Pharmacology Biochemistry and Behavior, Vol. 1, pp. 531–538. ANKHO International Inc., 1973. Printed in the U.S.A.

Feeding Elicited by α and β Adrenoceptor Agonists in Sheep and Cattle

CLIFTON A. BAILE, L. F. KRABILL AND C. WAYNE SIMPSON

Smith Kline and French Laboratories,
1600 Paoli Pike,
West Chester, Pennsylvania 19380

(Received 8 August 1972)

BAILE, C. A., L. F. KRABILL AND C. W. SIMPSON. *Feeding elicited by α and β adrenoceptor agonists in sheep and cattle* PHARMAC. BIOCHEM. BEHAV. 1(5) 531–538, 1973.–We have previously shown that α and β adrenoceptor agonists injected intraventricularly and intrahypothalamically elicit feeding in sheep and only β agonists readily elicit feeding in cattle. In the present work sheep and cattle, surgically prepared with lateral ventricular guides, were injected during 70 sec with 1.0 ml synthetic CSF with or without drug on experimental days. The animals were fed ad lib and fresh feed was given 1 hr prior to the injection to synchronize spontaneous meals. Injections of l-Epi, a universal adrenoceptor agonist, into sheep elicited feeding with doses of 33 to 66 nmoles and with higher doses of 267–534 nmoles; the lower dose range was similar to that required of dl-isoproterenol (dl-Isop), a β agonist, and the higher dose range was similar to that required of l-NE, an α agonist, to elicit feeding. The response to the upper range of l-Epi was specifically blocked by an α antagonist, phenoxybenzamine. Responses to the lower range were blocked, in part, by both α and β antagonists. Precursors of l-NE and l-Epi, i.e., l-Dopa and dopamine, did not elicit feeding in the same dose ranges as the products. More selective β agonists (β_2) were less potent for eliciting feeding than dl-Isop. In cattle, l-Epi did not elicit reliable feeding, although 7 doses were tested ranging from 50–3,240 nmoles. All of the feeding responses in sheep occurred at lower doses than those required for changes in body temperature. These data lend additional support and characterization to our previous conclusion that feeding in sheep can be elicited by both α and β adrenoceptor agonists, but the latter are much more potent. Agonists with α activity do not readily elicit feeding in cattle.

Epinephrine Norepinephrine dl-Isoproterenol Salbutamol Phenoxybenzamine
Propranolol L-dopa Dopamine Ruminants Body temperature Cattle Sheep

A NUMBER of precursors and derivatives of catecholamines and the probable adrenergic neurotransmitters are known to elicit feeding and are thought to play a role in the CNS control of feeding. Tyrosine (rat, [6]), l-Dopa (rat, [14]) and dopamine (rat, monkey, [6, 14, 21]) injections into the hypothalamus or cerebrospinal fluid (CSF) have been shown to result in feeding. A biosynthetic product of dopamine, l-norepinephrine (l-NE), an α adrenoceptor agonist, has been shown to elicit feeding in rats [6, 8, 11, 14, 22], monkeys [21] and sheep [4]. Injections of another biosynthetic product, l-epinephrine (l-Epi), a general adrenergic agonist, results in feeding in rats [6, 8 14] and monkeys [21]; however, l-Epi injected into the perifornical area elicits feeding only following the injection of a β adrenoceptor agonist [11]. Neither phenylalanine, which is a precursor of tyrosine, nor tryptamine, a decarboxylation metabolite, elicits feeding in rats in a similar dose range to the above metabolites [6]. Likewise, the injections of the degradation product of l-NE and l-Epi, normetanephrine and metanephrine, do not result in feeding in rats [6].

A chemical derivative of l-Epi, isoproterenol (dl-Isop), Table 4, has been shown to have no effect when injected into medial hypothalamic areas but results in hypophagia following injections into the perifornical or lateral hypothalamus [9,12]. In one experiment, dl-Isop injected into the lateral ventricle of rats resulted in a much delayed but increased feeding, i.e., significant 6 hr after injection [2].

In the present experiments we have extended our initial observations on feeding elicited in sheep by both α and β adrenoceptor agonists and by only β agonists in cattle [4]. We have measured both feeding and temperature following injections of precursors of l-NE (an α agonist), l-Epi (a universal adrenoceptor agonist), dl-Isop (a general β agonist) and other more specific β agonists, e.g., β_2,, Salbutamol which, for example, is a potent agonist for bronchial dilation, but relatively inactive an agonist for cardiac muscle [10]. Our objective was to further characterize our previously shown adrenergically elicited feeding in sheep and cattle [4].

METHOD

Eight sheep (wethers 30–40 kg) and 8 cattle (steers 200–300 kg) were prepared with bilateral lateral ventricu-

TABLE 1

BASIC DIETS FED TO SHEEP AND CATTLE DURING THE EXPERIMENTS

Ingredient	Sheep Diet 60% Concentrated % W/W	Cattle Diet 80% Concentrated % W/W
Medium Ground Corn	44.00	65.85
Mixed Ground Hay (11%)	40.00	20.00
Soybean Meal (44%)	7.00	6.00
Dried Molasses	8.00	6.00
Dicalcium Phosphate	0.50	0.40
Urea		0.55
Trace Mineral Salt	0.50	0.50
Ground Limestone		0.70
Vitamin A	240,000 IU/ton	2,000,000 IU/ton
Vitamin D_2	70,000 IU/ton	250,000 IU/ton

lar guides. Halothane was used to maintain anesthesia during the surgery. The procedure followed for the sheep was similar to that described by Pappenheimer, *et al.* [16] except that a stereotaxic instrument was used to hold the head and an electrode carrier was used to lower the guides into the brain. For an injection, an insert (22 gauge needle) was placed in the guide (18 gauge tubing) which punctured the ependyma at a level about 15 mm below the dura and at a plane about 1 cm caudal to the foramen of Monro. The guides (18 gauge tubing) for the steers were placed 1 cm lateral to midline in the frontal bones. The injection sites in the steers were rostral to the foramen of Monro. In both species the guides were secured with acrylic resin; 4 stainless steel screws were placed in the skull around the guides. To protect the guides, a 2.5 cm stainless steel tube with an 3 cm dia. was placed on the skull so that it encircled the guides and was held in place with the acrylic resin. The animals were given antibiotic treatment for 3–5 days. To insure that on the injection days the insert punctured the ventricle, it was requred that CSF dripped from the insert prior to beginning an injection.

A silastic tubing sealed at one end was implanted into the peritoneal cavity near the liver of the sheep and fixed in place by a Dacron mesh skirt cemented to the tubing and sewn under the skin. To measure body temperature a temperature probe was passed through the open and distal end of the tubing. The sheep were also prepared with ruminal fistulas fitted with cannulas. The animals were fed ad lib on the rations whose compositions are presented in Table 1. The animals were housed in a room in which the lights were left on 24 hr a day and the temperature was 21 ± 1 C.

One hour after fesh feed was given, the animals were injected intraventricularly with 1.0 ml of solution injected at the rate of 0.9 ml/min by a syringe pump. All solutions were passed through a 0.22 μ pore size sterilizing filter (Millipore Corporation) and all tubing and probes used during injections were sterilized in a 70% solution of ethanol and flushed with sterile saline prior to injection. On control days the animals were injected with synthetic cerebrospinal fluid (CSF) [16] and on drug days with drugs dissolved in synthetic CSF with a buffered pH of approximately 7.3. The drugs were injected together in a single solution in those treatments involving drug combinations. The injections were begun at 0930 on each injection day.

Each experimental day was preceded by a least one day on which no injections were given. No more than three injections were given per week per animal. Control injections of synthetic CSF were administered periodically during the experiment with approximately one control injection after every 5 drug injections. Control values used in the statistical analysis were calculated by averaging the values for the most recent three control days. Statistical comparisons were made by using the paired *t*-test.

The peritoneal cavity temperature of both sheep and cattle and the surface temperature of sheep were measured using general and banjo type thermistors. Feed weights were measured using load cells (BLH Model U3G1). Both temperature and feed weight analog signals were converted and recorded from a digital display (Orion, Model 701). Temperature and feed weight readings were taken 60 min before injection, at injection and 15, 30, 60 and 120 min after injection.

RESULTS

Injection of the α and β agonist l-Epi resulted in feeding with sheep at two dose ranges, at 33 and 66 nmoles and at 267 and 534 nmoles, Table 2. Doses of 16 nmoles of l-Epi and 132 and 200 nmoles in between the dose ranges resulted in feeding like that of the control. The latency of the feeding response was variable but averaged about 5 min.

The feeding elicited by 534 nmoles of l-Epi was blocked by 588 but not 289 nmoles of phenoxybenzamine, Table 2. In a previous experiment with sheep also injected intraventricularly we showed that 294 and 534 nmoles, respectively, of phenoxybenzamine resulted in 53, 66, 98 and 98,

TABLE 2

FEED INTAKES OF SHEEP FOLLOWING INTRAVENTRICULAR INJECTIONS OF l-EPI AND α (PHENOXYBENZAMINE) AND β (dl-PROPRANOLOL) ADRENERGIC ANTAGONISTS

Treatment	Dose nmoles	n	Intakes following inj. as a % of 2 hr control (min) 0–15	0–30	0–60	0–120	Intake (g) ± SEM 0–120
Syn CSF			14	28	48	100	
l-Epi	16	8	15	41	65	100	92 ± 20[1]
	33	8	20	46*	69*	149*	137* ± 25[1]
	66	8	48*	102†	118†	192†	177† ± 17[1]
	132	7	66	79	95	123	76 ± 14[2]
	200	6	36	69	74	92	69 ± 36[3]
	267	8	60	108	141	246*	153* ± 27[2]
	534	7	124*	145*	185*	287†	178† ± 19[2]
l-Epi + dl-Prop	66 974	8	100*	133	133	168	124 ± 29[3]
l-Epi + POB	66 68	7	73*	98	133	202	106 ± 23[4]
l-Epi + POB	534 289	8	51	108*	174*	272†	201† ± 27[3]
l-Epi + POB	534 588	8	48	59	63	71	52 ± 17[5]
l-Epi + dl-Prop	534 974	8	177*	277†	303†	343†	254† ± 44[3]

*$p<0.05$ †$p<0.01$

Corresponding 0–120 min control intakes: [1]92 ± 15 [2]62 ± 10 [3]74 ± 19 [4]52 ± 9 [5]73 ± 13 g

and 25, 65, 118 and 136% of the 120 min control value at 15, 30, 60 and 120 min postinjection; at none of these intervals were the cumulative feed intakes following phenoxybenzamine different from control; however, feeding during the 60–120 min period was suppressed ($p<0.05$) [4]. In contrast to the effect of phenoxybenzamine, 974 nmoles of dl-propranolol (dl-Prop) injected with the l-Epi resulted in even more feeding than with l-Epi alone ($p<0.01$). Sheep injected intraventricularly with 975 nmoles of dl-Prop or 330 nmoles of LB-46 ate 27, 35, 70 and 126% of control values at 15, 30, 60 and 120 min postinjection; none of these intakes were different from the control [4]. The attempts to block the feeding elicited by 66 nmoles of l-Epi by either a specific α or β antagonist were not conclusive. Injections of both dl-Prop and phenoxybenzamine each in combination with l-Epi reduced the l-Epi elicited feeding so that neither of the responses was significantly different from that of control and both of the reduced responses showed trends towards being less than that elicited by l-Epi injected alone.

An injection of 66 nmoles of l-NE did not elicit a feeding response in contrast to this dose of l-Epi. However, 294 nmoles of l-NE elicited a feeding response similar to that of the higher doses of l-Epi (267 and 534 nmoles). Neither l-NE precursor, l-Dopa or dopamine in similar dose ranges elicited feeding, Table 3.

Injections of the relatively pure β agonist, dl-Isop, in doses of 6.25 and 12.5 nmoles elicited feeding greater than that of control, Table 4. Higher doses resulted in only normal control feeding.

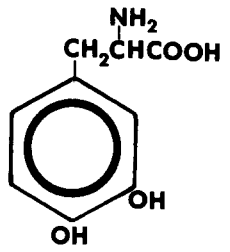
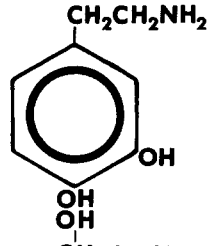
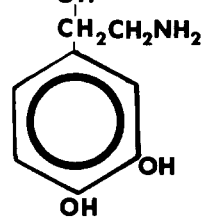
Two potent selective β agonists (β_2), 3,4-dihydroxy-β-hydroxyphenethyl-tert-butylamine, HCl (DPETB) and [α(tert-butylamino)methyl]-4-hydroxy-m-xylene-a',a[3]-diol (Salbutamol) were also tested. DPETB, with a tertiary-isobutyl amine group substitution for the isopropyl amine group of dl-Isop was less active as an agonist for eliciting feeding, Table 4. No feeding was elicited by Salbutamol injections in the doses tested; Salbutamol includes the additional substitution of a methylhydroxyl group for the meta hydroxyl group of DPETB.

In those tests for which body temperature data are available only one level of dl-Isop resulted in a significant change and that was an increase, Table 5. Although the mean temperatures following injections of l-Epi were higher, the variation of response between animals was too great for statistical significance.

No single dose of l-Epi affected feeding in cattle consistently to produce a significant feeding response although

TABLE 3

FEED INTAKES OF SHEEP FOLLOWING INTRAVENTRICULAR INJECTION OF l-NE, AN α ADRENERGIC AGONIST AND ITS BIOSYNTHETIC PRECURSORS, l-DOPA AND DOPAMINE

Treatment	Structure	Dose n moles	n	Intakes following inj. as a % of 2 hr control (min) 0–15	0–30	0–60	0–120	Intake (g) ± SEM 0–120
Syn CSF				14	28	48	100	
l-dopa		187	6	7	44	81	161	84 ± 42[1]
		294	7	42	98	50	164	86 ± 41[1]
		588	7	4	6	40	121	63 ± 31[1]
Dopamine		187	8	14	45	82	157	88 ± 24[2]
		294	7	9	39	116	166	93 ± 20[2]
		588	8	9	14	50	118	66 ± 16[2]
l-NE		66	8	33	62	67	80	58 ± 27[3]
		294	8	96	132†	167*	182*	133* ± 24[3]

*$p<0.05$ †$p<0.01$

Corresponding 0–120 min control intakes: [1]52 ± 9 [2]56 ± 12 [3]73 ± 13 g

there was a trend toward higher means with most doses, Table 6. However, the highest dose, 3,240 nmoles, depressed the feed intake significantly for the period 30–60 min after injection and all the cumulative means were below those of the control. A mixture of l-Epi and phenoxybenzamine also failed to elicit feeding. In previous studies with cattle also injected intraventricularly we showed that 2,940 nmoles of phenoxybenzamine resulted in 55, 93, 116 and 132% of the 120 min control value at 15, 30, 60 and 120 min postinjection [4].

In cattle one dose of l-NE, 445 nmoles, resulted in feeding greater than that of control, Table 6. Injections of 296 and 593 nmoles failed to elicit feeding.

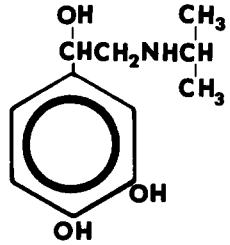
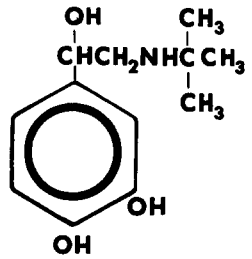
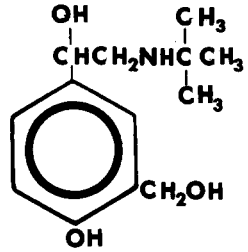
DISCUSSION

These experiments lend support to our previous conclusions that both α and β agonists can elicit feeding in sheep [4]. Intraventricular injections of l-Epi elicited feeding within two dose ranges; the lower dose range is comparable to the doses of the relatively pure β agonist, dl-Isop, required to elicit feeding and the higher dose range is comparable to the doses of the relatively pure α agonist, l-Ne, which stimulate feeding. l-Epi has nearly equal potency as an α agonist with l-NE and as a β agonist with dl-Isop, in at least some tissues [1]. We have previously shown that about 10 times as much l-NE as dl-Isop was required to elicit feeding when injected intraventricularly in sheep [4] and that about 30 times as much l-NE as dl-Isop injected intrahypothalamically was required to elicit feeding in sheep [3]. Each of these feeding responses elicited by α and β agonists injected either intrahypothalamically or intraventricularly was blocked only by the corresponding α and β antagonists [3].

In the present experiment the feeding elicited by the highest dose of l-Epi tested in sheep was clearly blocked by phenoxybenzamine, a specific α antagonist, and was actu-

TABLE 4

FEED INTAKES OF SHEEP FOLLOWING INTRAVENTRICULAR INJECTIONS OF β ADRENERGIC AGONISTS

Treatment	Structure	Dose nmoles	n	Intakes following inj. as a % of 2 hr control (min) 0–15	0–30	0–60	0–120	Intake (g) ± SEM 0–120
Syn CSF				14	28	48	100	
dl-Isop		6.25	8	42	62	132*	260*	138* ± 21[1]
		12.50	8	25	66*	120*	177	129 ± 27[2]
		25.00	8	33	46	85	130	95 ± 17[2]
		50.00	8	27	38	75	120	89 ± 26[2]
DPETB		12.50	7	10	21	40	76	70 ± 24[3]
		25.00	5	41	54	110*	172	158 ± 38[3]
		50.00	8	31	65	106*	136	71 ± 12[1]
Salbutamol		12.5	8	6	12	49	84	61 ± 23[2]
		25.00	6	14	28	45	112	103 ± 26[3]
		50.00	8	16	22	36	74	54 ± 13[2]

*$p<0.05$

Corresponding 0–120 min control intakes: [1]52 ± 9 [2]73 ± 13 [3]92 ± 15 g

ally increased by dl-Prop, a specific β antagonists, injected with the l-Epi. Similarly, the feeding elicited by l-NE in a previous experiment was blocked by phenoxybenzamine but not by dl-Prop [4]. Phenoxybenzamine did not affect feeding when injected alone although half of this dose caused hypophagia during the 60 to 120 min postinjection period [4]. The l-Epi apparently overcame this hypophagia when the two drugs were injected in combination.

We chose to inject the agonist and antagonist at the same time to minimize the handling and injections of the animals and because we had shown the single injection method was effective for blocking the feeding effects elicited by α and β agonists [4]. In may pharmacological studies using especially phenoxybenzamine the antagonist was given systemically hours before the agonist since complete blockade in at least some tissues only slowly develops [7]. However, in studies on several specific tissues or organs little or no time was required before the onset of blockade of adrenoceptors by phenoxybenzamine occurred; e.g. effects on: (1) hypothalamic blood flow in the conscious rabbit [20]; (2) vascular responses of rabbit ear [15]; (3) mouse brain glycolysis – decrease of glucose concentration within 30 min after systemic phenoxybenzamine [13]; (4) blocking of diazoxide effect on insulin secretion of perfused pancreases [5]; (5) α agonists elicited contraction of gall bladder strips [18]; (6) α agonist excitatory effect on isolated sphinctor of Oddi [17]; and, (7) α agonist elicited excitation of electrical activity of isolated colon [23]. The injecting of

TABLE 5

TEMPERATURE (IP) CHANGE AFTER CEREBROVENTRICULAR INJECTIONS OF α AND β AGONISTS IN SHEEP (C)

Treatment	Dose nmoles	n	Mean ± SE 0–30	Min Post Injection Mean ± SE 0–60	Mean ± SE 0–120
Syn CSF			0.0 ± 0.00	0.1 ± 0.10	0.0 ± 0.08
l-Epi	267	6	0.1 ± 0.13	0.1 ± 0.19	0.3 ± 0.21
	534	6	0.6 ± 0.32	0.3 ± 0.21	0.4 ± 0.29
l-Epi +	66				
POB	66	7	0.3 ± 0.20	0.2 ± 0.63	0.2 ± 0.22
l-Epi +	534				
POB	588	7	0.0 ± 0.05	0.0 ± 0.09	0.1 ± 0.12
dl-Isop HCl	6	7	0.1 ± 0.05	0.0 ± 0.06	0.1 ± 0.05
	25	8	0.1 ± 0.08	0.3 ± 0.08*	0.4 ± 0.14*
	50	8	−0.2 ± 0.09	−0.5 ± 0.19	−0.4 ± 0.22
Salbutamol	50	7	0.0 ± 0.04	0.0 ± 0.08	0.0 ± 0.08
DPETB	50	8	0.0 ± 0.08	0.0 ± 0.06	0.1 ± 0.07
l-NE	66	6	0.1 ± 0.10	0.2 ± 0.12	0.2 ± 0.08
l-Dopa	300	7	0.3 ± 0.30	0.3 ± 0.23	–
	600	7	0.0 ± 0.03	0.1 ± 0.08	−0.2 ± 0.12
Dopamine	150	7	0.1 ± 0.07	0.0 ± 0.13	0.1 ± 0.12
	300	7	0.0 ± 0.10	0.1 ± 0.20	0.3 ± 0.19
	600	6	0.1 ± 0.07	0.2 ± 0.11	0.0 ± 0.32

*$p<0.05$

the agonist and antagonist together may result in our measuring only a relative effect of the antagonist since there would be little time for the antagonist to equilibrate with the receptor molecule. We selected phenoxybenzamine instead of phentolamine for this experiment because it is more soluable and we showed in sheep, and Booth in rats [6], that it is equally as effective in blocking the feeding elicited by l-NE. Phenoxybenzamine causes a sustained blockade in at least some tissues [7]. We have not attempted to determine the duration of its action in the brain of sheep, however, l-NE injected 48 hr after a phenoxybenzamine injection resulted in a similar feeding response as that prior to any phenoxybenzamine treatments.

Neither of the immediate precursors of l-NE or l-Epi elicit feeding in sheep when they are injected over a similar dose range as that of the end products. It cannot be concluded that some other range of doses would not effect feeding in some way. It is interesting that lateral ventricular injections into rats of dopamine (21.7 to 43.4 nmoles) resulted in feeding [14].

We have previously shown that feeding elicited by 50 nmoles of dl-Isop is specifically blocked by either 974 nmoles of dl-Prop (a β antagonist) but not by 29.4 nmoles of phenoxybenzamine (an α antagonist) [4]. Therefore, in the present experiment we predicted that 974 nmoles of dl-Prop would block the feeding elicited by 66 nmoles of l-Epi. Although the l-Epi feeding response was reduced and not significantly different from the control, it was not significantly less than that elicited by l-Epi alone and the l-Epi feeding response was equally affected by 66 nmoles of phenoxybenzamine. Even though only β agonists have been found to elicit feeding at doses similar to the lower doses of l-Epi in sheep and a presumably equally active α agonist, l-NE, at these low doses was inactive, we did not show conclusively that this response following l-Epi was only β adrenergically mediated by blocking it with specific β antagonists. In a previous experiment larger doses of dl-Isop were required to elicit feeding than in the present experiments presumably because the previous sheep were more than twice as heavy and were mature and had a larger volume of CSF resulting in greater dilution of the drugs [4].

In a separate study it was shown that 7.5 nmoles of l-Epi elicited feeding at medial hypothalamic loci at which 240 nmoles, but not 7.5 nmoles, of l-NE also elicited feeding

TABLE 6

FEED INTAKES OF CATTLE FOLLOWING INTRAVENTRICULAR INJECTIONS OF ADRENERGIC AGONISTS

Treatment	Dose nmoles	n	Intakes following inj. as a % of 2 hr control (min) 0–15	0–30	0–60	0–120	Intake (g) ± SEM 0–120
Syn CSF			25	58	68	100	
l-Epi	50	8	75	84	108	121	355 ± 123[1]
	101	8	35	46	62	112	328 ± 89[1]
	202	8	42	82	109	156	456 ± 123[1]
	405	8	36	63	131	163	453 ± 149[2]
	810	8	32	56	66	145	402 ± 136[2]
	1620	8	48	78	101	123	342 ± 117[2]
	3240	8	11	27	27	40	110 ± 71[2]
l-Epi + POB	1014 + 1014	8	29	57	59	71	203 ± 116[3]
l-NE	296	8	22	66	69	77	210 ± 85[4]
	445	8	29	61	69	160*	438* ± 83[4]
	593	8	56	66	74	100	274 ± 117[4]

*$p<0.05$

Corresponding 0–120 min control intakes: [1] 293 ± 28 [2] 278 ± 21 [3] 286 ± 52 [4] 274 ± 44 g

[3]. However, unlike the feeding elicited by 240 nmoles of l-NE, that elicited by 7.5 nmoles of l-Epi was partially blocked when 7 nmoles of LB-46, a potent and specific β antagonist, was injected together with the l-Epi. An injection of 240 nmoles of l-Epi also elicited feeding, but with this dose phenoxybenzamine, a potent α antagonist, blocked the feeding response while LB-46 did not.

Other drugs known to be potent β agonists, but with selective β_2 activity, were tested for their feeding effects. Both DPETB and Salbutamol are known to be equally potent bronchial dialators (β_2) but much less potent as cardiovascular activators (β_1 activity) when compared to dl-Isop (10, 19). Neither of the β_2-like agonists was as active in eliciting feeding as dl-Isop. In other experiments we have found that much higher doses of Salbutamol (555 nmoles) injected intraventricularly elicted feeding in sheep (a total in 2 hr of 125 vs 51 g for CSF, n = 7, $p<0.05$, unpublished data, Baile and McLaughlin). Based on this limited series, it may be tentatively suggested that β_2 agonists are less potent for eliciting feeding than dl-Isop, the more general β agonist.

In comparing the doses of the 4 agonists which have strong β activities, the activity of racemates must be compared with those of the individual stereoisomers. We have previously shown that the l-isomer is the active form of Isop [4]. Therefore, because only 6.25 nmoles of dl-Isop elicited feeding even greater than 33 nmoles of l-Epi, it may be that l-Isop is at least 10 times as active in our system. Although the feeding elicited by DPETB was less striking, this racemic agonist is probably also more active than l-Epi assuming the l-stereoisomer is also the more active of these agonists for eliciting feeding in sheep. Also in comparing the effects of dl-Isop and l-Epi, it should be noted that while higher doses of dl-Isop result in hypophagia in sheep [4], l-Epi elicits feeding. Myers and Yaksh [14] reported a bimodal dose response to lateral ventricular injections of l-Epi in rats (13.6–54.6 and 109.2–873.2 nmoles). In an accompanying experiment they found no feeding elicited by 44.7–284 nmoles of Isop. It may be that the feeding elicited by l-Epi in rats was a β agonist response and the Isop doses tested were too high to confirm the β feeding in rats.

We have previously shown that intraventricularly injected dl-Isop in doses of 500–2000 nmoles will elicit feeding in cattle [4]. However, injections of l-NE over quite a large dose range, i. e. 50–3000 nmoles, generally resulted in hypophagia; within this range, we found that doses from 300–800 nmoles did not cause hypophagia, but no dose tested elicited reliable feeding [4]. The universal adrenoceptor agonist l-Epi did not elicit feeding in cattle although it was tested over a large dose range. This may have been because of a counteracting effect of activation of the α and β receptors. However, the combination injections of 1014 nmoles l-Epi and 1014 nmoles of phenoxybenzamine were expected to prevent the α agonist hypophagic effect and consequently resulted in a β-elicited feeding, but did not. We showed in a previous experiment that a mole-equivalent of the α antagonist blocked the hypophagic effect of l-NE [4]. Perhaps other doses of l-Epi and an α antagonist and injection at various times after the antagonist will be required to elicit feeding in cattle.

As we have discussed previously [4], there is probably

no effect of these doses of drugs on body temperature in either sheep or in cattle at the loci investigated. The present temperature data tend to support this conclusion since it appears that the feeding response is certainly primary to any change in body temperature.

ACKNOWLEDGEMENTS

The authors are grateful to Ms. Carol L. McLaughlin and Mr. James E. Denton for their assistance with this work.

The following are the sources for the drugs used: l-Epi (Ayerst Laboratories); Phenoxybenzamine, l-Dopa, Dopamine, 3,4-dihydroxy-β-hydroxyphenethyl-tert-butylamine, HCl (DPETB) (Smith Kline & French); l-NE bitartrate, B grade (CalBiochem); dl-Isop (Winthrop Laboratories); and Salbutamol (Allen & Hansburys, Ltd.).

REFERENCES

1. Ahlquist, R. P. A. study of the adrenotropic receptors. *Am. J. Physiol.* **153:** 586–600, 1948.
2. Antunes-Rodrigues, J. and S. M. McCann. Water, sodium chloride, and food intake induced by injections of cholinergic and adrenergic drugs into the third ventricle of the rat brain. *Proc. Soc. exp. Biol. Med.* **133:** 1464–1470, 1970.
3. Baile, C. A., F. H. Martin, C. W. Simpson, J. M. Forbes and J. S. Beyea. Feeding elicited by α and β adrenoceptor agonists injected intrahypothalamically in sheep. *J. Dairy Sci.* In press.
4. Baile, C. A., C. W. Simpson, L. F. Krabill and F. H. Martin. Adrenergic agonists and antagonists and feeding in sheep and cattle. *Life Sci.* **11:** 661-668, 1972.
5. Basabe, J. C., N. L. Lopez, J. K. Viktora and F. W. Wolff. Insulin secretion studied in the perfused rat pancreas. II. Effect of glucose, glucagon, 3'5' adenosine monophosphate, theophylline, imidazole and phenoxybenzamine; their interaction with diazoxide. *Diabetes* **20:** 457–466, 1971.
6. Booth, D. A. Mechanisms of action of norepinephrine in eliciting an eating response on injection into the rat hypothalamus. *J. Pharmac. exp. Ther.* **160:** 336–348, 1968.
7. Goodman, L. S. and A. Gilman. *The Pharmacological Basis of Therapeutics.* Fourth Ed., London: MacMillan Company, 1970. pp. 550–557.
8. Grossman, S. P. Direct adrenergic and cholinergic stimulation of hypothalamic mechanisms. *Am. J. Physiol.* **202:** 872–882, 1962.
9. Grunden, L. R., T. Fujita and K. L. Turner. Pharmacological analysis of hypothalamic mechanisms which control appetite. 7th Middle Atlantic Regional Meeting. American Chemical Society, Marriott Motor Hotel, Philadelphia, Penna. Feb. 14–17, 1972, p. 57.
10. Lands, A. M., A. Arnold, J. P. McAuliff, F. P. Luduena and T. G. Brown, Jr. Differentiation of receptor systems activated by sympathomimetic amines. *Nature* **214:** 597–598, 1967.
11. Leibowitz, S. F. Hypothalamic β-adrenergic "satiety" system antagonizes an α-adrenergic "hunger" system in the rat. *Nature* **226:** 963–964, 1970.
12. Leibowitz, S. F. Relative sensitivity and preponderance of hypothalamic alpha- and beta-adrenergic receptors. 7th Middle Atlantic Regional Meeting, American Chemical Society, Marriott Motor Hotel, Philadelphia, Penna., Feb. 14–17, 1972, p. 57.
13. Leonard, B. E. A. Comparison between the effects of phenoxybenzamine, phentolamine and propranolol on mouse brain glycolysis. *Biochem. Pharmac.* **21:** 109–113, 1972.
14. Myers, R. D. and T. L. Yaksh. Feeding and temperature responses in the unrestrained rat after injections of cholinergic and aminergic substances into the cerebral ventricles. *Physiol. Behav.* **3:** 917–928, 1968.
15. Nagasaka, T. and L. D. Carlson. Effects of blood temperature and perfused epinephrine on vascular responses of rabbit ear. *Am. J. Physiol.* **220:** 289–292, 1971.
16. Pappenheimer, J. R., S. R. Heisey, E. F. Jordan and J. de C. Downer. Perfusion of the cerebral ventricular system in unanesthetized goats. *Am. J. Physiol.* **203:** 763–774, 1962.
17. Persson, C. G. A. Adrenoceptor functions in the cat choledocho-duodenal junction *in vitro*. *Br. J. Pharmac.* **42:** 447–461, 1971.
18. Persson, C. G. A. Adrenoceptors in the gall bladder. *Acta pharmac. tox.* **31:** 177–185, 1972.
19. Phillips, E. M., M. Woolnough, V. M Marinova and P. Turner. A comparison of isoprenaline, salbutamol, and rimiteral inhalation on skin temperature, heart rate, and respiration in man. *J. clin. Pharmac.* **12:** 158–168, 1972.
20. Rosendorff, C. and W. I. Cranston. Effects of intrahypothalamic and intraventricular norepinephrine and 5-hydroxytryptamine on hypothalamic blood flow in the conscious rabbit. *Circulation Res.* **28:** 492–502. 1971.
21. Sharpe, L. G. and R. D. Myers. Feeding and drinking following stimulation of the diencephalon of the monkey with amines and other substances. *Expl Brain Res.* **8:** 295–310, 1969.
22. Slangen, J. L. and N. E. Miller. Pharmacological tests for the function of hypothalamic norepinephrine in eating behavior. *Physiol. Behav.* **4:** 543–552, 1969.
23. Weinbeck, M. and J. Christensen. Effects of some drugs on electrical activity of the isolated colon of the cat. *Gastroenterology* **61:** 470–478, 1971.