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Effects of conditioned running on plasma, liver and brain tryptophan and on brain 5-hydroxytryptamine metabolism of the rat

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1 An investigation was made into the effects of conditioned running (1 h and 2 h at 20 m min^{-1}), which accelerates lipolysis, on the concentrations of tryptophan (Trp) in plasma, liver and brain and on 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) levels in brain.

2 Running caused time-dependent increases in plasma free Trp and brain Trp of the rat, leading to increased brain 5-HT turnover as revealed by higher amounts of its metabolite, 5-HIAA. The ratio of brain Trp to plasma free Trp was decreased after 2 h of running.

3 Liver Trp content rose only after 3 h of running, while liver unesterified fatty acid (UFA) concentrations remained unmodified.

4 A comparison between food deprivation and running (both of which promote lipolysis) was performed. Running for 2 h affected to the same extent plasma Trp disposition when compared with 24 h food deprivation. Nevertheless, the ratio of brain Trp to plasma free Trp was decreased in the food-deprived rats, when compared to the runners.

5 Valine, an inhibitor of entry of Trp into the brain decreased its level there to the same extent in both controls and 1 h runners.

6 Nicotinic acid, which inhibits fat catabolism, completely abolished the plasma UFA increase induced by 1 h of running. The drug did not affect plasma free Trp, brain Trp, 5-HT or 5-HIAA but enhanced plasma total Trp level.

7 Naloxone, an opiate antagonist, which decreased running-induced lipolysis, did not alter plasma Trp disposition.

8 Desipramine, an antidepressant compound, affected only peripheral Trp concentrations of the runners. Plasma free and total Trp concentrations were increased in desipramine-treated runners, compared with saline-treated runners. In addition, desipramine increased the ratio of brain Trp to plasma free Trp of the runners. Brain 5-HT and 5-HIAA were increased in both desipramine-treated controls and runners.

9 The results suggest that running, which like food deprivation accelerates lipolysis, increases brain Trp content and then 5-HT turnover. Comparison of these two physiological situations suggests that effectiveness of brain Trp entry is much more altered by fasting.

Introduction

Synthesis of the brain neurotransmitter 5-hydroxytryptamine (5-HT) depends on the concentration of tryptophan (Trp), its precursor (Eccleston *et al.*, 1965). Since tryptophan hydroxylase is normally unsaturated, increases in brain Trp lead to enhanced 5-HT turnover (Eccleston *et al.*, 1965; Friedman *et al.*, 1972). The brain Trp level may be influenced by changes in the concentration of the relatively small fraction of unbound Trp in plasma (Knott & Curzon, 1972). This mechanism is largely involved during ontogenesis (Bourgoin *et al.*, 1974), food deprivation (Knott & Curzon, 1972) or after immobilization (Knott & Curzon, 1972). Variations in plasma unesterified fatty acids (UFA) promote these changes since UFA decrease the binding of plasma Trp to albumin (McMenamy, 1965) and thus, affect plasma Trp disposition (Knott & Curzon, 1972; Curzon *et al.*, 1973; Tagliamonte *et al.*, 1973).

Brain Trp concentration depends also on the relative blood levels of a group of neutral amino acids, which compete with Trp for uptake by the brain (Fernstrom & Wurtman, 1972; Pardridge, 1977). Brain Trp changes following food intake may be explained by this process (Fernstrom & Wurtman, 1972; Madras *et al.*, 1974) since brain Trp no longer correlates with free plasma Trp (Madras *et al.*, 1974).

Physiological benefits of exercise can lead to mood elevation (Ransford, 1982). Indeed, acute or chronic physical activity may have an antidepressant effect in clinically depressed subjects (Morgan *et al.*, 1970; 1971) but singling out the crucial brain amine has been controversial (Ransford, 1982). It was of interest therefore to investigate whether running which is known to alter insulin secretion (Felig & Wahren, 1971; Guezennec *et al.*, 1982) and consequently fat catabolism (Carlson *et al.*, 1963) also alters the concentrations of Trp in plasma, liver and brain and hence 5-HT biosynthesis in brain.

In order to assess the various mechanisms leading to such metabolic variations during limited exercise (1 h of running), pharmacological experiments were performed. These experiments included different inhibitors acting at various levels: nicotinic acid (Carlson *et al.*, 1966) and naloxone (Badawy & Morgan, 1982) blockade of lipolysis, prevention of the entry of Trp into the brain by use of valine (Fernstrom & Wurtman, 1972; Pardridge, 1977). Finally, an attempt to determine the influence of hepatic tryptophan pyrrolase during physical exercise was carried out. For this purpose, we administered desipramine which inhibits tryptophan pyrrolase activity (Badawy & Evans, 1981). Indeed, this enzyme, which catalyzes the first irreversible step in the degradation of Trp in the liver, may affect brain Trp availability by virtue of its activity (Joseph *et al.*, 1976).

Methods

Male Wistar rats (IFFA CREDO, Les Oncins, France; body weight ~220 g) were kept at a constant temperature and subjected to a 09 h 00 min–20 h 00 min light-dark cycle. All the animals were fed a normal diet, unless otherwise stated (Table 1). Water was continuously available, except during the experiments (see below). Exercise was performed on a horizontal treadmill driven by an electrical motor. Treadmill lanes were 50 cm long and 15 cm wide. In order to minimize stress during the experiments, rats were conditioned to run for 4 to 5 sessions and the time of running progressively increased so that during the last session, rats ran for 1 h at a speed of 20 m min^{-1}. Electrical foot shocks were delivered when the rats stepped down from the treadmill. Intensity and voltage of these shocks were 5 mA and 10 V respectively:

Table 1 Effects of running and food deprivation on plasma total and free tryptophan, plasma unesterified fatty acids (UFA) and brain tryptophan, 5-hydroxytryptamine (5-HT) and 5-hydroxyindolacetic acid (5-HIAA) concentrations in 220 g male Wistar rats

Group		*UFA* (mEq l^{-1})	*Plasma Tryptophan* (μg ml^{-1})		*Tryptophan*	*Brain 5-HT* (μg g^{-1} wet weight)	*5-HIAA*
			Total	*Free*			
Fed rats[1]	Controls	0.23 ± 0.03	19.21 ± 0.98	1.35 ± 0.16	2.82 ± 0.06	0.49 ± 0.02	0.27 ± 0.01
	Runners	0.56 ± 0.04***	16.65 ± 1.20	1.97 ± 0.12*	4.18 ± 0.12***	0.51 ± 0.03	0.33 ± 0.02*
Fasted rats[2]	Controls	0.74 ± 0.09	17.63 ± 1.22	2.75 ± 0.14	3.74 ± 0.15	0.55 ± 0.04	0.36 ± 0.02
	Runners	1.12 ± 0.07*	17.05 ± 1.53	4.17 ± 0.23***	6.17 ± 0.42**	0.55 ± 0.03	0.40 ± 0.02

Values are mean ± s.e.mean. There were 6 rats per group.
[1]The control rats were deprived of food and water for 1 h and then killed with the rats which had run for 1 h on a treadmill at a speed of 20 m per min.
[2]The control rats were deprived of food and water for 23 h and then deprived of both food and water for a further 1 h. They were killed at the same time as the 23 h food-deprived rats which had run for 1 h on a treadmill at a speed of 20 m per min.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ versus their respective controls (Student's t test).

the combination of these two parameters allows the delivery of weaker shocks (50 milliwatts) when compared to footshock levels used in other stress experiments in the literature (350–700 milliwatts). In addition, there were no visible signs of trauma produced by the running and shocks. This training obviated the need for electrical stimulation on the day of the experiment. Indeed, training sessions were undertaken in order to produce conditioned running. Each experiment was started between 10 h 00 min–11 h 00 min. The rats were divided randomly into two groups: those selected for running were placed on the treadmill and ran for 1 h, 2 h or 3 h at a speed of 20 m min^{-1} (a speed considered as being of low intensity), and the controls were placed in a cage without any food or water (Guezennec *et al.*, 1982).

Brain metabolite measurements

All the rats (runners and respective controls) were killed by decapitation and their brains rapidly removed. Each whole brain (minus cerebellum) was immersed in a 0.4 M perchloric acid, 4×10^{-6} M ascorbic acid solution containing 2×10^{-6} M α-methyl-5-HT as an internal index of indole losses (Chaouloff *et al.*, 1985). The tissue solution was then sonicated ($4-5 \times 15$ s) and the resulting homogenate centrifuged twice for 3 min at 15,000 *g*. From the supernatant, 25 µl was recovered for the measurements of α-methyl-5-HT loss and brain Trp, 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) concentrations by liquid chromatography coupled with simultaneous ultraviolet and amperometric detection (l.c.e.c.-u.v.) (Le Quan-Bui *et al.*, 1982; Chaouloff *et al.*, 1985).

Plasma metabolite measurements

Blood was collected into heparinized tubes with 25 iu heparin per ml of blood, a concentration which does not affect plasma Trp disposition (Bourgoin *et al.*, 1974). The blood was then centrifuged and the resulting plasma separated into two portions. Total Trp was determined on the whole plasma, while free Trp was measured from plasma ultrafiltrate as previously described (Chaouloff *et al.*, 1985). Plasma Trp determinations were assayed by l.c.e.c.-u.v. (Chaouloff *et al.*, 1985). Unesterified fatty acids (UFA) were measured by the acyl Coa synthetase method ('Nefa C Test' Wako) from plasma samples stored at −80°C.

Plasma corticosterone was determined by radiocompetition with cortico binding globulin (according to Fiorelli *et al.*, 1972).

Liver metabolite measurements

Liver UFA and Trp were determined from pieces of tissue frozen by freeze-clamping and then stored at −80°C. Trp measurements were performed as previously described (brain Trp measurements). In order to determine liver UFA contents, pieces of tissue – previously immersed in a Krebs solution – were sonicated (total time: 2 min). An aliquot (1 ml) of the cell homogenate was added to 2 ml of acetone and centrifuged at 3,000 *g* for 10 min. The supernatant was added to hexane (1:2, v/v) and liver UFA recovered in the hexane layer were measured by the 'Nefa C Test, Wako'. This extraction procedure allows a recovery rate (85%) equivalent to the one obtained by the method of Dole (1956) (Duval, personal communication).

Statistics

All values are expressed as mean ± s.e.mean. Differences between means were assessed by analysis of variance followed by Student's *t* test and considered not significant at $P > 0.05$.

Chemicals

All drugs were injected intraperitoneally 1 h before death, except for nicotinic acid which was injected subcutaneously. L-Valine (Sigma Ltd) was injected at a dose of 200 mg kg^{-1} body weight: the amino acid was dissolved in the minimum amount of 1 M HCl and diluted in 0.9% saline. The solution was neutralised with 0.1 M NaOH and the dilution completed by addition of 0.9% saline. Nicotinic acid (Sigma Ltd) was injected at a dose of 250 mg kg^{-1} body weight. The chemical was dissolved as L-valine. Naloxone (Sigma Ltd) and desipramine (Ciba-Geigy) were administered at doses of 5 mg kg^{-1} and 10 mg kg^{-1} body weight respectively. Both were dissolved in 0.9% saline solution. The injected volumes were 1.5 ml kg^{-1} body weight.

Results

Effects of running for 1 h and 2 h upon plasma and brain tryptophan disposition

Figure 1 shows that the disposition of plasma Trp varied during the physical exertion: although plasma total Trp did not change significantly, there was a large and significant increase in the plasma free Trp portion. Indeed, the plasma free Trp concentration was doubled after 2 h of running, when compared with the controls. This response to physical exercise reflects an accelerated fat catabolism since plasma UFA concentration was increased in the same manner (Figure 1). Lipolysis also affected the plasma Trp disposition during moderate exercise (1 h of running at a speed of 20 m min^{-1}).

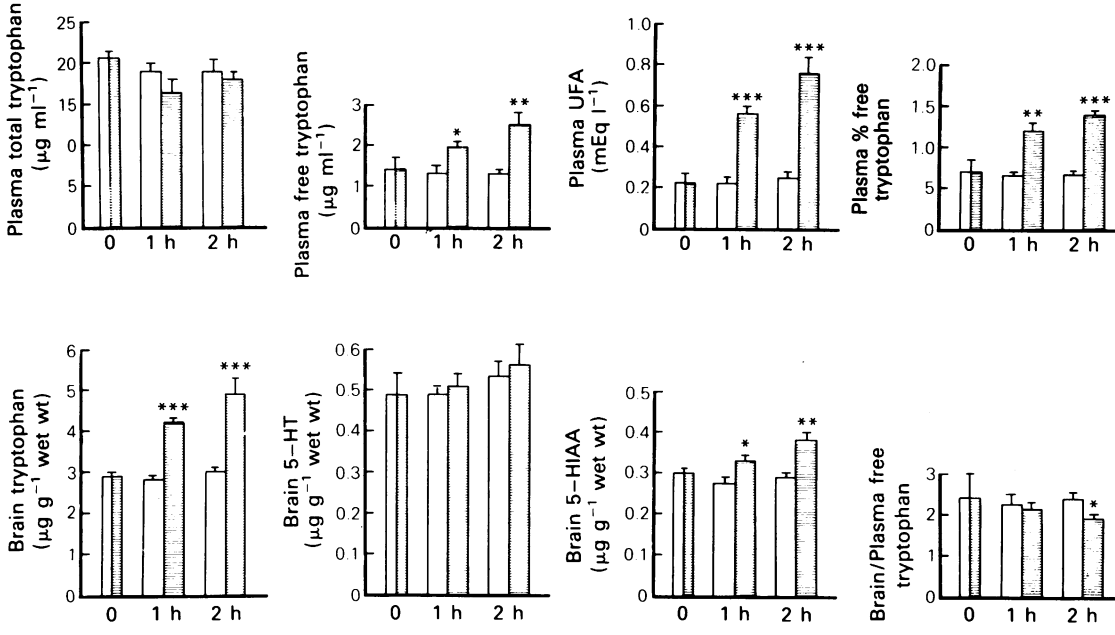

Figure 1 Effects of 1 h and 2 h of running (treadmill speed was 20 m min^{-1}) on rat plasma total and free tryptophan, plasma unesterified fatty acids (UFA) and brain tryptophan, 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA). The open and striped columns indicate the values for the controls and the runners respectively. Results are from 6 experiments with s.e.mean shown by vertical lines. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ compared with the respective controls (Student's *t* test).

The rise of that percentage of plasma Trp which is free, resulted in an absolute increase in brain Trp level. This increase was accompanied by an enhanced brain 5-HT biosynthesis, as indicated by the increased amounts of 5-HT metabolite, 5-HIAA (Figure 1). Linear regression analysis of brain Trp concentrations against plasma free Trp concentrations of the runners revealed a significant relationship between the two (Pearson's correlation coefficient, $r = 0.84$; $P < 0.001$). In addition, the ratio of brain Trp to plasma free Trp decreased slightly during running. After 2 h of running, the difference was significant: 2.39 ± 0.14 and 1.94 ± 0.11 for the controls and the runners respectively.

Effects of running upon liver tryptophan content

As shown in Figure 2, the liver Trp concentration was unaltered by 2 h of running and rose only after 3 h of physical exertion. Liver UFA content remained un-

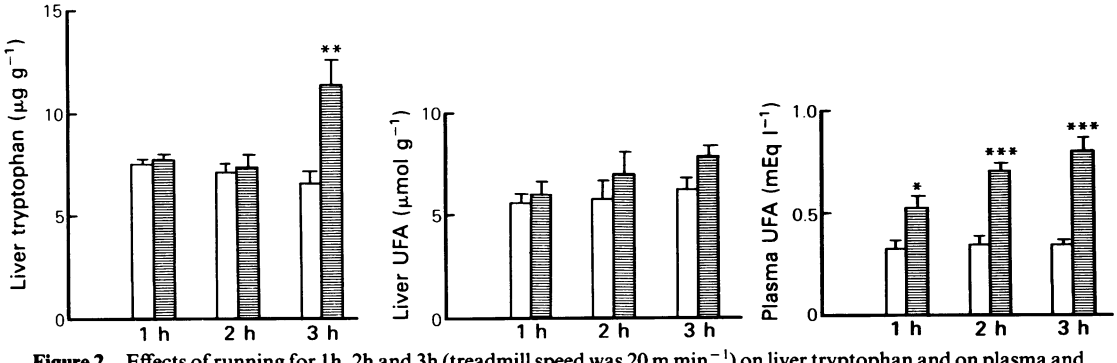

Figure 2 Effects of running for 1h, 2h and 3h (treadmill speed was 20 m min^{-1}) on liver tryptophan and on plasma and liver unesterified fatty acids (UFA). The open and striped columns indicate the values for the controls and the runners respectively. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ compared with the respective controls (Student's *t* test).

modified by running while plasma UFA concentration rose in a time-dependent way (Figure 2), as previously shown (Figure 1).

Comparative effects of running and fasting on the effectiveness of tryptophan uptake by the brain

Brain Trp and 5-HIAA levels both rose significantly after 24 h of food deprivation (Table 1). These variations were associated with an increased proportion of plasma free Trp. Changes in plasma free Trp (ultrafilterable) and UFA concentrations were similar to those found after 2 h of running (compare Table 1 and Figure 1). Nevertheless, the brain Trp concentration was increased to a lesser degree in the 24 h food-deprived rats, than in those which ran for 2 h (Table 1, Figure 1). Indeed, the low ratio of brain Trp to plasma free Trp (1.36 ± 0.16 in the fasted rats) reflects a significantly less efficient brain Trp uptake in these rats, when compared with the rats that ran for 2 h (brain Trp to plasma free Trp ratio : 1.94 ± 0.11, $P < 0.05$). This discrepancy appears despite equivalent degrees of lipolysis (as indicated by plasma UFA concentrations) and similar plasma Trp disposition (plasma free Trp to total Trp ratio). In addition, the brain Trp to plasma free Trp ratio was 1.48 ± 0.14 in rats subjected to physical exercise for 1 h after 23 h of food-deprivation (Table 1). In this situation, the effects of lipolysis induced by both the running and fasting were merely additive rather than synergistic, while the rise in brain Trp entry was limited by food deprivation, as indicated above by the changes in the brain Trp to plasma free Trp ratio.

Effects of valine, nicotinic acid, naloxone and desipramine on plasma tryptophan disposition and on brain tryptophan metabolism of the runner rats

Valine

Valine administration immediately before running completely prevented the physical exercise-induced increases in brain Trp and 5-HIAA (Table 2, compare saline injected controls and valine-treated runners). In addition, the percentage of brain Trp depleted was similar in the two groups (35% and 26% for the controls and the runners respectively).

Nicotinic acid

As shown in Table 2, nicotinic acid administration to the runners prior to their physical exertion attenuated the plasma UFA increase. This drug was also effective when given to the controls, as plasma UFA level was also significantly reduced. In these animals, plasma total and free Trp concentrations were not significantly affected, while after 1 h of running, plasma total Trp

Table 2 Effects of L-valine, nicotinic acid and naloxone on plasma total and free tryptophan, plasma unesterified fatty acids (UFA) and brain tryptophan, 5-hydroxytryptamine (5-HT) and 5-hydroxyindolacetic acid (5-HIAA) concentrations in 220 g male Wistar rats running for 1 h

Group	*Treatment*	*UFA* ($mEq\ l^{-1}$)	*Plasma Tryptophan* ($\mu g\ ml^{-1}$) *Total*	*Free*	*Tryptophan*	*Brain 5-HT* ($\mu g\ g^{-1}$ wet weight)	*5-HIAA*
Controls	0.9% saline	0.28 ± 0.05	18.56 ± 1.04	1.34 ± 0.14	2.87 ± 0.12	0.49 ± 0.03	0.29 ± 0.01
Runners	0.9% saline	0.57 ± 0.01**	15.40 ± 1.26	1.87 ± 0.13*	3.82 ± 0.10**	0.51 ± 0.01	0.33 ± 0.01*
Controls	L-Valine	0.23 ± 0.02	15.22 ± 0.73†	1.22 ± 0.10	1.86 ± 0.06†††	0.48 ± 0.01	0.29 ± 0.01
Runners	L-Valine	0.65 ± 0.08**	17.60 ± 1.92	1.95 ± 0.14**	2.83 ± 0.03***††	0.47 ± 0.02	0.29 ± 0.01†
Controls	Nicotinic acid	0.15 ± 0.01†	18.07 ± 1.04	1.65 ± 0.09	3.45 ± 0.17	0.46 ± 0.02	0.34 ± 0.01††
Runners	Nicotinic acid	0.16 ± 0.01†††	21.42 ± 0.88†	1.81 ± 0.13	4.30 ± 0.16*††	0.53 ± 0.04	0.35 ± 0.02
Controls	Naloxone	0.20 ± 0.03	17.62 ± 0.61	1.42 ± 0.11	2.68 ± 0.18	0.49 ± 0.02	0.29 ± 0.01
Runners	Naloxone	0.40 ± 0.06*†	16.52 ± 1.18	1.60 ± 0.14	3.69 ± 0.25*	0.48 ± 0.02	0.31 ± 0.01

Values are mean ± s.e.mean. There were 6 rats per group. The runners and controls were killed at the same time: after 1 h of running on a treadmill at a speed of 20 m per min or after 1 h of food and water deprivation respectively.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ versus the control which received the same treatment (Student's t test).
†$P < 0.05$; ††$P < 0.01$; †††$P < 0.001$ versus controls or runners which received 0.9% saline vehicle (Student's t test).

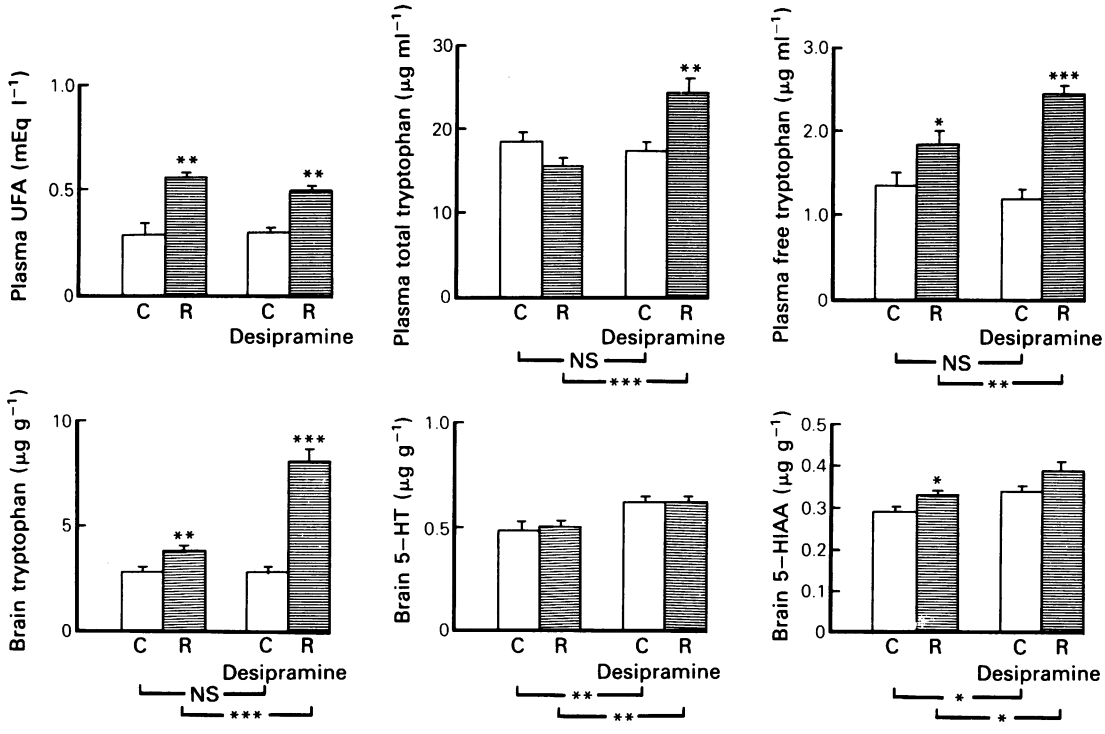

Figure 3 Effects of desipramine on plasma total and free tryptophan, plasma unesterified fatty acids (UFA) and brain tryptophan, 5-hydroxytryptamine (5-HT) and 5-hydroxyindolacetic acid (5-HIAA) of control (C; open columns) and 1 h runner (R; striped columns) rats. In each panel, left (C and R) columns and right (C and R) columns represent saline and desipramine-treated animals, respectively. Results mean from 6 experiments with s.e.mean shown by vertical lines; $*P<0.05$; $**P<0.01$; $***P<0.001$ against the respective treated (saline or desipramine) rats or controls. The statistics beneath the panels represent the significance of the effect of desipramine treatment against saline treatment. NS: non significant (Student's *t* test).

was greatly increased. Nicotinic acid pretreatment did not affect the plasma free Trp portion in the runners, despite fat catabolism inhibition, but decreased the percentage free Trp. Brain indole metabolism of the runners was unaffected by nicotinic acid (Table 2) while significant increases of brain Trp and brain 5-HIAA levels were observed in the controls, when compared with saline-injected control rats.

Naloxone

As shown in Table 2, naloxone pretreatment significantly decreased UFA mobilization in the runners. Nevertheless, plasma and brain indole levels of the runners were not affected by such a treatment compared to saline-injected runners (Table 2).

Desipramine

As shown in Figure 3, desipramine administration 1 h before the rats were killed did not affect peripheral and brain Trp concentrations in the controls. Brain 5-HT and 5-HIAA concentrations were increased, reflecting the predominantly central action of the drug in these conditions. On the other hand, antidepressant treatment given immediately before the runner's 1 h of exercise, affected their peripheral Trp metabolism to a large degree. Plasma total and free Trp levels were increased by 60% and 30% respectively, when compared with saline-injected runners. In addition, desipramine increased brain Trp uptake in the runners, as the brain Trp to plasma free Trp ratio was enhanced in desipramine-treated runners (3.27 ± 0.21), when compared with the saline-injected runners (2.24 ± 0.30; $P<0.05$). The marked elevation of brain Trp was only accompanied by moderate, but significant increases in brain 5-HIAA and 5-HT levels in the desipramine-treated runners. In addition, brain 5-HIAA (and 5-HT) levels were unchanged in the desipramine-treated runners compared to the desipramine-treated control rats (Figure 3).

Discussion

In the present study, the effects of running upon peripheral and brain Trp metabolism have been studied.

Brain Trp level, which increased in a time-dependent manner during running, correlated well with changes in plasma free Trp concentration. Since total Trp was not significantly affected by running, this clearly indicates that fat catabolism was responsible for the increased brain Trp availability. The ratio of brain Trp concentration to plasma free Trp concentration, which may be an index of the effectiveness of Trp uptake by the brain, was not significantly changed during running. The moderate decrease in Trp uptake by the brain after 2 h of running may be caused by increased competition between plasma neutral amino acids (valine, leucine, isoleucine, phenylalanine and tyrosine) for uptake by the carrier system (L-system) (Fernstrom & Wurtman, 1972; Pardridge, 1977). Indeed, running promotes hypoinsulinaemia (Guezennec *et al.*, 1982) which increases the plasma levels of these competing amino acids (Felig & Wahren, 1971; Fernando *et al.*, 1976). The increase in liver Trp content after 3 h of running may also partly reflect running-induced proteolysis which follows glycogenolysis at that time (Guezennec *et al.*, 1982). The liver UFA level was unaltered during running. This result is in good agreement with previous data indicating that exhaustive exercise (220 min at 28 m min^{-1}) does not influence liver UFA content of the rat (Barakat *et al.*, 1982).

Brain 5-HT turnover is indirectly increased during running as a consequence of an accelerated fat catabolism. This situation resembles the one previously described during food deprivation (Curzon & Knott, 1972; Tagliamonte *et al.*, 1973), after immobilization (Knott & Curzon, 1972), or after catecholamines, L-DOPA or aminophylline administration (Curzon & Knott, 1974). Indeed, the comparison between running and fasting shows that brain Trp uptake effectiveness (the ratio of brain Trp to plasma free Trp) is not similarly altered during these events. Running did not diminish brain Trp uptake as much as food deprivation while both conditions enhanced brain Trp content (when compared to sedentary fed rats). Interpretation of this observed discrepancy (between running and fasting) is not simple since plasma levels of the competing amino acids are unknown.

Valine administered immediately before exercise completely prevented brain Trp increases (compared to saline-injected runners). This confirmed that the enhanced brain 5-HT turnover of the runners was simply a consequence of an increased brain Trp availability. Valine, which inhibits both brain and neuronal Trp uptake (Fernstrom & Wurtman, 1972; Knowles & Pogson, 1984) inhibits in the same manner the stress-induced increase of brain Trp content (Kennett & Joseph, 1981). This result, taken with previous data concerning plasma Trp disposition during stress (Knott & Curzon, 1972) raises questions about the possible influence of stress during running. In fact, when animals are trained, stress induced metabolic variations may be minimized. Furthermore, a running-induced elevation of plasma UFA level has also been measured in healthy male human volunteers (Carlson *et al.*, 1963; Lassers *et al.*, 1972).

Acute nicotinic acid treatment inhibited running-induced lipolysis (Table 2). Nevertheless, the plasma free Trp level in the runners was not decreased by nicotinic acid treatment. Indeed, as plasma total Trp was enhanced, the percentage free Trp of the runners was reduced by the antilipolytic drug compared to saline-treated runners. In addition, in the runners, brain Trp and 5-HIAA were not affected by nicotinic acid treatment. Conversely, brain Trp levels of the treated controls were found to be enhanced compared with the saline-injected controls. The reason for such a discrepancy is unclear; nevertheless, that nicotinic acid affects other pathways of Trp metabolism remains a possibility.

Naloxone treatment partly inhibited exercise lipolysis; then, plasma free Trp and brain 5-HIAA concentrations, which were found to be significantly increased after 1 h of running, were no longer elevated when compared to naloxone-treated control or saline-injected control rats. Since drug administration did not fully prevent fat catabolism, hyperglucagonemia and hyperactivity of the sympatho-adrenal axis may be the major factors producing mild exercise lipolysis (Banister & Griffiths, 1972; Galbo *et al.*, 1975).

Administration of antidepressants such as mianserin, viloxazine, tranylcypromine or desipramine (3.5 h prior to analysis) elevates brain Trp levels by inhibiting liver tryptophan pyrrolase of control rats (Badawy & Evans, 1981). Our results suggest that running may increase liver tryptophan pyrrolase activity.

Indeed, plasma corticosteroids were increased in animals running for 1 h, when compared with controls: 363 ± 25 and 256 ± 17 ng ml^{-1} of plasma, respectively ($P < 0.01$, from 11 experiments). Corticosteroids are known to activate tryptophan pyrrolase and thus accelerate hepatic Trp utilization (Knox & Auerbach, 1955). These metabolites could then be involved in the above difference.

Conversely, the ratio of brain 5-HIAA to brain 5-HT (an index of brain 5-HT turnover), which was slightly decreased by desipramine treatment, was not different between treated control and treated runner rats. This discrepancy between the peripheral and the central effects of the drug during running and resting may implicate the central effect of desipramine upon

brain monoamine (essentially noradrenergic and 5-HTergic) systems (Carlsson & Lindqvist, 1978). Although the main purpose of desipramine treatment was to appreciate tryptophan pyrrolase activity during running, the changes concerning Trp uptake by the brain may be of importance (Figure 3). The positive effect of desipramine on the effectiveness of Trp uptake by the brain during running may indicate the involvement of vascular adrenoceptors. A β-adrenoceptor sensitive to adenylate cyclase is present in intracranial blood vessels (Nathanson & Glaser, 1979). This nucleotide system may modulate vascular permeability, which may contribute to brain Trp entry (Nathanson & Glaser, 1979). The marked elevation of circulating catecholamines resulting from running (Banister & Griffiths, 1972; Galbo *et al.*, 1975) plus a catecholamine uptake inhibition pretreatment (desipramine) (Langer *et al.*, 1981), could elevate Trp transport through this vascular stimulation mechanism.

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