Acetylsalicylic acid inhibits the pituitary response to exercise-related stress in humans

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ABSTRACT

DI LUIGI, L., L. GUIDETTI, F. ROMANELLI, C. BALDARI, and D. CONTE. Acetylsalicylic acid inhibits the pituitary response to exercise-related stress in humans. *Med. Sci. Sports Exerc.*, Vol. 33, No. 12, 2001, pp. 2029–2035. **Purpose:** Prostaglandins (PGs) modulate the activity of the hypothalamus-pituitary axis, and pituitary hormones are largely involved in the physiological responses to exercise. The purpose of this study was to analyze the effects of acetylsalicylic acid (ASA), an inhibitor of PGs synthesis, in the pituitary responses to physical stress in humans. **Methods:** Adrenocorticotropin (ACTH), β-endorphin, cortisol, growth hormone (GH), and prolactin (PRL) responses to exercise were evaluated after administration of either placebo or ASA. Blood samples for hormone evaluations before (−30, −15, and 0 pre) and after (0 post, +15, +30, +45, +60, and +90 min) a 30-min treadmill exercise (75% of $\dot{V}O_{2max}$) were taken from 12 male athletes during two exercise trials. One tablet of ASA (800 mg), or placebo, was administered two times daily for 3 d before and on the morning of each exercise-test. **Results:** The results clearly show that, compared with placebo, ASA ingestion significantly blunted the increased serum ACTH, β-endorphin, cortisol, and GH levels before exercise (anticipatory response) and was associated with reduced cortisol concentrations after exercise. Furthermore, although no differences in the GH response to exercise were shown, a significantly reduced total PRL response to stress condition was observed after ASA. **Conclusion:** ASA influences ACTH, β-endorphin, cortisol, GH, and PRL responses to exercise-related stress in humans (preexercise activation/exercise-linked response). Even though it is not possible to exclude direct action for ASA, our data indirectly confirm a role of PGs in these responses. We have to further evaluate the nature of the preexercise endocrine activation and, because of the large use of anti-inflammatory drugs in athletes, whether the interaction between ASA and hormones might positively or negatively influence health status, performance, and/or recovery. **Key Words:** ADRENOCORTICOTROPIN, β-ENDORPHIN, CORTISOL, EXERCISE, GROWTH HORMONE, PROLACTIN, PROSTAGLANDINS

Arachidonic acid (AA) and its metabolites play an important role in the secretory processes of many endocrine tissues. AA is stored in plasma membrane phospholipids and can be released after agonist-induced stimulation of phosphatidylinositol turnover. Upon release, AA undergoes metabolization through cyclooxygenase, lipoxygenase, and epoxygenase pathways leading to the formation of 1) prostaglandins (PGs) and thromboxanes, 2) hydroxyeicosatetraenoic acids (HETEs) and leukotrienes (LTs), and 3) epoxyeicosatrienoic acids (EETs), respectively.

It is well documented that PGs and other arachidonate metabolites, collectively known as eicosanoids, modulate the secretory activity of the hypothalamus-pituitary axis. Different studies in humans and in animals showed that the secretion of adrenocorticotropin (ACTH) (3,16,20,30), β-endorphin (27), growth hormone (GH) (19), gonadotropins (FSH and LH) (8,9,21), prolactin (PRL) (8,18,21), and thyrotropin (TSH) (29) are influenced by eicosanoids. Furthermore, although it is well known that some pituitary hormones (i.e., ACTH, GH, PRL, etc.) are involved in the physiological responses to physical exercise (for review see 11), few data are available on the possible involvement of AA metabolites in the hormonal responses to exercise (28).

Therefore, from a physiological point of view, it is of interest to verify the involvement of eicosanoids, particularly cyclooxygenate compounds such as PGs, in the regulation of the hormonal responses to physical stress, considering also the widespread use of inhibitors of PGs synthesis, such as nonsteroidal antiinflammatory drugs (NSAIDs), by competitive athletes and recreational exercisers. In particular, the aim of the present investigation was to analyze the effect of acetylsalicylic acid (ASA), and indirectly the role of PGs, on the hypothalamus-pituitary response to short-term physical exercise in healthy trained humans. To our knowledge, this is the first report on the effects of ASA on the pituitary responses to physical exercise in humans.

MATERIALS AND METHODS

Experimental design. We evaluated, in trained male volunteers, morning β-endorphin, GH, PRL, and ACTH-cortisol axis responses to the same acute physical exercise after a short-term treatment with placebo or ASA, an inhibitor of the cyclooxygenase pathway of AA metabolism. To verify

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the efficacy of ASA, as prostaglandin-blocker at the doses and times used in the experimental protocol, and the compliance of our volunteers to the therapy, seminal PGE_2 levels were also determined before and after treatments.

Subjects. Twelve healthy male Caucasian trained volunteers, soccer players (from 5 to 6 yr) and training at least 4 $d \cdot wk^{-1}$(3–4 $h \cdot d^{-1}$) over the last year, participated in the study. The subjects had the following baseline characteristics (mean ± SE): chronological age of 20.2 ± 0.1 yr, height 173.2 ± 0.9 cm, weight 68.1 ± 1.3 kg, body mass index (BMI) 21.7 ± 0.3, and $\dot{V}O_{2max}$ 63 ± 1 $mL \cdot kg^{-1} \cdot min^{-1}$. All the subjects were recruited from the University Institute of Motor Sciences (IUSM) of Rome. The experimental protocol was approved by the Institutional Ethical and Scientific Committee. The nature of the study was explained to each subject in detail, and written informed consent was obtained.

A preliminary screening assessment was designed to detect risk factors that might contraindicate participation in the study. All the subjects were in good health and were not taking medication, amino acids (12), or other drugs, including anabolic-doping agents that could influence the experimental protocol. None of the subjects was a smoker. A preinclusion resting hormonal evaluation (ACTH, cortisol, FSH, LH, PRL, testosterone, FT3, FT4, TSH, GH, and IGF-I) was normal in all subjects. Routine biochemical and hematological analyses were also in the normal ranges.

One week before starting the exercise trials, all training was stopped and the subjects underwent an incremental exercise test until exhaustion on a treadmill to evaluate individual maximal aerobic power ($\dot{V}O_{2max}$). All the subjects were counseled by a nutritionist and had a diet-regimen sufficient for each individual's needs (about 40–42 $kcal \cdot kg^{-1} \cdot d^{-1}$: 50–55% carbohydrates, 15–20% proteins, and about 30% lipids). This diet regimen started 2 wk before the experimental phases and was maintained throughout the study. The subjects were counseled weekly and their food records reviewed to maintain the correct diet throughout the study.

Trials protocol. In the first experimental session, each subject randomly performed an acute exercise test after the administration of ASA (ASA trial) or placebo (placebo trial) in a double-blind, cross-over method. After a washout period of 2 wk, each subject performed a second identical exercise test receiving the other treatment. Therefore, each subject was his own control, receiving both ASA and placebo.

To inhibit PGs production, according to a recent experimental study design (10), ASA was administered in an oral dose of 800 mg (1 tablet of Cemirit, Bayer, Italy) two times daily for 3 d before and one tablet in the morning (at 07.00 a.m.) of each exercise-test session day. The rationale for 3-d ASA administration is linked to its maximal effect by 48–72 h of treatment. In the placebo trial, one tablet of placebo was administered in exactly the same way as the ASA trial.

The experimental sessions began for all the subjects between 08:30 a.m. and 09:30 a.m., and the environmental conditions were always identical (temperature 20–21°C; humidity 50–65%). The subjects were requested to have breakfast (about the same $kcal \cdot kg^{-1}$ and nutrient composition) at 07:00 a.m. and then to refrain from food throughout the experimental session. They could drink water at will.

The subjects exercised on a motor-driven treadmill (2.5% slope) and were monitored by spirometry (K2-COSMED, Rome, Italy), O_2 uptake analyzer, and continuously by ECG. After 4 min of warm-up (at 6 $km \cdot h^{-1}$), the treadmill speed was set at the individual value corresponding to 75% of $\dot{V}O_{2max}$ (as previously evaluated during the incremental test). This speed was then maintained for 30 min. Indications for stopping the test were muscular pain, fatigue, heart rate derangement, and severe ECG abnormalities.

On the day of each exercise session, starting from 1 h before exercise, the subjects were seated in a comfortable armchair. To reduce the effects of acupuncture stress on endocrine system, immediately after sitting, a catheter was introduced into a forearm vein 30 min before starting the first blood collection (60 min before starting exercise) and maintained *in situ* throughout the experiment. Blood collections were performed at −30, −15 min, and immediately before (0 pre) starting the treadmill test, to evaluate the hormonal status both in terms of absolute values at different time points (resting rhythm) and the resting area under curves (AUCs), at the end of the exercise (0 post), and during the recovery phase (+15, +30, +45, +60, and +90 min).

In all the tests the catheter was flushed with physiological saline to avoid blood clotting after taking each blood sample. The i.v. line was cleared of saline/blood waste. After blood sample collection, the serum was separated and stored at −70°C until it was assayed. All the samples were analyzed for ACTH, β-endorphin, cortisol, GH, and PRL. Blood collections for immediate lactate and hematocrit analysis were performed at the same time points.

Before starting either ASA or placebo treatment and 3 h after the exercise tests, the volunteers were also asked to collect semen specimens by masturbation for seminal PGE_2 measurement. After ejaculation, each semen sample was placed in liquid nitrogen and stored until assayed.

Hormonal assays. PGE_2 was extracted from seminal fluid, as previously described, and measured by RIA (9) (NEN-Du Pont, Wilmington, DE). For seminal PGE_2 the intra- and inter-assay coefficients of variation were 6.4% and 8.2%, respectively.

The hormonal evaluations were performed in duplicate in a single assay. ACTH, β-endorphin, cortisol, GH, and PRL were determined by immunoradiometric assays. The hormone assay kits for ACTH, cortisol, and GH were purchased from CIS (CIS Bio International, Gif-Sur-Yvette Cedex, France), for β-endorphin from Nichols Institute Diagnostic (San Juan Capistrano, CA), and for PRL from ICN Pharmaceuticals (Asse Relegen, Belgium). The intra- and inter-assay coefficients of variation were 2.1% and 5.3% for ACTH, 4.1% and 9% for β-endorphin, 2.6% and 6.5% for cortisol, 2.3% and 3.3% for GH and 8.6% and 9.2% for PRL, respectively. The reference ranges reported for men (20–30 yr) were as follows: ACTH, < 13 $pmol \cdot L^{-1}$; β-en-

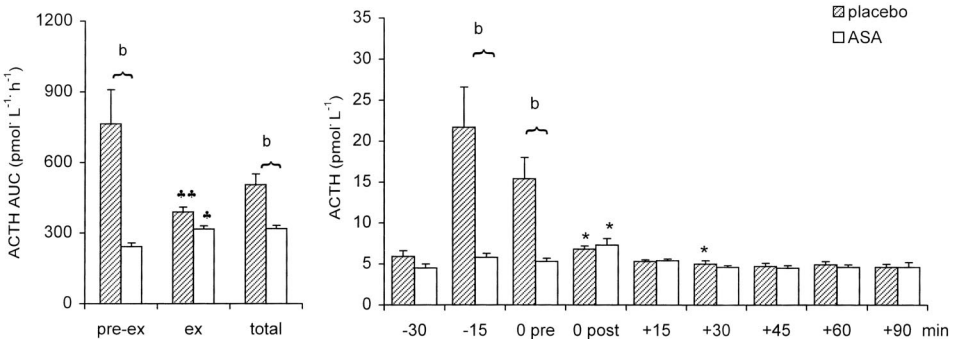

FIGURE 1—ACTH AUCs (mean ± SE), before (pre-ex), during both exercise and recovery (ex) and total (pre-ex plus ex), and ACTH (mean ± SE) absolute responses to 30-min exercise on a treadmill at 75% of $\dot{V}O_{2max}$ in trained male subjects ($N = 12$) after placebo or acetylsalicylic acid (ASA) administration (## $P < 0.01$ vs respective −30 time value; * $P < 0.05$ and ** $P < 0.01$ vs respective 0 pre time value; ♣ $P < 0.05$ and ♣♣ $P < 0.01$ vs pre-ex; b: $P < 0.01$ placebo vs ASA).

dorphin < 138 pmol·L^{-1}; morning cortisol, 154–638 nmol·L^{-1}; GH, 0–10 μg·L^{-1}; and PRL, 60–400 mIU·L^{-1}.

Serum lactate and hematocrit assay. Duplicate evaluations of blood lactate were performed using capillary blood from a prewarmed fingertip. Blood lactate concentration was analyzed using an enzymatic method (YSI lactate analyzer model 23 L, Yellow Springs, OH). The lactate intra- and inter-assay coefficients of variation were 3.0% and 3.7%, respectively, and the sensitivity was 0.6 mmol·L^{-1}. A capillary tube sample of blood was spun at 3000 rpm for 3 min, and the hematocrit was determined in conventional fashion. Percent changes in plasma volume were also estimated using the hematocrit equation (26).

Statistical analysis. The hormonal data are expressed as mean ± SE. Areas under curves (AUCs) were calculated by trapezoidal integration. For each hormone and treatment, total AUCs were calculated from all values (total AUC: from −30 min to + 90 min), the preexercise AUCs from values before exercise (pre-ex-AUC: from −30 to 0 pre), and the exercise-related AUCs from start-exercise to end-recovery values (ex-AUC: from 0 pre to + 90 min). In addition, we calculated for ex-AUCs the percentage of variation (Δ %) with respect to their pre-ex-AUCs. For all hormones, the Δ % was also calculated for each time point values compared to their preexercise values (values at −30 min for preexercise modifications and at 0 pre for exercise-dependent modifications). Furthermore, considering the pre-exercise endocrine activation as a part of the global (psychological and physical) stress-dependent hormonal response to exercise, the statistical evaluation of total AUCs (from −30 to +90 min) and the comparison of all absolute values versus −30 values were also performed by means of paired Student *t*-test between placebo and ASA treatment. Then, a factorial analysis on each dependent variable (i.e., pre-ex-AUCs and ex-AUCs) was performed to study the effect of both pharmacological treatment (placebo or ASA) and exercise condition (preexercise and exercise). For each hormone, a two-way factorial ANOVA with repeated measures, where the first independent variable was placebo or ASA treatment and the second independent variable was the timing with respect to exercise (time points before and after exercise: −30, −15, 0 pre, 0 post, +15, +30, +45, +60, and +90 min), was performed followed by a Duncan *post hoc* test comparison. Differences were considered statistically significant when $P \leq 0.05$.

RESULTS

All the subjects completed all the experimental sessions. None showed side effects during or after treatments or exercise. In the two exercise sessions, the preexercise serum lactate levels were similar in both trials (placebo trial: 1.8 ± 0.03 mmol·L^{-1} and ASA trial: 1.8 ± 0.02 mmol·L^{-1}). During exercise, lactate increased significantly to the same level in both trials (placebo trial: 4.0 ± 0.2 mmol·L^{-1} and ASA trial: 3.9 ± 0.1 mmol·L^{-1}; $P < 0.05$ vs preexercise levels in both trials). No differences in serum lactate concentration or heart rate were found between exercise trials during exercise or recovery. In the two exercise trials, hematocrit and plasma volume did not change during or after exercise, and no differences were found both within each trial and between trials.

The inhibitory action of the ASA treatment on endogenous PGs and the good compliance to ASA ingestion of our volunteers were confirmed by the observed significant reduction of the pretreatment seminal PGE_2 levels (from 84 ± 4 μg·mL^{-1} to 11 ± 3 μg·mL^{-1}, $P < 0.05$). In placebo-treated group, the pretreatment seminal PGE_2 levels were not modified after placebo ingestion (79 ± 5 μg·mL^{-1} and 85 ± 7 μg·mL^{-1}, respectively).

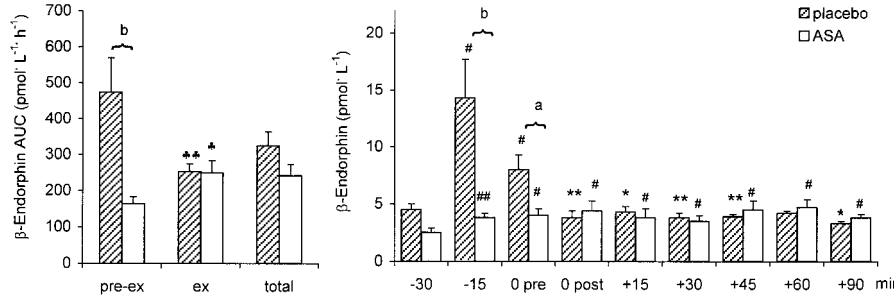

FIGURE 2—β-Endorphin AUCs (mean ± SE), before (pre-ex), during both exercise and recovery (ex) and total (pre-ex plus ex), and β-endorphin (mean ± SE) absolute responses to 30-min exercise on a treadmill at 75% of $\dot{V}O_{2max}$ in trained male subjects ($N = 12$) after placebo or acetylsalicylic acid (ASA) administration (# $P < 0.05$, ## $P < 0.01$ vs respective −30 time value; * $P < 0.05$, ** $P < 0.01$ vs respective 0 pre time value; ♣ $P < 0.05$ and ♣♣ $P < 0.01$ vs pre-ex; a: $P < 0.05$, b: $P < 0.01$, placebo vs ASA).

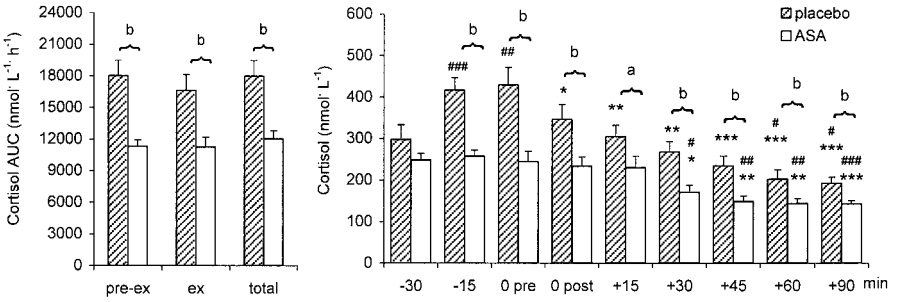

FIGURE 3—Cortisol AUCs (mean ± SE), before (pre-ex), during both exercise and recovery (ex) and total (pre-ex plus ex), and cortisol (mean ± SE) absolute responses to 30-min exercise on a treadmill at 75% of $\dot{V}O_{2max}$ in trained male subjects ($N = 12$) after placebo or acetylsalicylic acid (ASA) administration (# $P < 0.05$, ## $P < 0.01$ and ### $P < 0.001$ vs respective −30 time value; * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ vs respective 0 pre time value; a: $P < 0.05$ and b: $P < 0.01$ placebo vs ASA).

ACTH. (Fig. 1). Regarding ACTH in the placebo trial, both the pre-ex- and the total AUCs (764 ± 145 pmol·L^{-1}·h^{-1} and 505 ± 46 pmol·L^{-1}·h^{-1}, respectively) were significantly higher compared with the respective pre-ex- and total AUCs of the ASA trial (242 ± 16 pmol·L^{-1}·h^{-1} and 318 ± 14 pmol·L^{-1}·h^{-1}, respectively; $P < 0.01$ for both). Furthermore, the ACTH AUC increased significantly (+ 31%; $P < 0.05$) after exercise only in the ASA trial, whereas in the placebo trial a significant decrease after exercise was observed (− 49%; $P < 0.01$).

In the placebo trial, the absolute plasma ACTH concentrations increased significantly 15 min before and immediately before exercise (+ 343% and + 202% vs −30, respectively; $P < 0.01$) and decreased significantly after exercise. In the ASA trial, no modifications of plasma absolute ACTH values were observed before exercise, and a slight but significant increase was observed at end-exercise (+ 55% vs 0 pre, $P < 0.05$). The comparison between trials showed significantly higher plasma ACTH levels in the placebo group 15 min and immediately before exercise.

β-endorphin. (Fig. 2). For β-endorphin in the placebo trial, the pre-ex-AUC was significantly higher than in the ASA trial (474 ± 96 pmol·L^{-1}·h^{-1} and 164 ± 19 pmol·L^{-1}·h^{-1} respectively, $P < 0.01$), whereas no differences were observed between the placebo and the ASA trial for ex-AUCs (253 ± 22 pmol·L^{-1}·h^{-1}and 250 ± 34 pmol·L^{-1}·h^{-1}, respectively) or for total AUCs (325 ± 38 pmol·L^{-1}·h^{-1} and 242 ± 31 pmol·L^{-1}·h^{-1}, respectively) The β-endorphin AUC increased significantly (+52%; $P < 0.05$) after exercise in the ASA trial, whereas in the placebo trial a significant decrease after exercise was observed (−47%; $P < 0.01$).

In the placebo trial, the absolute plasma β-endorphin concentrations increased significantly fifteen min before and immediately before exercise (+ 246% and + 95%, respectively, vs −30; $P < 0.05$) and decreased significantly after exercise (vs 0 pre). In the ASA trial, significantly higher β-endorphin concentrations compared to −30 values were observed from 15 min before exercise to end recovery. The comparison between trials showed significantly higher plasma β-endorphin levels in the placebo group 15 min before and immediately before exercise.

Cortisol. (Fig. 3). In the placebo trial, the cortisol pre-ex-, ex-, and total AUCs (18,013 ± 1497 nmol·L^{-1}·h^{-1}, 16,615 ± 1518 nmol·L^{-1}·h^{-1} and 17,963 ± 1503 nmol·L^{-1}·h^{-1}, respectively) were significantly higher compared with the respective AUCs of the ASA trial (11,303 ± 637 nmol·L^{-1}·h^{-1}, 11,233 ± 938 nmol·L^{-1}·h^{-1} and 12,004 ± 787 nmol·L^{-1}·h^{-1}, respectively; $P < 0.01$). In both trials, no modifications of cortisol AUCs were observed after exercise.

In the placebo-treated subjects, the absolute plasma cortisol concentrations increased significantly 15 min before and immediately before exercise (+ 56% and + 65% vs −30; $P < 0.001$ and $P < 0.01$, respectively), then decreased significantly after exercise compared with the maximum preexercise values. In the ASA trial, a significant decrease of plasma cortisol concentration was observed during the recovery phase (from +30 to +90 min vs 0 pre and vs −30). The comparison between trials showed significantly higher plasma cortisol levels in the placebo trial at all time points, from fifteen min before starting exercise to the end-recovery.

GH. (Fig. 4). In the placebo trial, the GH pre-ex-AUC was significantly higher compared with the respective AUC in the ASA trial (343 ± 116 μg·L^{-1}·h^{-1} and 118 ± 47 μg·L^{-1}·h^{-1}, respectively; $P < 0.01$). The GH AUC increased significantly after exercise both in the placebo and in the ASA trial (+ 1219% and + 5750%; $P < 0.05$ and $P < 0.01$ respectively). No differences were observed between the placebo and the ASA trial for the GH ex-AUC (908 ± 318 μg·L^{-1}·h^{-1} and 838 ± 207 μg·L^{-1}·h^{-1}, respectively) or for the GH total AUC (803 ± 280 μg·L^{-1}·h^{-1} and 696 ± 175 μg·L^{-1}·h^{-1}, respectively).

In the placebo-treated subjects, the absolute GH serum concentrations increased significantly from 15 min before exercise reaching the maximum at the end of exercise. In the ASA trial, serum GH started to increase significantly immediately before exercise and reached the maximum significant value immediately after exercise. During recovery, the serum GH concentrations decreased progressively in both trials. The comparison between trials showed significantly higher serum GH levels in the placebo trial 15 min before and immediately before starting exercise, whereas no differences between trials were observed in the serum absolute GH responses to exercise.

PRL. (Fig. 5). No differences for the PRL pre-ex-AUC were observed between the placebo and the ASA trial (7112 ± 689 mIU·L^{-1}·h^{-1} and 6124 ± 653 mIU·L^{-1}·h^{-1}, respectively.). The PRL AUC increased significantly after exercise both in the placebo and in the ASA trial (+34% and +40%; $P < 0.05$ and $P < 0.01$, respectively), and no differences were observed in the PRL ex-AUC between trials (9508 ± 1105 mIU·L^{-1}·h^{-1} and 8613 ± 954 mIU·L^{-1}·h^{-1}, respec-

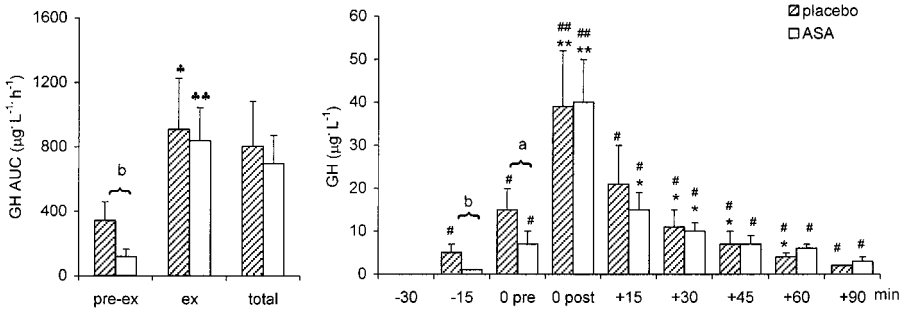

FIGURE 4—GH AUCs (mean ± SE), before (pre-ex), during both exercise and recovery (ex) and total (pre-ex plus ex), and GH (mean ± SE) absolute responses to 30-min exercise on a treadmill at 75% of $\dot{V}O_{2max}$ in trained male subjects ($N = 12$) after placebo or acetylsalicylic acid (ASA) administration (# $P < 0.05$ and ## $P < 0.01$ vs respective −30 time value; * $P < 0.05$ and ** $P < 0.01$ vs respective 0 pre time value; ♣ $P < 0.05$ and ♣♣ $P < 0.01$ vs pre-ex; a: $P < 0.05$ and b: $P < 0.01$ placebo vs ASA).

tively). However, the PRL total AUC was significantly lower in the ASA trial (8538 ± 933 mIU·L^{-1}·h^{-1} vs 9843 ± 1013 mIU·L^{-1}·h^{-1} of the placebo trial, −14%; $P < 0.05$).

Immediately before exercise a slight but significant reduction of PRL was observed in the ASA trial (−9%; $P < 0.05$ vs 30). The absolute PRL serum concentrations increased significantly after exercise in the placebo trial (+ 41% at 0 post vs −30) and in the ASA trial (+ 27% and + 14% at 0 post and at + 15 respectively vs −30; + 40% and + 25% at 0 post and at + 15 respectively vs 0 pre). The comparison between trials showed a significantly higher serum PRL concentration in placebo-treated subjects immediately after exercise ($P < 0.05$).

DISCUSSION

First of all, our data indicated that ASA treatment was effective as cyclooxygenase inhibitor because it significantly decreased seminal PGE_2 levels. The results obtained clearly show that short-term ASA administration is able to modify the pituitary response to physical exercise-related stress in humans. Indeed, serum ACTH, β-endorphin, cortisol, GH, and PRL concentrations were influenced by ASA both at rest (preexercise) and after exercise. It is of particular interest that ASA ingestion blunted the observed ACTH, β-endorphin, cortisol, and GH anticipatory responses to exercise and was associated with reduced mean serum cortisol concentrations after exercise. Furthermore, although no differences in the GH response to exercise were shown between the placebo and the ASA trial, a reduced total PRL response to the stress condition (preexercise activation plus exercise-related response) was observed in ASA treated athletes.

In the placebo trial, we observed an evident anticipatory response of ACTH, β-endorphin, cortisol, and GH, which increased significantly in blood 15 min before and immediately before exercise. Furthermore, in the same trial, a significant exercise-related increase of blood PRL and GH serum concentrations and a significant decrease of ACTH and cortisol levels after exercise were also observed. Whereas the hormonal responses to exercise in the placebo trial are in agreement with previous reports and are widely discussed elsewhere (11), the observed preexercise hormonal modifications represent a relatively unknown topic. To reduce as much as possible all confounding factors, we tried to optimize the experimental conditions and no stressful noise or other physical/psychological stress, unrelated to the experimental conditions, were apparently present. We do not know if a late onset hormonal response to the acupuncture stress was present. However, an endocrine anticipatory response to a stress condition may be hypothesized, even if it has not been so frequently observed in the literature (15,23,24). This hormonal anticipation to a stress condition, if further confirmed, probably reflects a particular ability of trained athletes to protect homeostasis, during a predetermined stress situation, also through a "preactivation" of the neuroendocrine axis modulating the physiological (physical and behavioral) adaptation to physical stress. These endocrine anticipatory responses are mediated by unknown complex processes influencing psycho-neuro-endocrine pathways and are probably related to all the different factors involved in the physiological adaptation to physical stress (genetic factors, physical and psychological training, etc.).

In the present experiment, we indirectly evaluated the role of the AA metabolites, i.e., PGs, on the pituitary responses to exercise by inhibiting their production with ASA. Our results indirectly support the idea of an involvement of PGs pathways in the control of endocrine responses to exercise-related stress in humans.

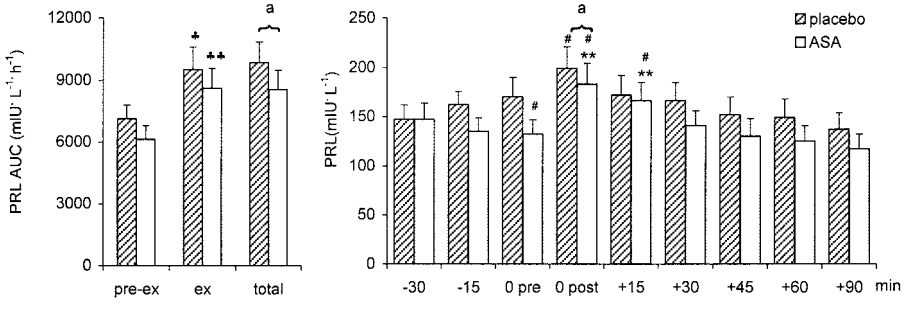

FIGURE 5—PRL AUCs (mean ± SE), before (pre-ex), during both exercise and recovery (ex) and total (pre-ex plus ex), and PRL (mean ± SE) absolute responses to 30-min exercise on a treadmill at 75% of $\dot{V}O_{2max}$ in trained male subjects ($N = 12$) after placebo or acetylsalicylic acid (ASA) administration (# $P < 0.05$ vs respective −30 time value; ** $P < 0.01$ vs respective 0 pre time value; ♣ $P < 0.05$ and ♣♣ $P < 0.01$ vs pre-ex; a: $P < 0.05$ placebo vs ASA).

A possible involvement of PGE_2 in the development of the ACTH response to swimming exercise has been observed in rats (28). In these animals, an intravenous injection of indomethacin significantly suppressed the ACTH response to exercise. PGs may influence ACTH secretion by stimulating or inhibiting the hypothalamus-pituitary-adrenal axis (HPA) at different levels. For example, PGE_2 positively modulates CRH-induced ACTH secretion, probably increasing the sensitivity of corticotrophs to CRH (30). Male subjects treated with ASA had a blunted HPA response, in terms of cortisol response to the pituitary corticotroph stimulator arginine vasopressin (AVP), whereas no significant modification of the ACTH response was observed (20). In healthy humans, ASA augmented the ACTH response to naloxone, which increases endogenous CRH release and did not influence the cortisol response to ACTH (16), whereas, paradoxically, in patients with myotonic dystrophy acetylsalicylic acid inhibited the naloxone-induced ACTH secretion (17). Studies in animals showed that PGs enhance hypothalamic CRH release and adrenal steroidogenesis and may restrain ACTH secretion in the pituitary (6). Furthermore, in rats, indomethacin attenuated the ACTH response to lipopolysaccharide, histamine, and nicotine (2,3). As in testicular steroidogenesis (10,22), PGs are directly and indirectly involved in adrenal steroidogenesis, as observed for example when the interleukins-linked HPA axis activity is concerned (25).

In terms of PRL secretion, it has been observed that cyclooxygenase product may modulate the prolactin response to dopamine antagonism. In fact, indomethacin administration blunted the PRL response to metoclopramide (14). Furthermore, diclofenac administration resulted in a significant decrease in the plasma level of PRL (18), whereas no modification of β-endorphin was observed. With regard to GH, it has been shown that ASA treatment reduces the GH response to both hypoglycemia and arginine, without influencing the basal serum GH concentration (5,7). PGE_2 is also involved in the GHRH-induced GH secretion, as observed using cyclooxygenase inhibitors (ASA or indomethacin), which inhibit GH release (13).

Previous reports clearly show that PGs are able to modulate the secretory activity of the hypothalamus-pituitary axis. However, much remains to be learned about their specific role in modulating the activity of the human hypothalamic-pituitary axis before, during, and after physical stress. We observed the inhibitory activity of ASA on the ACTH, β-endorphin, cortisol GH, and PRL responses to stress, indirectly confirming a possible stimulatory role of PGs on the endocrine pathways regulating the hormonal responses to experimental stress. Furthermore, the lack of ASA effects on the GH response to exercise might suggest the possible existence of at least two different GH pathways regulating both the preexercise and the exercise-dependent hormone secretion. On the basis of the present experiment, PGs would probably be mainly involved in the first pathway. This may be due to the possible relative role of GHRH and somatostatin in modulating the GH response to different types of stress.

In conclusion, we can state that ASA administration is able to influence the physiological ACTH, β-endorphin, cortisol, GH, and PRL responses to exercise-test-related stress. Even though it is not possible to exclude that prostaglandin inhibition may be of different amount in tissues directly influenced by physical stress than in the seminal fluid and to rule out other mechanisms of action for ASA at neuroendocrine and/or at peripheral levels, as for example the inhibition of nitric oxide synthase (1), our data suggest a PGs involvement in the neuroendocrine responses to stress. The contribution of PGs to stress-induced responses has not been established. However, the possible involvement of endogenous pyrogen-like substances in the induction of PGs during stressful conditions has been hypothesized (4).

In the future, we should study all the possible interactions between drug administration and physiological responses (hormonal and nonhormonal) to different types of stress (physical and/or psychological). In particular, on the basis of the present results, we can hypothesize that other NSAIDs might modify the physiological pituitary responses to exercise in athletes. Furthermore, at this moment, it is difficult to say whether the interaction between ASA and the endocrine responses to exercise might positively or negatively influence health status, performance, and/or recovery in athletes. Further studies are needed using different doses and types of NSAIDs in different exercise-types, training situations, and, in particular, in competition conditions.

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