feeding, the results of both were pooled.

Satiated rats

Experiments were also conducted in satiated animals with access to food *ad libitum*. The effect of injecting 20 μg of prostaglandin $F_{2\alpha}$ which has been shown to suppress food intake for at least 30 min in hungry and partially satiated animals (Figures 1 and 3) was studied and compared with control rats. Figure 4 summarizes the results. In these experimental conditions even when the food intake is minimal prostaglandin $F_{2\alpha}$ still exhibits some anorectic activity.

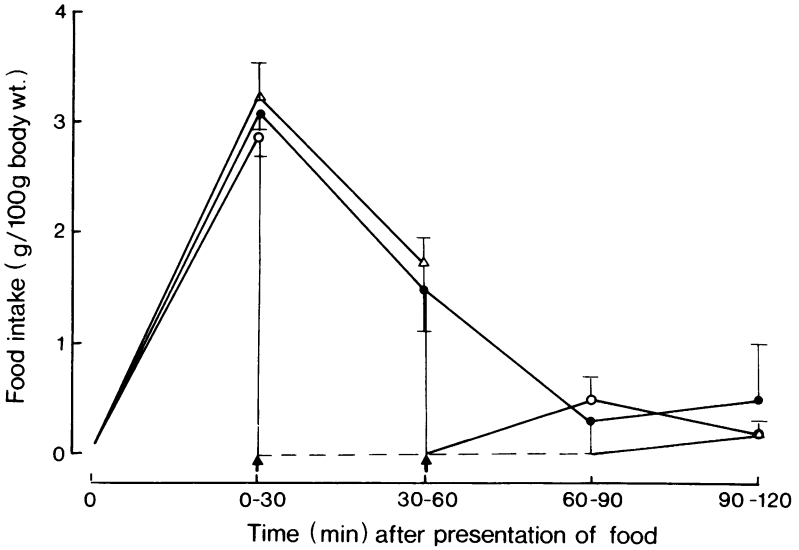

Figure 3 Effect of intracerebroventricular injection at the arrow of prostaglandin $F_{2\alpha}$ 20 μg 30 min after access to food (○) and of prostaglandin $F_{2\alpha}$ 60 min after access to food (△). Broken lines indicate no eating period. Control group (●). Vertical lines show s.e. mean.

Involvement of pain in prostaglandin $F_{2\alpha}$-induced anorexia

Prostaglandins when injected cause pain (Collier & Schneider, 1972), thus raising the possibility that prostaglandin $F_{2\alpha}$-induced anorexia is only secondary to its ability to induce pain. Therefore the effect of similar pain on food intake was studied. Rats deprived of food for 22 h received intraperitoneally vehicle, 1 mg/kg of prostaglandin $F_{2\alpha}$ or 3% acetic acid 5 min before presentation of food. Injection of acetic acid has been shown to produce similar pain (Chernov, Wilson, Fowler & Plummer, 1967) by this route. There was no statistically significant difference in food intake between vehicle and either acetic acid or non-treated animals. Prostaglandin $F_{2\alpha}$ 1 mg/kg by the same route completely suppressed food intake for the initial 30 min (Figure 5).

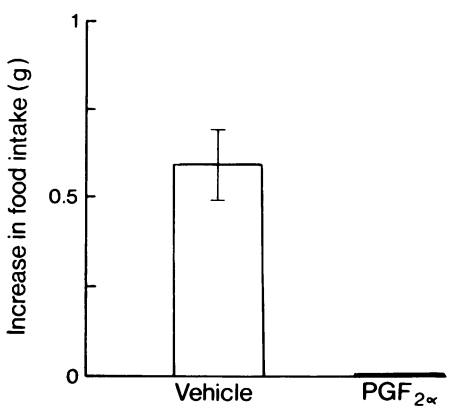

Figure 4 Effect of intracerebroventricular injection of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) 20 μg or vehicle on food intake in the satiated rat. Each column is the mean of results from 15 rats; vertical lines show s.e. mean.

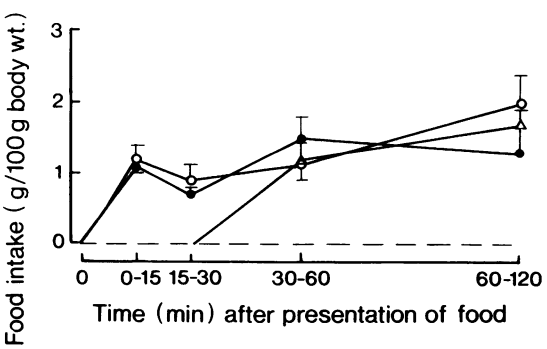

Figure 5 Intraperitoneal administration of vehicle 1 ml/kg (control) (●), prostaglandin $F_{2\alpha}$ 1 mg/kg (△) or 3% acetic acid 1 ml/kg (○) on food intake in 22 h food deprived rat. Each point represents the mean of results from at least 6 rats; vertical lines show s.e. mean. Broken lines indicate complete suppression of food intake.

Effect of prostaglandin $F_{2\alpha}$ on body temperature

Prostaglandin $F_{2\alpha}$ when injected intracerebroventricularly in rats causes hyperthermia and anorexia (Doggett & Jawaharlal, 1975) so the possibility exists that its anorectic activity is secondary to its hyperthermic effect. Intraperitoneal injection of 0.5 and 1 mg/kg body weight of prostaglandin $F_{2\alpha}$ to rats deprived of food for 22 h produced whole body hypothermia (Figure 6) which was maximal at 90 min after administration.

Behavioural effect of prostaglandin $F_{2\alpha}$

Injection of prostaglandin $F_{2\alpha}$ either intracerebroventricularly or intraperitoneally in food-deprived rats caused no signs of central nervous depression, ptosis or catatonia nor was there any effect on respiration. The enhanced locomotor activity associated with searching for food, restlessness and the aggressive behaviour resulting from food deprivation were all decreased after prostaglandin $F_{2\alpha}$ treatment. The rats showed disinterest in food even when food pellets were placed near them. The 'behavioural tranquillization' that occurs after a meal is the appropriate description for the prostaglandin-treated rat, which becomes behaviourally indistinguishable from the satiated animal.

Other effects

No changes on water intake were observed after prostaglandin $F_{2\alpha}$. Intracerebroventricular injections of this prostaglandin did not induce salivation as in dogs (Hahn & Patil, 1972) or produce gastrointestinal symptoms such as diarrhoea, as in cats (Milton & Wendlandt, 1971).

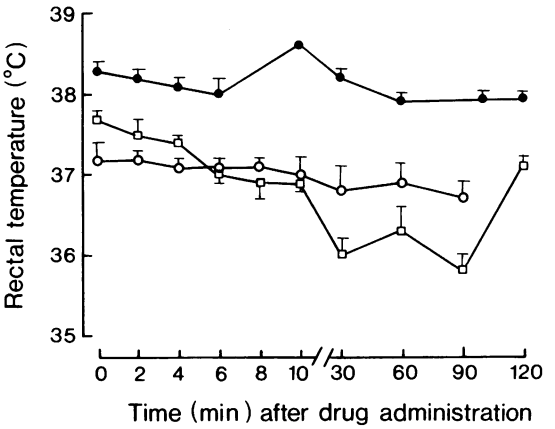

Figure 6 Effect of intraperitoneal administration of vehicle (control) (●), prostaglandin $F_{2\alpha}$ 0.5 mg/kg (○) or 1 mg/kg (□) on the rectal temperature in 22 h food deprived rat. Each point represents the mean of results from 8 rats. Vertical lines show s.e. mean.

Discussion

Studies from a number of laboratories in the last few years (Horton, 1964; Scaramuzzi *et al.*, 1971; Baile *et al.*, 1973; Doggett & Jawaharlal, 1975) have implicated prostaglandins in regulation of food intake in a number of species. Prostaglandins have been shown to have many other actions which affect food intake. They cause irritation and pain (Collier & Schneider, 1972); when injected into the ventricular system of the brain they produce hyperthermia (Milton & Wendlandt, 1971; Doggett & Jawaharlal, 1975). Therefore it is possible that the anorectic activity of prostaglandins is only secondary to those actions. In the present study induction of similar irritation and pain with acetic acid did not affect food intake. Furthermore, in view of the chemospecific and loci-specific activity of prostaglandins when injected into hypothalamic areas, the possibility of pain and irritation as the causes for their anorectic activity can be excluded. A number of other reasons also exclude hyperthermia as the cause of their anorectic activity. There is no correlation between their anorectic and hyperthermic activities (Baile *et al.*, 1973; Doggett & Jawaharlal, 1975). Injection of prostaglandins peripherally cause anorexia and hypothermia (Figure 6). Substances that cause hyperthermia when injected intracerebroventricularly have also been shown to produce 'hyperphagia' (Myers & Yaksh, 1968). However, this does not exclude prostaglandins being the cause of the depressant effect of pyrogens on food intake (Beamer, Thomas & Moore, 1954) since pyrogens increase prostaglandin levels (Feldberg, Gupta, Milton & Wendlandt, 1973). One theory of food intake regulation concerns temperature. This theory assumes that the specific dynamic action of food, which is the cause of increased temperature after a meal, is related to the onset of satiety (Anand, 1961). It has been shown that prostaglandin levels increase after a meal (Greaves, Mcdonald-Gibson & Mcdonald-Gibson, 1972) and whether this release is due to specific dynamic action of food and the cause of increased temperature and the onset of satiety seems an interesting possibility.

Possible explanations for the anorectic effect were looked for but nothing inconsistent with satiety was found. Practically all the prostaglandins so far studied cause anorexia (see Introduction) with the exception of prostaglandin E_1 in certain regions of the hypothalamus in sheep where an increase in food intake was produced (Martin *et al.*, 1972; Baile & Martin, 1973; Baile *et al.*, 1974). However, whether this is a genuine species difference or due to other factors is not clear, because a similar study with pro-

staglandin $F_{2\alpha}$ has not been made, in spite of it being the commonest prostaglandin found in all the mammalian brains studied (Holmes & Horton, 1968).

From the present results it is interesting to note that the anorectic activity of prostaglandin $F_{2\alpha}$ is not influenced by the changes in the internal environment of the animal, such as an increase in blood glucose and insulin levels and a decrease in free fatty acids. This indicates that prostaglandins probably act on basic mechanisms of food intake regulation and so may act as mediators of both pre- and post-absorptive satiety signals.

It could be postulated that prostaglandins are involved in the physiological satiety mechanism, particularly since they have more than one site of action, both peripheral and central. This is supported by the fact that prostaglandins B_1 and E_2 injected peripherally depress food intake (Scaramuzzi *et al.*, 1971), while they are devoid of activity when injected into some areas of the hypothalamus, unlike prostaglandin E_1 (Baile *et al.*, 1973; Baile *et al.*, 1974). This raises the possibility that the release of specific prostaglandins might mediate satiety at different sites. Release of prostaglandins has been demonstrated after distension of the stomach (Bennet, Friedman & Vane, 1967) and stretching of the stomach itself causes satiety (Anand, 1961). Furthermore, there are other factors from the gastrointestinal tract which induce release of prostaglandins that can contribute to satiety. For example, Vane (1972) suggested that prostaglandins might be released by many stimuli including gentle massage, comparable to the 'massage' induced by gastrointestinal churning of ingested food. Prostaglandins of the E and A series are potent inhibitors of gastric secretion in several species (Main, 1973), where they might alter the pH of the stomach and therefore might be responsible for stimulation of postulated pH receptors of the gastrointestinal system (Sharma, 1967) which participate in the regulation of food intake.

The most important post-obsorptive sites where prostaglandins may have a role are adipose tissue and liver. Since they are released from adipose tissue (Shaw & Ramwell, 1968), and since depot fat plays an important role in the regulation of food intake (Kennedy, 1953), it has been suggested (Baile *et al.*, 1973) that prostaglandins may be the intermediaries between hypothalamic feeding centres and depot fat. However, in view of their effective degradation by lung (Nakano, Morsy & Distler, 1970) the amount that is likely to reach the hypothalamic centres must be small and hence an effect there is unlikely. Since an adipokinetic mechanism has been demonstrated (Panksepp & Pilcher, 1973) within the hypothalamus it is most likely that prostaglandins might be released there and act as local transmitters. Since the liver contains receptors for regulation of food intake (Russek, 1971) and since prostaglandins are accumulated in large quantities (Bergstrom, Carlson & Weeks, 1968) in this organ, this might be their other site of action.

Recent studies have demonstrated that changes in the level of cyclic adenosine 3',5'-monophosphate (cyclic AMP) affect feeding in the rat (Booth, 1972). However, the anorectic action of centrally administered prostaglandin $F_{2\alpha}$ is unlikely to be mediated through this mechanism because it has been shown that this prostaglandin does not affect formation of cyclic AMP in the cerebral cortex of the rat (Berti, Trabucchi, Bernareggi & Fumagalli, 1973).

We wish to thank Dr J.E. Pike, Upjohn Co., Kalamazoo, Michigan, U.S.A. and Professor B. Samuelsson, Karolinska Institute, Stockholm, Sweden for generously supplying prostaglandin $F_{2\alpha}$.

References

ANAND, B.K. Nervous regulation of food intake. *Physiol. Rev.*, **41**, 677–708.

BAILE, C.A., BEAN, S.M., SIMPSON, C.W. & JACOBS, H.L. (1971). Feeding effects of hypothalamic injections of prostaglandins. *Fedn Proc.*, **20**, 375 Abs.

BAILE, C.A. & MARTIN, F.H. (1973). Relationship between prostaglandin E_1, polyphloretin phosphate and β-adrenoceptor-bound feeding loci in the hypothalamus of sheep. *Pharmac. Biochem. Behav.*, **1**, 539–545.

BAILE, C.A., MARTIN, F.H., FORBES, J.M., WEBB, R.L. & KINGSBURY, W. (1974). Intrahypothalamic injections of prostaglandins and prostaglandin antagonists and feeding in sheep. *J. Dairy Sci.*, **54**, 81–88.

BAILE, C.A., SIMPSON, C.W., BEAN, S.M., McLAUGHLIN, C.L. & JACOBS, H.L. (1973). Prostaglandins and food intake of rats. A component of energy balance regulation? *Physiol. Behav.*, **10**, 1077–1085.

BEAMER, W.D., THOMAS, J.E. & MOORE, B. (1954). The effect on appetite in dogs of pyrogenic substances in intravenous infusions. *Gastroenterology*, **27**, 347–352.

BENNETT, A., FRIEDMAN, C.A. & VANE, J.R. (1967). Release of prostaglandin E_1, from the rat stomach. *Nature, Lond.*, **216**, 873–876.

BERGSTROM, S., CARLSON, L.A. & WEEKS, J.R. (1968). The prostaglandins: A family of biologically active lipids. *Pharmac. Rev.*, **20**, 1–48.

BERTI, F., TRABUCCHI, M., BERNAREGGI, V. & FUMAGALLI, R. (1973). Prostaglandins on cyclic-AMP formation in cerebral cortex of different mammalian species. *Adv. Biosci.*, **9**, 475–479.

BLUNDELL, J.E., LATHAM, C.J. & LESHEM, M.B. (1976). Differences between the anorexic actions of amphetamine and fenfluramine–possible effects on hunger and satiety. *J. Pharm. Pharmac.*, **28**, 471–477.

BOOTH, D.A. (1972). Unlearned and learned effects of intrahypothalamic cyclic AMP on feeding. *Nature, New Biol.*, **237**, 222–224.

CHERNOV, H.I., WILSON, D.E., FOWLER, F. & PLUMMER, A.J. (1967). Non-specificity of the mouse writhing test. *Archs int. Pharmacodyn.*, **167**, 171–178.

COLLIER, H.O.J. & SCHNEIDER, C. (1972). Nociceptive response to prostaglandins and analgesic actions of aspirin and morphine. *Nature, New Biol.*, **234**, 141–143.

DOGGETT, N.S. & JAWAHARLAL, K. (1975). Anorectic activity of prostaglandin F_{2a} in the rat. In *Advances in Prostaglandin and Thromboxane Research*. ed. Samuelsson, B. & Paoletti, R. Vol. 2, p. 837. New York: Raven Press.

FELDBERG, W. (1974). Fever, prostaglandins and antipyretics. In *Prostaglandin Synthetase Inhibitors*, ed. Robinson, H.J. & Vane, J.R. pp. 197–203. New York: Raven Press.

FELDBERG, W., GUPTA, K.P., MILTON, A.S. & WENDLANDT, S. (1973). Effect of pyrogen and antipyretics on prostaglandin activity in cisternal CSF of unanaesthetized cats. *J. Physiol., Lond.*, **234**, 279–303.

GREAVES, M.W., MCDONALD-GIBSON, W.J. & MCDONALD-GIBSON, R.G. (1972). The effect of venous occlusion, starvation and exercise on prostaglandin activity in whole human blood. *Life Sci.*, **11**, 919–924.

GROSSMAN, S.P. (1962). Direct adrenergic and cholinergic stimulation of hypothalamic mechanisms. *Am. J. Physiol.*, **202**(5), 872–882.

HAHN, R.A. & PATIL, P.N. (1972). Salivation induced by prostaglandin F_{2a} and modification of the response by atropine and physostigmine. *Br. J. Pharmac.*, **44**, 527–533.

HOLLIFIELD, G. & PARSON, W. (1962). Metabolic adaptations to a "Stuff and Starve" feeding program. I. Studies of adipose tissue and liver glycogen in rats limited to a short daily period. *J. clin. Invest.*, **41**, 245–249.

HOLMES, S.W. & HORTON, E.W. (1968). Prostaglandins and the central nervous system. In *Prostaglandin* Symposium of the Worcester Foundation for Experimental Biology, ed. Ramwell, P. & Shaw, J.E., pp. 21–38. New York: Wiley.

HORTON, E.W. (1964). Actions of prostaglandins E_1, E_2 and E_3 on the central nervous system. *Br. J. Pharmac. Chemother.*, **22**, 189–192.

KENNEDY, G.C. (1953). The role of depot fat in the hypothalamic control of food intake in the cat. *Proc. R. Soc. B.*, **140**, 578–592.

LOMAX, P. (1966). Measurement of core temperature in the rat. *Nature, Lond.*, **210**, 854.

MAIN, I.H.M. (1973). Prostaglandins and the gastrointestinal tract. In *The Prostaglandins*, ed. Cuthbert, M.F., pp. 287–323. London: Heinemann.

MARTIN, F.H., BAILE, C.A., WEBB, R.L. & KINGSBURY, W. (1972). Prostaglandin inhibition and prostaglandin antagonist induction of feeding following hypothalamic injections into sheep. *Summaria IX. Int. Congr. of Nutr.*, Mexico City, p. 9.

MILTON, A.S. & WENDLANDT, S. (1971). Effects on body temperature of prostaglandins of the A, E and F series on injection into the third ventricle of unanaesthetized cats and rabbits. *J. Physiol., Lond.*, **218**, 325–336.

MYERS, R.D. & YAKSH, T.L. (1968). Feeding and temperature responses in the unrestrained rat after injections of cholinergic and aminergic substances into the cerebral ventricles. *Physiol. Behav.*, **3**, 917–928.

NAKANO, J., MORSBY, N.H. & DISTLER, M. (1970). Metabolism of prostaglandin in rat plasma, brain, heart, lung, kidney and testicle. *Clin. Res.*, **18**, 675.

PANKSEPP, J. & PILCHER, C.W.T. (1973). Evidence for an adipokinetic mechanism in the ventromedial hypothalamus. *Experientia*, **29**, 793–794.

RUSSEK, M. (1971). Hepatic receptor and the neurophysiological mechanisms controlling feeding behaviour. In *Neurosciences Research*, ed. Ehrenpreis, S. & Solnitzky, O.C., Vol. 4, pp 213–282. London: Academic Press.

SCARAMUZZI, O.E., BAILE, C.A. & MAYER, J. (1971). Prostaglandins and food intake of rats. *Experientia*, **27**, 256–257.

SHARMA, K.N. (1967). Alimentary receptors and food intake regulation. In *The Chemical Senses and Nutrition*, ed. Kare, M.R. & Maller, O., pp. 281–291. Baltimore: The Johns Hopkins Press.

SHAW, J.E. & RAMWELL, P.W. (1968). Release of prostanglandin from rat epididymal fat pad on nervous and hormonal stimulation. *J. biol. Chem.*, **243**, 1498–1503.

SPARKES, C.G. & SPENCER, P.S.J. (1971). Antinociceptive activity of morphine after injection of biogenic amines in the cerebral ventricles of the conscious rat. *Br. J. Pharmac.*, **42**, 230–241.

STEFFENS, A.B. (1969). Blood glucose and FFA levels in relation to meal pattern in the normal rat and the ventromedial hypothalamic lesioned rat. *Physiol. Behav.*, **4**, 215–225.

STEFFENS, A.B. (1970). Plasma insulin content in relation to blood glucose level and meal pattern in the normal and hypothalamic hyperphagic rat. *Physiol. Behav.*, **5**, 147–151.

VANE, J.R. (1972). Prostaglandins and the aspirin-like drugs. *Hosp. Pract.*, **7**, 62–71.

(Received November 12, 1976. Revised December 10, 1976.)