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Effect of D- and/or L-Aspartic Acids on Feeding, Drinking, Urine Outflow and Core Temperature

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KOYUNCUOĞLU, H. AND K. BERKMAN. *Effect of D- and/or L-aspartic acids on feeding, drinking, urine outflow and core temperature.* PHARMAC. BIOCHEM. BEHAV. 17(6) 1265–1269, 1982.—Rats were given D- and/or L-aspartic acids (Asp) in saccharine solution for one week. Body weight gain, daily food and fluid intake, weight of faeces, urine outflow and osmolality, and rectal temperature were compared with those of the pretreatment period. After the rats had been sacrificed the weights of liver, spleen and kidney were estimated and compared with those of the control. The long-term oral administration of D-Asp caused a significant decrease in the weights of total body, liver and kidney, in the daily food and fluid intake, in the weight of faeces and in the volume of urine. The osmolality of urine of the rats administered D-Asp was significantly higher than that of the control. The concomitant oral administration of L-Asp seemed to antagonize the effects of D-Asp.

Aspartic acid Eating Drinking Urine outflow Core temperature

SYSTEMIC administration of D-amino acids has been shown to produce analgesia (anti-nociceptive response) in men and mice. D-Phenylalanine, an inhibitor of carboxypeptidase A and D-leucine, an inhibitor of leucine aminopeptidase have been postulated to possess a hypalgesic effect via endorphinergic system because D-phenylalanine and D-leucine produced analgesia is naloxone-reversible. Moreover, a clear cross-tolerance between the anti-nociceptive responses of D-amino acids and morphine has been reported [5, 8, 9]. On the other hand, it has been hypothesized by Margules [29] that opioid systems may be involved in the regulation of behaviour regarding acquisition of nutrients and in the conservation and expenditure of energy.

Supporting this hypothesis several studies have shown that naloxone, an opiate antagonist reduces food and water intakes in laboratory animals. Food intake is decreased in food-deprived [2, 10, 14, 15, 37] and also in freely-feeding animals [6,30]. Similarly, water intake is reduced under a variety of experimental conditions [2, 3, 6, 10, 35, 37, 38]. Although the effects of opiate antagonist naloxone on food and fluid intakes seem to be quite well established the same cannot be said for the actions of opiate agonists. If, as has been suggested, endogenous opioids take part in the mediation of feeding and drinking, administration of morphine and other opiates should, under certain conditions, increase food and water intakes. There have been some reports of such effects [1, 12, 27, 34, 40], but several other studies have generally found attenuation of such behaviour [4, 10, 25, 28, 36, 38, 39]. In addition, it is generally accepted that morphine and its surrogates induce antidiuresis by the liberation of antidiuretic hormone from the hypophysis as was first advanced by De Bodo [7]. Recently Tseng *et al.* [41] documented that systemic or intraventricular injection of beta-endorphin produced oliguria, and demonstrated that this effect of the peptide was related to that of morphine since cross-tolerance developed between morphine and beta-endorphin. Several other studies have confirmed the antidiuretic effect of opiate and opioid [11, 13, 16, 17, 18, 19, 33, 42] although they have not unanimously substantiated the mechanism of action regarding the release of antidiuretic hormone [11, 13, 16, 17, 18, 19].

In previous studies we showed that L-Asp antagonizes some acute effects of morphine [22] including those on the dependence of L-asparaginase [23], prevents the development of physical dependence on and tolerance to morphine [20,24], the morphine withdrawal and levallorphan-precipitated abstinence signs [21]; furthermore L-Asp antagonizes some changes caused by D-Asp (Koyuncuoğlu *et al. Drug Res.* in press) which is a powerful inhibitor of L-asparaginase [26].

Taken altogether the information given above it was considered of interest to investigate the effects of long term oral administration of D- and/or L-Asp on the total weight of body, the weights of liver, spleen and kidneys, food and fluid intakes, volume and osmolality of urine, and rectal temperature.

METHOD

Forty-nine male inbred *Rattus norvegicus var.* albinos (WISW, SPF TNO, F. Winkelmann, Germany) weighing 170 g ± were used. The rats were divided into four groups

TABLE 1

THE MEAN VALUES (±STANDARD ERRORS) OF THE TOTAL BODY WEIGHT (BEFORE PRETREATMENT PERIOD, BEFORE AND AT THE END OF THE ADMINISTRATION PERIOD), THE WEIGHTS OF THE LIVER, SPLEEN AND KIDNEY, AND THE RECTAL TEMPERATURE (BEFORE AND AT THE END OF THE ADMINISTRATION PERIOD). STATISTICAL ANALYSIS WAS CARRIED OUT BY THE STUDENT'S *t*-TEST

	Total Body Weight (g)			Weights of Some Organs (g)			Rectal Temperature (°C)	
	1	2	3	Liver	Spleen	Kidney	2	3
Control	169.1	197.1¶	222.0§	9.38	0.51	1.70	37.07	37.20
(9)	±1.61	±4.74	±5.95	±0.55	±0.02	±0.04	±0.07	±0.07
D-Asp group	171.2	196.9¶	179.3‡§	6.62‡	0.39†	1.71	37.05	36.69‡§
(10)	±1.09	±4.94	±4.54	±0.29	±0.02	±0.05	±0.06	±0.11
L-Asp group	169.9	190.5¶	213.7¶	8.68	0.48	1.74	37.01	37.14
(10)	±0.95	±2.64	±2.83	±0.24	±0.02	±0.04	±0.07	±0.04
D+L-Asp	168.5	195.4¶	207.3§	8.31	0.44*	1.73	37.02	37.07
group (10)	±0.77	±2.53	±3.63	±0.20	±0.02	±0.04	±0.07	±0.07

*$p<0.05$; †$p<0.01$; ‡$p<0.001$: referring to control.
§$p<0.01$; ¶$p<0.001$: referring to the previous value of the same group.
The figures in the brackets indicate the number of the rats in each group.
(1) Before the pretreatment period, (2) At the end of the pretreatment period, (3) At the end of the administration period.

namely Control (9), D-Asp (10) and D+L-Asp (10) and were placed in metabolism cages separately in a room at 20–22°C with 12 hr light/dark (6:00 a.m.–6:00 p.m.). They were given free access to standard powdered food and 0.1% saccharin solution, instead of drinking water, for one week. At the end of the so-called pretreatment period their body weight and rectal temperature (by means of a Tele-thermometer Model 46 TUC, Yellow Spring Instruments, Ohio/USA) were determined. Then, the Control group kept on drinking 0.1% saccharine solution for another week, whereas the D-Asp, L-Asp and D+L-Asp groups received 0.1% saccharine solution containing 2% D-Asp, 2% L-Asp and 1% D-Asp + 2% L-Asp, respectively. Following the determinations of body weight and rectal temperature once again, all the rats were killed by cervical dislocation and their livers, spleens and kidneys were immediately removed, cleaned from other tissues and weighed.

The solutions were prepared freshly and their pH was adjusted to 7.4 with N.NaOH. Throughout both pretreatment and administration periods daily food and fluid intakes, weight of faeces, volume of urine and osmolality of urine (by means of a Knauer osmometer, Dr. H. Knauer KG/ Germany) were estimated.

Student's *t*-test was used for statistical evaluation.

RESULTS

The mean values of the weights of body, liver, spleen and kidney, and those of rectal temperatures (±SE) are shown in Table 1. The body weights of the Control, L-Asp and D+L-Asp groups increased steadily during both pretreatment and administration periods while the body weight of the D-Asp group significantly decreased during the administration of D-Asp. The increase in the body weight of the D+L-Asp group during the administration period was not as large as those of the Control and L-Asp groups even though the difference between the Control and D+L-Asp groups was not found statistically significant (Table 1).

The weights of liver and spleen in the D-Asp group and the weight of spleen in the D+L-Asp group were significantly lower than control. The rectal temperature determined at the end of the administration period was found to be significantly decreased when compared to both previous value of the D-Asp group and that of the Control group (Table 1).

The mean values and the statistical evaluation of the daily food and fluid intake, weight of faeces, volume and osmolality of urine can be seen in Table 2. The daily food and fluid intake, weight of faeces, volume of urine in the D-Asp and D+L-Asp groups significantly decreased during the administration period when referred to both values of the Control group and those of the same group obtained during the pretreatment period (Table 2), whereas the osmolality of urine in the D-Asp and D+L-Asp significantly increased (Table 2).

When the weights of livers and spleens, which appeared to have some significant changes (Table 1) were expressed as pro 100 g of body weight only the liver weight of the D-Asp groups showed a significant decrease (Table 3).

DISCUSSION

The decrease observed in fluid intake of the D-Asp group and to a lesser extent in that of the D+L-Asp group cannot be attributed to a probable change in the taste of the saccharine solution as D-isomers of amino acids are sweet (to human taste) compared to the corresponding L-enantiomorphs, which have generally been described as tasteless or even bitter. L-Asp is slightly bitter while its D-isomer is described flat [32]. Our personal close observations made especially on the first days of the experiments during the present study as well as the previous one (Koyuncuoğlu *et al., Drug Res.* in press) did not at all show any sign of taste aversion. Moreover it has been known from our previous studies [20, 21, 24] that the slightly bitter taste of L-Asp should rather be disguised; this is the main reason why D- and/or L-Asp were administered in saccharine solution. In addition, the changes in the liver glycogen and triglyceride contents caused by the long-term oral administra-

TABLE 2

THE MEAN VALUES (±STANDARD ERRORS) OF THE FOOD INTAKE (g/day), WEIGHT OF FAECES (g/day), FLUID INTAKE (ml/day), VOLUME OF URINE (ml/day) AND OSMOLALITY OF URINE (m Osmol/kg) DURING THE PRETREATMENT AND ADMINISTRATION PERIODS. STATISICAL ANALYSIS WAS CARRIED OUT BY THE STUDENT'S *t*-test

	Food Intake (g/day)		Weight of faeces (g/day)		Fluid Intake (ml/day)		Volume of Urine (ml/day)		Osmolality of Urine (m Osmol/kg)	
	1	2	1	2	1	2	1	2	1	2
Control	17.4	17.1	9.6	9.2	27.9	26.4	16.2	14.7	1697.5	1849
(9)	±0.66	±0.49	±0.39	±0.34	±4.03	±1.55	±1.66	±1.15	±147	±107
D-Asp group	16.8	9.4‡#	9.7	4.8‡#	29.1	10.9‡#	17.5	5.4‡#	1749	3743‡#
(10)	±0.93	±0.62	±0.63	±0.39	±3.11	±1.06	±2.42	±0.53	±155	±131
L-Asp group	16.7	15.9	9.6	9.1	27.4	28.7	17.3	18.8*	1704	1684
(10)	±0.54	±0.27	±0.37	±0.25	±0.58	±1.18	±1.85	±1.11	±142	±98
D+L-Asp group	16.8	13.7‡#	9.2	6.6‡#	28.6	21.1*§	17.9	9.1†¶	1648	2654†#
(10)	±0.55	±0.51	±0.42	±0.30	±3.18	±1.43	±2.55	±1.05	±168	±185

*$p<0.05$; †$p<0.01$; ‡$p<0.001$: referring to control.
§$p<0.05$; ¶$p<0.01$; #$p<0.001$: referring the mean value of the administration period to that of the pretreatment period.
(1) During the pretreatment period, (2) During the administration period.

TABLE 3

THE MEAN VALUES (±SE) OF THE WEIGHTS OF LIVER AND SPLEEN PRO 100 g OF BODY WEIGHT

	Weight of liver pro 100 g body weight	Weight of spleen pro 100 g body weight
Control	4.18 ± 0.21	0.229 ± 0.09
D-Asp group	3.60 ± 0.13*	0.219 ± 0.10
L-Asp group	4.10 ± 0.11	0.226 ± 0.09
D+L-Asp group	4.08 ± 0.11	0.214 ± 0.11

*$p<0.05$ referring to control.

tion of D-Asp which were found completely different from those seen after food and fluid deprivation (Koyuncuoğlu *et al., Drug Res.* in press) can be considered as compelling evidence for the fact that the decrease in fluid intake of the D-Asp group might not be related to the aversive effect of D-Asp. The remarkable difference between the fluid intake of D-Asp group and that of the D+L-Asp group might also be added to the points mentioned above. On the other hand, parenteral administration of D- and/or L-Asp solutions having enough quantity of D- and/or L-Asp to be effective must have led us to give the rats a much larger quantity of water than normally taken by the D- or D+L-Asp groups since a solution of 2% Asp in distilled water is isotonic. Oral administration by means of a gastric sonda more than twice a day did not seem to be convenient because handling and administration in this fashion might have altered the findings by stress. Therefore, the oral administration of D- and/or L-Asp in saccharine solution was considered as the most suitable procedure for the aim of the present study.

As seen in Table 1, the total body weight of all the groups significantly increased during the pretreatment period. The body weights of the Control, L-Asp and D+L-Asp groups continued increasing also during the pretreatment period wheras the D-Asp group showed a rather large fall. Although the increase in the body weight of the D+L-Asp group does not seem to be equal to those of the Control and L-Asp groups no significant difference was found between the Control and D+L-Asp groups (Table 1).

Once the rats began taking D-Asp the daily food and fluid intakes, weight of faeces, volume of urine were sharply reduced; and the osmolality of urine in the groups received D-Asp followed them strictly. Thus, the expression of the daily food and fluid intake, the weight of faeces and the volume of urine pro 100 g body weight should have been meaningless. Instead, when the weight of liver and spleen of the D-Asp and D+L-Asp groups which appeared to have a significant decrease (Table 1) were expressed as the weight pro 100 g body weight only the decrease in the liver weight of the D-Asp group kept on being significantly lower than control. This is in good agreement with our previous findings (Koyuncuoğlu *et al., Drug Res.* in press) showing a significant decrease in the liver triglyceride and glycogen contents of the rats given D-Asp.

The administration of D-Asp decreased rectal temperature, food and fluid intake, weight of liver, and as a possible consequence of these the body weight, weight of faeces and presumably volume of urine were also decreased (Tables 1, 2 and 3). The increase in the osmolality may be associated with the decrease in fluid intake and in volume of urine or not. Since the analgesia produced by D-amino acids is naloxone reversible, a cross-tolerance between D-amino acids and morphine can develop [5, 8, 9] and the decrease in rectal temperature caused by D-Asp also is naloxone reversible (Koyuncuoğlu *et al., Pol. J. Pharmac. Pharm.*, submitted) the changes found following the long-term administration of D-Asp can be easily explained by the increased level of endogenous opioids. In spite of some controversial reports, in the majority of which a single dose was used [1, 12, 27, 34, 40] quite a large number of studies favours the inhibitory effect of opioids and opiates on feeding and drinking behaviours. The decreasing effect of D-Asp on food and fluid intake does not seem to be consistent with a possible damaging or debilitating effect since such effects have not been reported after the long-term use of D-amino acids for the

treatment of chronic rheumatic pains in man [8]. Despite many different D-amino acids from various origins such as proteins, bacteria and antibiotics are normally absorbed in gastrointestinal tract and they are normally metabolized by D-amino oxidase like their L-enantiomorphs [32]. And again the decrease in the volume of urine and the increase in the osmolality of urine may not be dependent only on the decrease in the fluid intake and in the volume of urine but an increase in the release and/or biosynthesis of vasopressin may play an important role [7, 33, 41, 42].

The concomitant administration of L-Asp prevents D-Asp from decreasing the total body weight, weight of liver, rectal temperature, food and fluid intakes, weight of faeces, volume of urine, and from increasing the osmolality of urine. In addition to these L-Asp antagonizes the effects of morphine including those on the activity of L-asparaginase [20–24]. As D-Asp is an inhibitor of L-asparaginase [26] and also morphine inhibits the activity of L-asparaginase in the brain, which is antagonized by L-Asp [23] the results of the present study and the previous ones suggest that the effects of D-Asp observed by us may be concerned with the manipulation of the activity of L-asparaginase.

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