Feeding Elicited in Sheep by Intrahypothalamic Injections of PGE_1

Prostaglandin E_1 (PGE_1 injected peripherally[1] or into the anterior hypothalamus of rats[2] decreases feed intake and raises rectal temperature. Intraventricular injections of PGE_1 in cats, rabbits and rats causes hyperthermia[3,4]. A number of studies have shown that injections of approximately 60 nmoles of norepinephrine (l-NE) (an α agonist) into the perifornical region of the hypothalamus of rats induced feeding[5–7]. Smaller doses of l-NE (15–37 nmoles) injected into the mid-hypothalamic region of monkeys elicited feeding[8]. Injections of 240 nmoles of l-NE into the anterior hypothalamus of satiated sheep also elicited feeding[9]. Thus l-NE may be a neural transmitter involved in the control of feeding.

When PGE_1 was injected into loci where l-NE bound feeding was elicited feeding decreased[10]. That 1. PGE_1 and E_2 antagonize the l-NE effect on cerebellar Purkinje cells[11] and 2. reduce l-NE release from sympathetic nerves[12] are possible explanations of the mechanism involved in the PG elicited hypophagia.

This report describes one of a series of experiments designed to test the effects of PGE_1 and of α and β agonists and antagonists on feeding behavior of sheep.

Six crossbred wethers (30–35 kg) were surgically prepared under halothane anesthesia with a set of 3 guides implanted 1.5 mm on either side of midline and directed towards the medial hypothalamus[13]. To measure abdominal temperature a blind silastic tube with a dacron mesh collar was implanted in the left paralumbar fossa. A thermistor was inserted into the open distal end protruding out of the skin, to measure abdominal temperature.

On injection days the ad libitum fed sheep were given feed 1 h prior to a test. This elicited a spontaneous meal and helped to synchronize normal feeding to insure satiety at the time of injection. In preliminary tests, loci were selected that showed either l-NE or dl-isoproterenol-HCl (dl-Isop) bound feeding, following 1.0 µl injections containing either 236 nmoles of l-NE (α loci) or 8 nmoles of dl-Isop (β loci). To define a locus as responsive after injections of l-NE or dl-Isop, the doses injected elicited intakes of at least 100 or 70 g of feed, respectively, over a 30 min period. The mean feed intakes following 0.9% sodium chloride (NaCl) injected into these loci were 36 and 38 g respectively. In these preliminary tests only one injection was given to each sheep on test days. In the main experiment, sheep were injected with the test chemicals listed in the Table. Tests were separated by at least 48 h and alternated between α and β loci. PGE_1 (7.5 mg/ml) was dissolved in 0.9% NaCl containing 10% ethyl alcohol and the pH was adjusted to 6.0–7.0 with sodium carbonate[1]. All injections were of 1.0 µl; the first chemical preceded the second by 5 min in the order listed in the Table. Feed intake was determined for 60 min prior to and at 15, 30, 60 min and 24 h post injection while abdominal temperatures were measured every 15 min for 1 h prior to injection and at 5, 10, 15, 30 and 60 min post injection.

There were no differences in intake between PGE_1 (21 nmoles) and either the saline or the 10% ethanol control carriers injected at α adrenoceptor loci where 236 nmoles of l-NE elicited feeding ($P < 0.01$) (this l-NE test was a replication of the preliminary tests). When a similar dose of PGE_1 was injected at β responsive loci there was a significant increase in feeding ($P < 0.02$) when compared to the saline or 10% ethanol control carriers. This feeding response was similar to that obtained with 8 nmoles of dl-Isop (this dl-Isop test was a replication of preliminary tests). The PGE_1 feeding response at the β loci was blocked when 21 nmoles of LB-46 (a β blocker) were injected 5 min prior to PGE_1 injection but not when 21 nmoles of phentolamine (an α adrenoceptor antagonist) preceded the PGE_1 injection

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Hypothalamic injections in sheep ($n = 6$)

Treatments		Loci	Dose (nmoles)	Feed intake (g ± SEM)		
— 5 min	0 min			0–15 min	0–30 min	0–60 min
C_1 [a]	+ C_1	α	—	19 ± 10 [a]	32 ± 10 [a,b]	55 ± 5 [a]
C_1	+ C_1	β	—	18 ± 8 [a]	41 ± 8 [a,b]	53 ± 8 [a]
C_2 [b]	+ l-NE	α	236	83 ± 9 [c]	112 ± 7 [d]	122 ± 6 [c]
C_2	+ dl-Isop	β	8	51 ± 10 [b]	77 ± 8 [b,c,d]	116 ± 15 [b,c]
C_1	+ PGE_1	α	21	19 ± 7 [a]	37 ± 12 [a,b]	56 ± 14 [a]
C_1	+ PGE_1	β	21	75 ± 23 [b,c]	100 ± 23 [c,d]	131 ± 21 [c]
LB-46 [c]	+ PGE_1	β	21 + 21	10 ± 4 [a]	30 ± 9 [a,b]	35 ± 11 [a]
LB-46	+ C_2	β	21	17 + 10 [a]	54 ± 18 [a,b,c]	72 ± 25 [a,b]
Phentolamine	+ PGE_1	β	21 + 21	91 ± 28 [c]	121 ± 23 [d]	121 ± 23 [c]
Phentolamine	+ C_2	β	21	12 ± 6 [a]	16 ± 9 [a]	46 ± 11 [a]

All means within a time period which are not denoted by a common superscript are different ($P < 0.05$); analysis of variance and least significant difference tests were used. [a] Saline plus 10% ethyl alcohol. [b] Saline (0.9% soldum chloride). [c] LB-46 was dissolved with equimolar 3 *N* HCl and the pH was adjusted to 6.0–6.5 with sodium carbonate.

(Table). Neither the α nor β antagonists injected by themselves affected feeding when compared to that of the controls.

Abdominal temperatures were not significantly affected by any of the treatments. This is unlike the response of other species which when injected with prostaglandins have shown hyperthermia[2,4]. In most cases, including controls, there appeared to be a slight elevation in temperatures during the 15 min prior to injection. This change was probably due to the handling of the animals.

After sacrificing the sheep, the injection loci were located in the anterior hypothalamus at 28, 29 and 30 mm anterior of the external auditory canal according to the coordinates of RICHARD[14].

In the present experiment we have shown as in a previous experiment[13] that a β agonist, dl-Isop, injected intrahypothalamically will elicit feeding in sheep with smaller doses (8 nmoles) than those injected into the perifornical region of the hypothalamus of rats which have either no effect[5,7] or cause hypophagia (150 nmoles)[15]. Injections of PGE_1 into these loci also caused marked feeding which was blocked by a specific β antagonist. A prostaglandin antagonist, polyphloretin phosphate, injected at α and β loci by itself also caused significant feeding (BAILE and MARTIN, manuscript in preparation).

The feeding effect produced by PGE_1 at the β loci was similar to that of dl-Isop. This could be a β adrenoceptor effect. A model of a β receptor for PGE_1 has been presented[16] and it was suggested that the 'receptor modulating substance'[17,18] is either a prostaglandin or a substance promoting the synthesis of prostaglandin. PGE_1 and E_2 appear to mimic some of the actions of the β agonist, isoproterenol: both have been shown to stimulate the short circuit current of frog skin[19]; both have a bronchodilator effect[20,21]; both decrease (PGE_2 and dl-Isop) filterability of red blood cells of man, rat and mouse[22] while the Ca^{++} influx is increased. These effects are known to be associated with activation of adenyl cyclase[22,23] a probable link in some β adrenoceptor actions[24]. Whether the feeding effect in sheep following PGE_1 injection at β loci is related to changes in adenyl cyclase level has not been shown.

Depending upon characteristics of the loci tested, PG E_1 either caused no change in feeding or increased feeding (α or β adrenoceptor loci, respectively), but the physiological role in either control of feed intake or regulation of energy balance remain to be shown.

Résumé. Une augmentation de la prise de nourriture a lieu après injection intrahypothalamique du PGE_1, en dose de 21 nmoles, chez les brebis. La température de la cavité abdominale n'est pas affectée par ces injections, sauf une légère augmentation au moment de l'injection et qui peut provenir du maniement des animaux.

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The Effect of Chelating Agents on the Distribution of ^{210}Po in Rats

Since HURSH's observation that 2,3-dimercaptopropanol (BAL) increases the excretion of ^{210}Po and reduces its toxicity[1,2], 2 other substances were demonstrated to affect the behaviour of ^{210}Po in animals: sodium 2,3-dimercaptopropane-1-sulfonate (DMPS)[3,4], i.e. a water-soluble derivative of BAL, and sodium diethyldithiocarbamate (DDC)[5]. The aim of this screening study was to compare the effectiveness of these 2 chelating agents, as well as of D-penicillamine (PA)[6], 2-mercaptopropionylglycine (MPG)[7] and the Na_3Ca-chelate of diethylenetriaminepentaacetate (DTPA). Furthermore, this is the first attempt to influence behaviour of ^{210}Po also by oral treatment.

Adult female albino rats (weighing 170–200 g) were injected i.v. with $\sim$ 0.3 μCi of ^{210}Po in 0.1 *N* HNO_3. Injection solutions were prepared for each group separately and immediately before administration. Chelating agents (1 mmol/kg) were administered 1.5 min after ^{210}Po i.p. or orally. In the latter case rats were deprived of food for 20 h before administration of the compounds. The animals were sacrificed after 48 h by exsanguination in ether narcosis. The α-activity of tissue samples was determined by liquid scintillation counting[8].

The effect of chelates injected i.p. is summarized in Table I. In general, their effectiveness decreases in the order: DMPS > DDC > MPG > PA; DTPA showed hardly any effect. There is a marked diminution of ^{210}Po-retention in blood, spleen and bone and, less, in blood plasma. Retention of ^{210}Po by the kidneys, however, was reduced by DDC only, while with other chelates a substantial fraction of ^{210}Po was transported into but not excreted from the kidneys. It is feasible that the accumulation of ^{210}Po in the liver following administration of DDC might be due to a temporary storage of ^{210}Po in the excretory organ of DDC. When taking into

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