Effects of physical training on IL-1β, IL-6 and IL-1ra concentrations in various brain areas of the rat

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ABSTRACT. There is increasing evidence that voluntary physical activity and exercise training have beneficial effects on brain function by facilitating neurovegetative, neuroadaptative and neuroprotective processes. Cytokines are chronically expressed at elevated levels within the CNS in many neurological disorders and may contribute to the histopathological, pathophysiological, and cognitive deficits associated with such disorders. In the present study, we examined the influence of seven weeks of physical training on IL-1b, IL-6 and IL-1ra concentrations in hypothalamus, pituitary, hippocampus, cerebellum and frontal cortex in rats. We determined circulating concentrations of cytokines, corticosterone, prolactin and leptin. Two groups of 10 rats were investigated: one group (trained rats) was progressively trained (5 days/week); the other group (sedentary rats) was used as a sedentary group. The training program induced a decrease of (*i*) IL-1b concentration in the hippocampus (0.7 ± 0.16 *versus* 0.99 ± 0.14 pg/mg protein; $p < 0.05$), (*ii*) IL-6 concentration in the cerebellum (10.7 ± 1.00 in trained rats *versus* 14.8 ± 1.34 pg/mg protein in sedentary rats; $p < 0.05$), (*iii*) IL-1ra concentration in the pituitary (245 ± 14.31 *versus* 328 ± 17.73 pg/mg protein; $p < 0.01$). We also found positive correlations between (*i*) serum prolactin and the concentration of IL-6 in the cerebellum, (*ii*) serum leptin and the concentration of IL-1ra in the pituitary. There was no effect of physical training on IL-1b, IL-6, and IL-1ra serum levels. These findings suggest that the decrease in particular pro-inflammatory, central cytokines such as IL-1b and IL-6 induced by the training program may play a role in the positive effects of regular physical activity on the central nervous system.

Keywords: exercise training, brain, cytokines, rat

The positive effects of exercise on many physiological systems, including the central nervous system (CNS), are well-established. In animals, the functional benefits of regular physical exercise have been well studied. Both voluntary and forced exercise protocols have been used to explore the effect of exercise on brain function. Although it has been argued that forced exercise may better "encourage" some human exercise regimes, it may increase stress and thus abrogate the positive effects observed with voluntary exercise. Interestingly, treadmill exercise for rats has been shown to improve cognitive function [1]. Wheel running and treadmill training improve spatial learning in rats [2]. In addition, physical activity in rats enhanced memory retention [3], reduced escape latency [4] and diminished age-related declines in spontaneous activity [5] in comparison to sedentary controls. Exercise can modulate neuronal vulnerability to insults [6]. For example, recent studies have shown that exercise may have neuroprotective effects in the brain via the up-regulation of neurotrophic factors such as insulin-like growth factor 1 (IGF-I) [7], brain-derived factor neurotrophic factor (BDNF) [8] and nerve growth factor (NGF) [9]. Tong *et al*. recently showed that IL-1β impairs BDNF signal transduction. From this we might assume an influence of exercise on brain IL-1β [10].

We, and others, have shown in trained humans that circulating levels of anti-inflammatory cytokines such as IL-1ra, increase transiently after prolonged endurance exercise and then return to basal levels, while the pro-inflammatory cytokine IL-1β remains unchanged [11]. Fischer *et al.* have also demonstrated that endurance training does not change resting levels of IL-6 [12].

Most of the studies on rodents have reported that physical activity improves the overall immune condition of the brain by reducing TNF-α expression [13]. Cytokines can be produced and secreted by many immune cells, along with a variety of other cell types in both muscle and brain. They regulate inflammatory and immunological processes involved peripherally in the repair of damaged tissue [14], as well as centrally, inducing alterations in neuroendocrine and neurotransmitter activity, and inducing sickness behaviors [15]. Mechanical damage and corresponding inflammation are likely to affect both skeletal muscle and the CNS thereby reducing exercise performance [15]. Central pro-and anti-inflammatory cytokines appear to play a key role in neuronal death occurring during acute (*e.g.* brain

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injury, cerebral ischemia) and chronic conditions (*e.g.* neurodegenerative diseases) [16]. Several neurodegenerative disorders are accompanied by changes in the concentration of cytokines such as brain IL-1β [17] or IL-6 [18]. In view of the suggested role of these cytokines in brain function and neurological disorders, we investigated the influence of an exercise training program (treadmill running over 7 weeks) for rats on IL-1β, IL-6 and IL-1ra concentrations in different brain regions (hippocampus, hypothalamus, pituitary, cerebellum and frontal cortex). Most studies investigating the role of cytokines in brain disorders have explored these brain areas, particularly the hippocampus, because of its implication in memory processes. In addition there are few data on the influence of exercise training on the brain protein cytokine content. We also determined cytokine concentrations in blood, and circulating concentrations of immune-related hormones such as corticosterone, prolactin and leptin. The possible mechanisms and the physiological relevance of the related effects of endurance training on the production of cytokines by the brain are discussed.

METHODS

Animals

The experiments were performed using male Wistar rats (Centre d'élevage R Janvier, Le Genest-Saint-Isle, France), aged four weeks, and weighing 125-130 g at the beginning of the experiments. The animals were housed five per cage under controlled conditions of temperature (20-23°C), humidity (40%) and light/dark cycle (12 h/12 h, lights on at 7 am) with *ad libitum* access to food and water. The care and treatment of animals were supervised by the veterinary surgeons of the Institut de Médecine Aérospatiale du Service de Santé des Armées. The animals arrived in the laboratory at least one week before the experiments.

Experimental training protocol

The experimental training protocols were designed to increase mitochondrial oxidation in skeletal muscle by the 4th week of the training program [19]. The animals were randomly allocated into two groups: a sedentary group (sedentary rats; n = 10) and an exercise-trained group (trained rats; n = 10). The training group was exercised by running on a motorized treadmill over a 7 week period. In order to minimize stress, rats were progressively accustomed to treadmill training for one week (five days, 10-15 min at a speed of 15 m/min). Animals reluctant to run during this training period were not used in the experiment. At the end of this period, the training program began: trained rats exercised 60 min each day, for two weeks, at 18 m/min. At the end of the 2nd week, the trained rats had run for 60 min at a speed of 18 m/min. The trained group was submitted to a progressive increase in workload over three weeks, up to 25 m/min, 7% gradient, 120 min per day, five days per week. This level of training remained stable throughout the last two weeks of training. During the training session, rats in the exercise-trained group were weighed three times a week. Rats belonging to the sedentary groups were placed daily in a novel cage and weighed three times a week as for the trained rats. To check for normal growth patterns in the trained rats, we also weighed adrenal glands since adrenal hypertrophy in rats has been described as a potentially negative physiological adaptation to chronic, intensive exercise [20].

Blood and tissue processing and cytokine measurement

In order to prevent acute exercise effects, the day after the last exercise session (between 9-12 am), rats were weighed and sacrificed by decapitation. Trunk blood was then collected in vials and centrifuged at 3 000 rpm for 10 min to separate serum. The pituitary and brain were quickly dissected on a cold plate. Brain tissue samples, which included the hypothalamus, pituitary, hippocampus, cerebellum and frontal cortex were immediately placed in microfuge tubes and quickly immersed in liquid nitrogen and stored at -80°C.

Each tissue was thawed in 0.300-2.5 mL of ice cold buffer (pH 7.4, +4°C) containing 25 mM Hepes, 0.1% CHAPS, 5 mM $MgCl_2$, 2 mM AEBSF, 1 mM EDTA, 130 μM Bestatin, 14 μM E64, 1 mM Leupeptin, 0.3 μM Aprotinin. Tissues were then homogenized. The homogenates were centrifuged for 20 min at 16 0000 g (+4°C). Total protein content was measured in each supernatant using the method of Bradford (BioRad, Hercules, CA, USA). Supernatants were aliquoted and stored at -80°C until ELISA.

Levels of IL-1β, IL-6 and IL-1ra were determined using commercially available rat ELISA kits (R&D systems, Minneapolis, MN, and Biosource, Camarillo, CA, USA). The assays were performed according to the manufacturer's instructions. All data are expressed as pg of cytokine per mg total protein except serum samples, which are expressed as pg cytokine per ml serum. The minimum detectable concentrations were < 5 pg·mL-1 for IL-1β, < 20 pg·mL-1 for IL-6, and < 12 pg·mL-1 for IL-1ra.

Blood hormone and metabolite assays

Corticosterone, prolactin and leptin concentrations were determined in duplicate by radioimmunoassay using commercial kits (DSLabs, Spi-Bio; France).The limits of sensitivity were: 2.7 ng/mL for corticosterone, 0.5 ng/mL for prolactin, and 0.04 ng/mg for leptin.

Statistical analysis

Statistica Version 6.1 (Statsoft, Tulsa, OK, USA) was used for all analyses. All data are presented as means ± SE. To analyze differences between the two groups, Student's t test was used. Person product-moment correlations were used to relate the variables identified in the ANOVA.

RESULTS

Body and adrenal gland weight after program training

At the end of the training program, body weight gain (final body weight – initial body weight) of trained rats was significantly lower than that of the sedentary rats (222 ± 9 g and 253 ± 6 g, respectively, $p < 0.01$). The

mean weight of the two adrenal glands did not differ between the two groups (63.5 ± 1.4 mg for sedentary rats and 70.6 ± 4.6 mg for trained rats).

Effect of physical training on brain cytokine concentrations

IL-1β

The IL-1β concentration was reduced in the hippocampus of the trained rats compared to sedentary rats (0.7 ± 0.16 *versus* 0.99 ± 0.14 pg/mg protein; $p < 0.05$). No statistically significant effect of physical training on IL-1β concentration was observed in the pituitary, frontal cortex or cerebellum. The concentration of IL-1β in the hypothalamus was below the detection limit in both groups *(figure 1A)*.

IL-6

The IL-6 concentration was reduced in the cerebellum of the trained rats compared to the sedentary rats (10.7 ± 1.00 *versus* 14.8 ± 1.34 pg/mg protein; $p < 0.05$). No statistically significant effect of physical training on IL-6 concentration was observed in the pituitary, hypothalamus, frontal cortex or hippocampus *(figure 1B)*.

IL-1ra

The IL-1ra concentration was reduced in the pituitary of the trained rats compared to the sedentary rats (245 ± 14.31 *versus* 328 ± 17.73 pg/mg protein; $p < 0.01$). No statistically significant effect of physical training on IL-1ra concentration was observed in the frontal cortex, hippocampus or cerebellum *(figure 1C)*.

Effect of physical training on serum cytokine concentrations

There was no effect of physical training on IL-6, IL-1ra and IL-1β concentrations in serum. No changes in concentration were observed between the sedentary and trained groups for IL-6 (9.5 ± 2.0 *versus* 14 ± 2.0), IL-1β (51 ± 9.88 *versus* 39 ± 11.66) or IL-1ra (1515 ± 174.73 *versus* 1545 ± 203.79) *(figure 2)*.

Effect of physical training on hormone concentrations in blood

Serum levels of leptin and prolactin were decreased and increased respectively in trained compared to sedentary rats (0.33 ± 0.13 *versus* 1.60 ± 0.49 ng/mL; $p < 0.01$ and 15.02 ± 1.98 *versus* 25.52 ± 3.04 ng/mL; $p < 0.01$, respectively), while levels of corticosterone were unchanged *(table 1)*.

Correlation analysis

A significant, positive correlation was observed between serum prolactin and the concentration of IL-6 in the cerebellum ($r = 0.45$; $p < 0.05$). A significant, positive correlation was observed between serum leptin and the concentration of IL-1ra in the pituitary ($r = 0.65$; $p < 0.05$).

DISCUSSION

In the present study, we examined the effect of physical training on IL-6, IL-1β and IL-1ra concentrations in different brain regions of the rat, and analyzed circulating concentrations of corticosterone, prolactin, leptin and cytokines in blood. We demonstrated for the first time that a physical training program (treadmill run for rat), led to a decrease in concentration of IL-1β in the hippocampus, IL-6 in the cerebellum and IL-1ra in the pituitary. We also noted significant positive correlations between *(i)* serum prolactin and the concentration of IL-6 in the cerebellum, *(ii)* serum leptin and the concentration of IL-1ra in the pituitary. Moreover, our training program did not modify circulating cytokines, confirming our previous results and those of other groups: circulating cytokines increased transiently after prolonged endurance exercise and then returned to basal levels [11]; endurance training did not change basal cytokine levels [12]. Thus, the exercise effects that we found on circulating and brain cytokines were likely due to specific, exercise training effects.

Il-1β is a proinflammatory cytokine, which exerts a wide range of effects in the central nervous system. This cytokine is expressed in the hippocampus, and increases with age [21]. This distribution is reflected by the fact that many of the actions of IL-1β rely on the integrity of these brain areas. Several neurodegenerative disorders are accompanied by an increase in brain IL-1β concentrations [22]. Brain IL-1β has a negative impact on synaptic plasticity [17] and therefore an increased concentration of IL-1β, such as that in the hippocampus of aged rats, has been shown to be associated with a deficit in long-term potentiation (LTP). The positive effects of physical activity on many physiological systems, including the central nervous system, are well established. For example, exercise-induced improvements in learning and memory have been directly associated with improved neurogenesis, an increase in activity-dependent, synaptic plasticity and altered gene expression [23]. Many of these improvements have been observed in the hippocampus, a highly plastic structure located in the medial temporal region of brain that is vital to activity-dependent learning and memory [24]. We observed here that a training program (treadmill running over seven weeks) reduced the IL-1β concentration in the rat hippocampus. This result suggests that the decrease in IL-1β in the hippocampus induced by an exercise program may have contributed to the positive effect of physical activity on the CNS. We hypothesize that the decrease in the IL-1β content of the hippocampus induced by physical training may limit or suppress the interference with BDNF neuroprotection. Indeed, it has been showed,

Table 1
Hormones concentrations in serum from the two groups of rats

	Corticosterone (ng/mL)	Prolactin (ng/mL)	Leptin (ng/mL)
Sedentary rats	144.2 + 31.4	15.02 + 1.98	1.60 + 0.49
Trained rats	98.5 + 19.7	25.52 + 3.04**	0.33 + 0.13**

Mean + SE, n = 10; ** $p < 0.01$: trained *versus* sedentary rats.

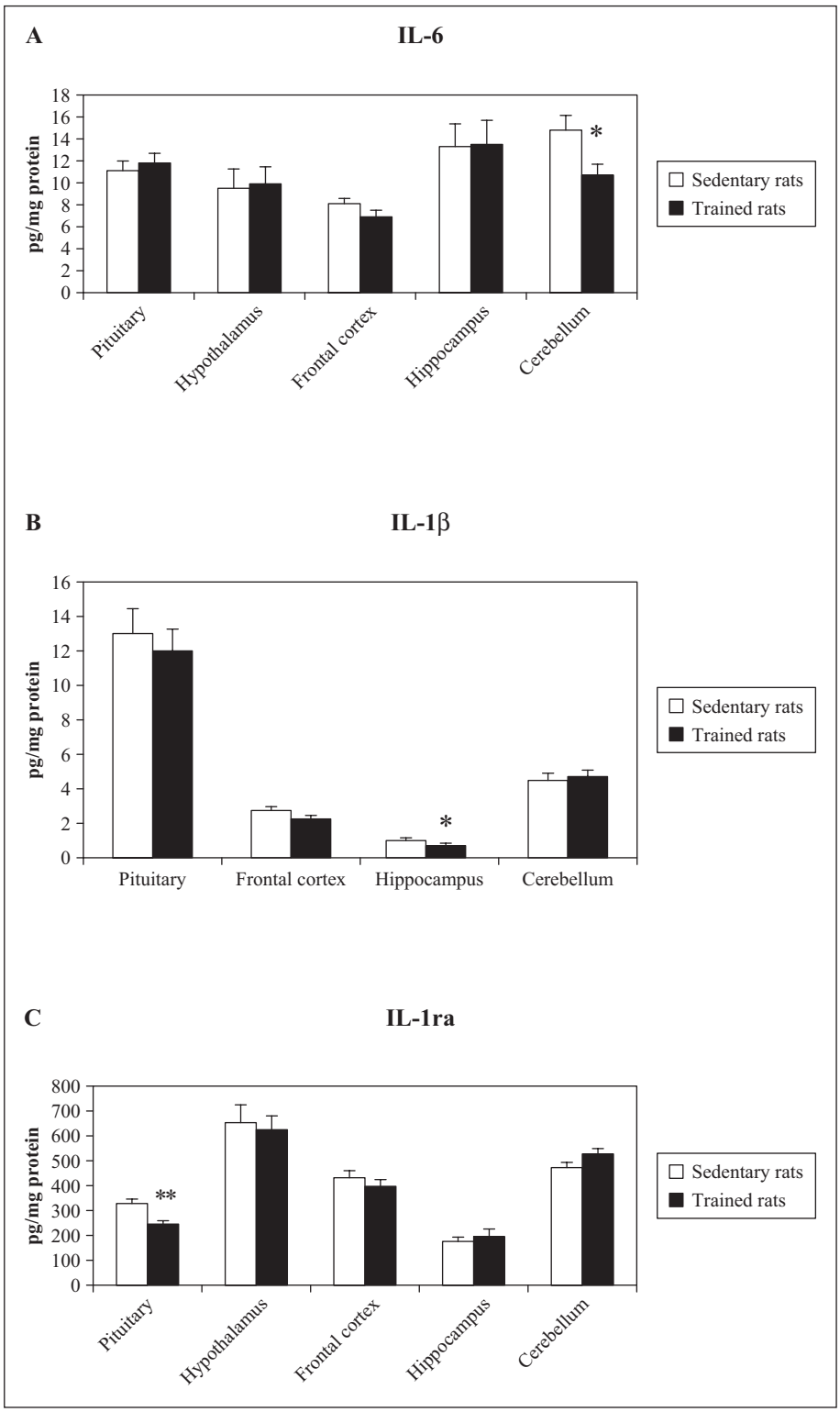

Figure 1

Cytokine concentrations in different brain areas in sedentary (□) and trained (■) rats. **A**) Interleukin-6 (IL-6); **B**) interleukin-1beta (IL-1β); **C**) interleukin 1 receptor antagonist (IL-1ra). Levels are expressed as pg of cytokine per mg of total of protein.
Mean ± SE, n = 10; *$p < 0.05$: trained *versus* sedentary rats; **$p < 0.01$: trained *versus* sedentary rats.

on one hand, that exercise increased BDNF, a neuroprotective factor [8], and on the other hand, that IL-1β impaired BDNF function [10].

Interleukin-6, is one of a number of cytokines known to be an important mediator of inflammation and immune responses [25]. IL-6 in the CNS originates not only from the immune system but also *via* endogenous production by brain cells, the hippocampus, the habenular nucleus, the dorsomedial and ventromedial hypothalamus, the cerebral cortex, and Purkinje and granular cells in the cerebellum [26]. Dysregulation of IL-6 production in the brain is associated with a number of neurological diseases, and chronic exposure to increased amounts of IL-6 may contribute to the neuropathological and pathophysiological

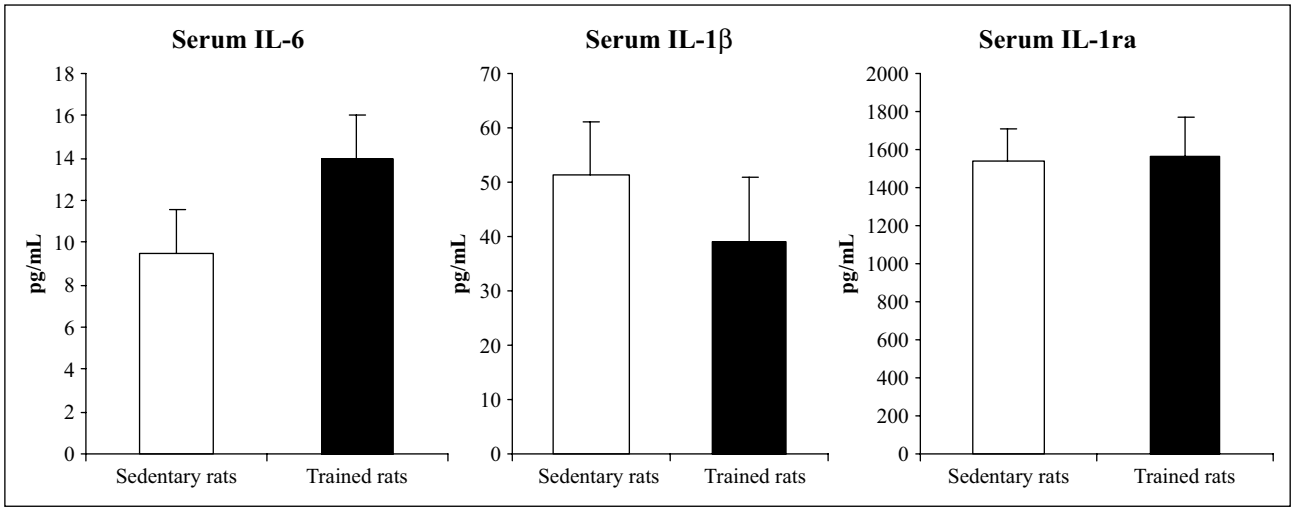

Figure 2
Cytokine concentrations in serum from sedentary (□) and trained (■) rats.
Mean ± SE, n = 10.

sequelae of these disorders [16, 27, 28]. Nelson *et al.* demonstrated that chronic exposure to elevated levels of IL-6 can alter important aspects of CNS neuronal physiology [18]. Such IL-6-induced neurophysiological changes could well contribute to deficits in overall CNS function, as evidenced by the decline in cognitive and motor skills of GFAP-IL-6 mice [29]. In addition, changes in the physiology of cultured Purkinje neurons occurred in the absence of any gross structural abnormalities of these neurons, suggesting that IL-6, and perhaps other cytokines such as IL-1β, can exert regulatory effects on CNS function during conditions of neuroinflammation or infection that precede or are independent of, neuronal damage or death.

In the present study, we noted that the training program only reduced the IL-6 concentration in the cerebellum, the brain area of motor learning. As for brain IL-1β, this result suggests that the decrease in cerebellar IL-6 induced by training could contribute to the positive effect of physical activity on the CNS. Moreover, we observed a significant correlation between serum prolactin and the concentration of IL-6 in the cerebellum. Deb *et al.* have shown that prolactin reduced the level of IL-6 and mRNA expression of IL-6 receptor [30]. In parallel, Motta *et al.* have demonstrated that prolactin enhanced the cytokine signalling 1 (SOCS-1) gene expression [31], the negative regulator of many cytokines [32]. In view of these considerations, prolactin may have been involved directly or indirectly in the decreased IL-6 concentration we found in the cerebellum.

The natural IL-1 receptor antagonist (IL-1ra) is an anti-inflammatory cytokine that binds to IL-1 receptors without inducing a cellular response, thereby antagonizing the effects of IL-1β and IL-1α [33]. It is mainly expressed by activated monocytes and macrophages [34]. By competitively binding to IL-1 receptors, it neutralizes the biological action of IL-1 during endoxemia and inflammatory processes [35]. IL-1ra mRNA has been detected in several regions of the rat [36] and mouse brain [37], but was found to be very low in the cortex and hippocampus. These observations indicate that IL-1ra mRNA is constitutively expressed in normal brain. Pro-inflammatory cytokines contribute to neuronal inflammation and cell death induced by ischemia, excitotoxicity, or trauma, while administration of IL-1ra reduces neuronal injury [38], and inhibits the detrimental effects of heat stroke and epilepsy [39, 40]. IL-1ra protects striatal as well as cortical tissue in focal cerebral ischemia (middle cerebral artery occlusion) [40]. It also reduces edema, inhibits glial activation, and improves neurological function [41]. More particularly, the production of IL-1ra within the anterior pituitary may act as a protective mechanism, modulating the sensitivity of pituitary cells to circulating or intrinsically produced IL-1 during inflammatory or tumoral processes [42].

Physical training induced a decrease in IL-1ra concentration in the pituitary gland of our rats, so the beneficial effects of physical training on the brain may be limited. However, we noted a tendency for an increase in IL-1ra concentration in both the cerebellum and hippocampus, the two brain areas where we observed a decrease in the content of two, central, pro-inflammatory cytokines, IL-6 and IL-1β. The decrease in IL-1ra content in the pituitary could be explained by the fact that the marked decrease in circulating leptin (the adipocyte-derived hormone) concentration observed after the training program may have reduced IL-1ra expression. Indeed, the correlation observed between IL-1ra and leptin concentrations in the pituitary gland indicated that an endocrine and/or paracrine mechanism might be involved directly or indirectly. Leptin, which plays a crucial role in regulating energy balance [43], plays a role in the inflammatory response [44] mainly *via* interactions in the brain [45]. Its receptors have been found in various brain regions including the cortex, cerebellum, brain stem, basal ganglia and hippocampus. Many studies have implicated leptin in anterior pituitary function [46]. Hosoi *et al.* suggested that leptin increased IL-1ra expression in the hypothalamus, mediated *via* STAT 3-independent mechanisms [47].

In summary, our study showed, for the first time, that seven weeks of physical training altered the brain content of pro- and anti-inflammatory cytokines. This may account, in part, for the beneficial health effects of physical activity and exercise by preventing or reducing the deleterious effects of pathological conditions. In particular, we noted a reduction in central, pro-inflammatory cytokine responses in both the hippocampus and cerebellum, regions involved in common neurological disorders. Further studies are

warranted to determine interactions between cytokines and neurotrophic factors during exercise training.

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