15(R)-15-M-PGE_2 (group III) prior to the administration of ^{59}Fe was accompanied by a significant reduction of counts in comparison with controls (group I) in blood ($p < 0.02$) spleen ($p < 0.05$), liver ($p < 0.02$), femur ($p < 0.01$) and dried intestine ($p < 0.02$). On the other hand, following the administration of ^{59}Fe accompanied by ASA (group II) there is a significant increase of counts in comparison with controls (group I) in blood ($p < 0.02$), spleen ($p < 0.02$), liver ($p < 0.002$) and femur ($p < 0.005$). No differences were observed in dried intestine.

Results obtained with ASA (groups II) were reversed to control values (group I) when the animals were pretreated with 15(R)-15-M-PGE_2 (group IV) in blood, spleen, liver and femur whereas in dry intestine counts were significantly lower ($p < 0.002$). In freshly removed as well as in wet-washed empty intestine counts were not significantly different in the 4 groups.

Discussion. The foregoing results document that in the rat the action of ASA is to augment the absorption of iron. This effect is clearly observed at 180 min following the administration of ^{59}Fe via a catheter placed in the stomach. Indeed, an enhanced count of ^{59}Fe was found in blood, spleen, liver and femur and comparable results were detected in the intestine. These results are in keeping with previous findings[11] suggesting that the enhanced intestinal absorption is followed by higher circulating iron levels and enhanced deposit in storage organs.

The administration of a methyllated derivative of PGE_2 diminished iron absorption, circulation and deposit in storage organs. These findings support our previous observations in vitro regarding the effect of PGE_1 and PGE_2 on iron transport across the isolated intestine of the rat. Therefore, it is documented for the first time that among the several actions on the intestinal tract ascribed to PGs there is a distinct influence inhibiting iron absorption both in vivo and in vitro.

On the other hand, the 15(R)-15-M-PGE_2 was able to reverse the stimulatory action of ASA on iron absorption. This suggest that the increment of iron absorption produced by ASA is related to an inhibition of prostaglandin synthesis via the blockade of the intestinal cyclooxygenase system. The findings suggest that endogenous PGs may play an important role influencing iron absorption at the intestinal level.

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2 Reprint requests should be addressed to: A.L. Gimeno, CEFAPRIN, Serrano 665/69, 1414 Buenos Aires (Argentina).
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Effects of L-aspartic acid, L-asparagine and/or L-asparaginase on forced swimming-induced immobility, analgesia, and decrease in rectal temperature in rats

H. Koyuncuoğlu, L. Eroğlu and T. Altuğ

Max-Planck-Institut für experimentelle Medizin, D-3400 Göttingen (Federal Republic of Germany), and Department of Pharmacology and Clinical Pharmacology, Istanbul Medical Faculty, Istanbul (Turkey), 14 April 1981

Summary. The effect of L-aspartic acid, L-asparagine and/or L-asparaginase were compared with those of imipramine on immobility, number of defecations, increase of nociceptive threshold, and hypothermia, induced by forced swimming in rats. L-Aspartic acid was found to be as effective as imipramine in reducing the effects of forced swimming, presumable by normalizing the decreased level of endogenous L-aspartic acid, due to the inhibition of L-asparaginase activity and/or by stimulating the inhibited enzyme. The other treatments antagonized the immobility, but not the increased number of defecations. All compounds abolished the elevation of nociceptive threshold and hypothermia.

There are few, if any, animal models which both resemble the clinical phenomenon of depressive illness and are selectively sensitive to treatments known to be effective in its management. Porsolt et al.[1,2] have recently proposed that the immobile behaviour observed during forced swimming in rats and mice may serve as a screening model for potential antidepressants, and have shown that it was reduced by a variety of drugs that are therapeutically effective in depression. As a stressful event, forced swimming also produces analgesia in rats[3–5]. Akil et al.[6] and Chance et al.[7] have attributed the analgesia induced by stressful events to endogenous opioids whereas other workers[3–5] claim that there is little, if any, relationship between this analgesia and endorphin system in the brain. In addition to the many well-known similar effects of endogenous opioids and opiates they both affect central thermoregulation[8] and beta-endorphin administered into the lateral ventricle of rats causes, like opiates, a profound state of immobilization characterized by the absence of spontaneous movements. On the other hand, morphine has been shown to cause increases and decreases in the activity of L-asparaginase[9] which can be antagonized by L-aspartic acid. Additionally L-aspartic acid antagonizes the acute and chronic effects of morphine[9,10] and the manipulation of L-asparaginase activity by administering D- and/or L-aspartic acid causes body weight loss, decreases in food and fluid intakes[11], naloxone reversible decrease in rectal temperature, increases in the releases of ACTH, vasopressin and

The mean values of the immobility (sec) and the number of defecations during 5 min of forced swimming, and the nociceptive threshold (g) and rectal temperature (centigrade) before and after forced swimming (± SE)

Groups	Immobility sec in 5 min	No. of defecations in 5 min	Nociceptive threshold (g) Before swimming	Nociceptive threshold (g) After swimming	Rectal temperature (°C) Before swimming	Rectal temperature (°C) After swimming
Control (18)	58.1 ± 8.69	5.4 ± 0.34	4.70 ± 0.26	6.99 ± 0.35 $p < 0.001$	38.1 ± 0.02	36.7 ± 0.04 $p < 0.001$
Imipramine 30 mg/kg (10)	19.5 ± 7.89[b]	0.2 ± 0.20[c]	4.91 ± 0.29	5.12 ± 0.33[c]	38.0 ± 0.01	37.8 ± 0.03[c]
L-Aspartic acid 30 mg/kg (10)	17.3 ± 3.51[c]	3.2 ± 0.36[c]	4.98 ± 0.27	4.66 ± 0.24[c]	38.2 ± 0.02	37.9 ± 0.04[c]
L-Asparaginase 500 IU (10)	23.0 ± 3.94[b]	4.1 ± 0.93	4.65 ± 0.11	4.95 ± 0.31[c]	37.1 ± 0.01	37.7 ± 0.03[c]
L-Asparagine 30 mg/kg (10)	21.9 ± 4.70[b]	5.1 ± 0.49	4.74 ± 0.33	5.098 ± 0.36[c]	38.3 ± 0.02	37.8 ± 0.04[c]
L-Asparagine 30 mg/kg + L-Asparaginase 500 IU (10)	16.8 ± 3.78[c]	4.4 ± 0.34[a]	5.04 ± 0.32	4.91 ± 0.29[c]	37.9 ± 0.03	38.1 ± 0.03[c]

The figures in brackets indicate the number of rats. [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$ referring to the control. $p < 0.001$ referring the after swimming values to the before swimming values.

endorphins (Koyuncuoğlu et al. unpublished observations) presumably through changes in the synthesis and/or release of peptide hormones. In view of these experimental findings it was considered to be of interest to investigate the effects of L-aspartic acid, L-asparagine and/or L-asparaginase on the immobility, elevation of the nociceptive threshold and decrease of rectal temperature caused by forced swimming, in comparison with the effects of a classical antidepressant drug, imipramine.

The experiment was performed on 68 inbred rats (*Rattus norvegicus* var. albinos) weighing 220–250 g. 21 days after birth they were separately placed in rat cages for 60 days. After they had been forced to swim for 15 min in water at 20–22 °C they were allowed to dry for 15 min in a heated enclosure[1,2,12] and were divided into 6 groups, being always kept in their home cages. Then they were injected with either 0.2 ml of 0.9% saline i.v. or 30 mg/kg of imipramine i.p. or 30 mg/kg of L-aspartic acid i.v. or 500 IU of L-asparaginase i.v. (Crasnitin, Bayer, Leverkusen/FRG) or 30 mg/kg of L-asparagine i.v. and/or 30 mg/kg of L-asparagine + 500 IU of L-asparaginase i.v. 24 and 25 h following the 1 administration, the same quantities of the drugs were administered. 1 h after the last injection the nociceptive threshold and rectal temperature were determined by means of an 'Analgesymeter for rat paw' (Ugo Basile, Milan/Italy) and 'Tele-thermometer Model 46 TUC' (Yellow Springs Instruments, Ohio/USA) and they were expressed as g and °C, respectively. Then the rats were subject to forced swimming for 5 min according to the test described by Porsolt et al.[1,2,12]. The duration of immobility and the number of defecations were estimated and expressed as sec and number, respectively. 15 min after swimming the nociceptive threshold and body temperature were measured again. Throughout the experiment all the animals were given free access to food and water at 20–22 °C with 12 h dark/light cycles. For statistical analysis the Student's t-test was used.

As seen in the table, forced swimming caused a significant increase in the nociceptive threshold and a significant decrease in the rectal temperature in the control group. All the drugs used in the experiment significantly decreased the total duration of immobility in a 5-min period of forced swimming whereas only imipramine, L-aspartic acid and L-apsaragine + L-asparaginase appeared to be effective in decreasing the number of defecation. The treatment with imipramine, L-aspartic acid, L-asparaginase, L-asparagine and L-asparagine + L-asparaginase prevented the increase in nociceptive threshold and the decrease in rectal temperature seen following forced swimming.

The results of the present study are compatible with the view that forced swimming-induced immobility, increase in defecation, increase in nociceptive threshold and decrease in rectal temperature are mediated by opioid peptides. In preventing the effects of forced swimming the agents used seem to be more or less equipotent to those of imipramine, a powerful antidepressant drug. Since L-aspartic acid antagonizes the acute and chronic effects of morphine including that on L-asparaginase activity and the administration of D-aspartic acid, an inhibitor of L-asparaginase[13] produces a state clinically and biochemically similar to depression characterized by body weight loss, decreases in food and fluid intakes, increases in the releases of ACTH, vasopressin and endorphins[9–11] (Koyuncuoğlu et al. unpublished observations) the prevention of the changes induced by forced swimming is not unexpected. The failure of the administration of asparagine as well as L-asparaginase to decrease the number of defecation supports the evidence that L-aspartic acid is the active agent because, to provide the required amount of L-aspartic acid, L-asparagine and L-asparaginase need sufficient activity of endogenous L-asparaginase, and a sufficient amount of endogenous asparagine, respectively.

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