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ORIGINAL ARTICLE

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The influence of aspirin on exercise-induced changes in adrenocorticotrophic hormone (ACTH), cortisol and aldosterone (ALD) concentrations

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Abstract The influence of aspirin (ASA) on the endocrinology system and prostaglandin (PGs) synthesis is not completely clear. The aim of the study was to estimate the influence of ASA on the changes in the concentration of ACTH, cortisol and aldosterone (ALD) induced by physical exercise. This study was conducted on 19 healthy students (age 21–23 years). They were subjected to intensive physical exercise on a cycle ergometer. On the day prior to the experiment, 12 subjects took two 0.5-g doses of ASA in a wafer, and another 0.5 g 3–4 h before the test on the day of the investigation (ASA group). The remaining seven subjects (control group) received placebo. Hematocrit, lactate concentration and concentrations of ACTH, cortisol and ALD were determined before exercise, after exercise, and after 30 min of recovery, in a blood sample taken from a cubital vein. Before exercise, the degree of platelet aggregation in response to arachidonic acid was estimated, in order to confirm the correct allocation to the two groups. Aggregation should only occur in the ASA group. ASA and control groups exercised for 30.3 (3.1) min and 30.2 (1.6) min, respectively. Maximal heart rate and lactate concentration were similar in both groups, as were the basal concentrations of ACTH and cortisol; the ALD concentration seemed lower in the ASA group, but the difference was not significant ($p < 0.1$). In both groups after exercise ACTH, cortisol and ALD concentrations were significantly increased, however when compared to the control group, the increase of ACTH in the ASA group was significantly higher, and ALD increase significantly lower. After recovery there was a significant decrease in ACTH concentration, whereas the concentrations of ALD and cortisol did not change. The concentrations of cortisol in both groups after exercise and recovery were similar. That is most likely because the ACTH concentrations in the ASA and control groups were sufficient for almost maximal cortisol secretion. It is proposed that ASA administration caused prostaglandin synthesis to decrease, and that this led to a lower basal concentration of ALD and a significantly lower level of ALD after exercise.

Keywords ACTH · Aldosterone · Aspirin · Cortisol · Physical exercise

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Introduction

Physical exercise and aspirin (ASA) treatment are currently used generally in the prevention, treatment and rehabilitation of ischemic heart disease. The favourable activity of ASA is caused by the inhibition of platelet cyclooxygenase (COX), which diminishes thromboxane A_2 (TXA_2) synthesis from arachidonic acid (AA) in platelets, decreases their aggregation and adhesion, and diminishes the ability of blood to coagulate. The inhibition of COX by ASA and other non-steroidal anti-inflammatory drugs (NSAIDs) in endothelial and a variety of tissues may decrease the synthesis of endogenic prostaglandins (PGs). PGs modulate the secretion of many hormones, and administration of ASA may change this action (Metz 1981; Smith 1992; Roth and Caverly1994; Marnett et al. 1999).

Despite the fact that ASA is now the most frequently used drug in the world (Fuster et al. 1993), its

influence on the endocrinology system is not completely clear. Most investigations have been carried out on humans, after stimulation of the hypothalamic–pituitary–adrenal (HPA) axis and the renin–angiotensin–aldosterone (RAA) system by hypoglycaemic states (Berine and Jubiz 1978; Cavagnini et al. 1979; Halter and Metz 1982), or the administration of certain drugs and hormones (Norbiato et al. 1978; Franco- Saenz et al. 1980; Zacharieva et al. 1992; Hockings et al. 1993; Nye et al. 1997). It has been shown that COX inhibitors such as indomethacin (INDO), ASA and sodium salicylate may influence the hypoglycemia-induced release of several hormones. Contradictory results have often been obtained, and it should be noted that the ASA doses were about twice those generally applied in medical care, and much greater than those recommended in the prevention of ischemic heart disease. Reports concerning the influence of NSAIDs on hormonal changes caused by exercise in humans are limited to two reports of the effects of INDO (Staessen et al. 1984; Mittelman and Zambraski 1992). As yet no-one has looked at the effect of medicinal doses of ASA on the hormonal changes caused by exercise of varied intensity and duration.

This problem acquires a special significance in connection with reports that ASA may have counter-regulatory effects compared to angiotensin-converting enzyme (ACE) inhibitors in patients treated for cardiovascular disease (Guazzi et al 1999; Harjai et al 2001).

In a previous study (Przybyłowski et al. 1999), we showed that oral administration of 0.5 g ASA about 30 h before an intensive short-term bout of exercise diminishes the exercise-induced increase in aldosterone (ALD) concentration and causes a tendency to lower the cortisol concentration. In light of this, it was thought interesting to analyze the effect of increased exercise duration and ASA dose on exercise-induced changes of ACTH, cortisol and ALD concentrations.

Method

Non-smoking males ($n = 21$) recruited from the students of the Physical and Health Education Institute were selected. Subjects did not take any medication for at least 2 weeks before the study, and they did not perform any intensive physical exercise for at least 3 days before the study. All had normal medical histories and physical examination, and the results of their screening test (full blood counts, urinalysis, electrocardiogram and chest Xray) were within normal range. The study protocol was approved by the local ethics committee and all subjects provided written consent prior to their participation in the study.

The subjects were randomly divided into two groups:

I ASA group: 12 subjects. All received 0.5 g ASA orally twice on the day before the test (at 8:00 hours after breakfast and at 18:00 hours after an evening meal), and 0.5 g on the day of the test, 3–4 h before the exercise. ASA was given in a wafer.

II Control group: nine subjects received placebo at the times outlined for group I, in an identical wafer.

There were two league team competitors in the ASA group (a volleyball and a football player). The others practised various sport disciplines for recreation. Therefore, it was assumed that their physical efficiency topped the average level for young males of the same age.

Protocol

The subjects performed a graded exercise test on a bicycle ergometer until exhaustion in the afternoon (between 16:00 and 18:00 hours). After 10 min of warm-up at 10 W, the initial workload of 30 W was increased every 4 min by 30 W until exhaustion. Heart rate was recorded every 1 min from 12 electrocardiographic leads and blood pressure was measured every 4 min using a mercury manometer.

Two subjects of the control group did not complete the test: one on account of 'flu symptoms was not admitted to the test; the other subject had to interrupt the test when numerous ventricular extrasystole events occurred during effort. In consequence, the control group was reduced to seven persons.

Blood was drawn from a cubital vein three times: 0 before exercise; 1 about 3 min post exercise; and 2 after 30 min of recovery in the sitting position.

Measurement

Haematocrit was determined using Coulter STKS apparatus manufactured by Beckman Coulter (USA). Changes in plasma volume (PV) were calculated according to Beaumont et al. (1973). Plasma lactate was determined by an enzymatic method using reagents produced by BioMerieux (France). Plasma ACTH was determined by immunoluminometric assay using Lia-mat 300 apparatus and kits from B.R.H.M.S. Diagnostica (Germany). Serum cortisol was analyzed by an immunochemiluminescence method using ASC 180 PLUS apparatus and kits from Bayer (Germany). Plasma ALD was determined by radioimmunoassay using kits produced by CIS Bio international (France).

Platelet aggregation in response to arachidonic acid (AA) is almost completely inhibited by low doses of ASA (Dabaghi et al. 1994). To be sure that subjects were in the correct groups, we determined the degree of platelet aggregation in response to AA (300 μM and 600 μM in blood) taken before exercise according to the method of Spławiński et al. (1984) using the Sysnex F820 apparatus manufactured by Electronic Coba (Japan).

The changes in hormone concentration induced by exercise were corrected each time taking into account PV changes.

Statistical analysis

Results are expressed as mean (SD). Statistical significance was taken as $p < 0.5$. Differential changes were compared using one-way Anova analysis of variance and Student's t-test for paired samples.

Results

Subjects' physical characteristics, exercise parameters and the degree of platelet aggregation in response to AA are represented in Table 1. The time of exercise duration, the workload and maximal heart rate were similar in both groups. A decrease in platelet aggregation in response to AA occurred in each subject of the ASA group, and did not occur in the control group. Mean aggregation values were significantly lower in the ASA group.

Table 1 Physical characteristics, exercise parameters of subjects, and platelet aggregation in response to arachidonic acid (*AA*) in control (*con*) and aspirin (*ASA*) group. Data are given as means (SD)

Parameter	Con ($n=7$)		ASA ($n=12$)	
	Mean	SD	Mean	SD
Age (years)	22.1	(0.9)	22.6	(1.1)
BMI (kg/m^2)	22.2	(2.0)	22.9	(1.4)
Maximal heart rate (beats min^{-1})	193.1	(9.2)	192.2	(6.6)
Duration oftest (min)	32.0	(1.6)	30.9	(3.1)
Maximal work load (W)	244.3	(20.7)	235.0	(25.5)
Platelets aggregation in response to AA				
AA 300 μM**	78.2	(15.0)	3.5	(4.76)
AA 600 μM**	91.6	(4.2)	16.1	(6.5)

Con/ASA $^{**}p<0.001$

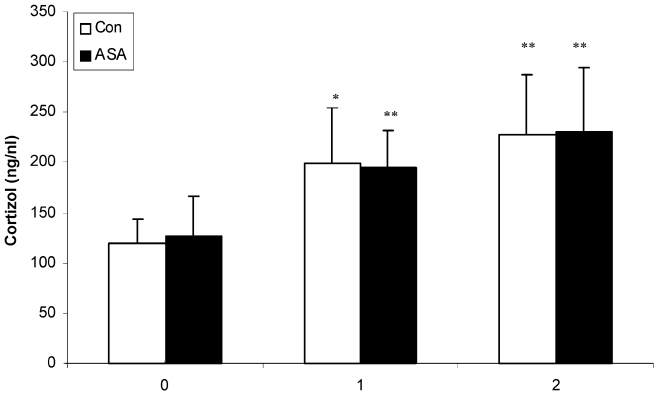

Fig. 2 Cortisol concentration (ng/ml). Values pre-exercise control: 120.1 (23.5); ASA: 126.9 (39.3). 0/1, 0/2 $^{*}p<0.02$, $^{**}p<0.01$

The ACTH concentration after exercise in both groups was significantly higher than the basal level. In the ASA group the ACTH increase was significantly greater in this period compared to the control group. After recovery, the values in the control group were the same as basal, whereas in the ASA group they remained significantly greater (Fig. 1).

The cortisol concentration increased considerably after exercise in both ASA and control groups. After recovery an insignificant increase of cortisol concentration was observed, with similar values in both groups (Fig. 2).

The basal ALD concentration in the ASA group was lower than that in the control group (differences on the border of statistical significance $p<0.1$). ALD concentrations after exercise increased significantly in both groups, although those in the ASA group were significantly lower than those in the control group. After recovery there were no significant changes of ALD concentration in either group (Fig. 3).

The basal lactate concentrations were similar in both groups. After exercise the values significantly increased and after recovery we observed a significant decrease of concentrations (Fig. 4).

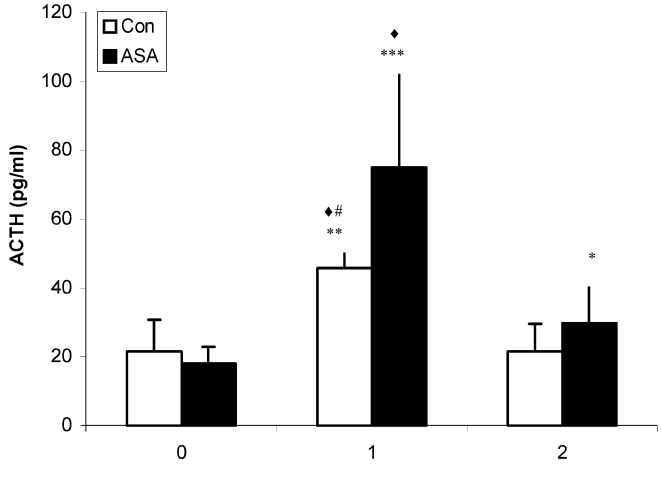

Fig. 1 Adrenocorticotrophic hormone (*ACTH*) concentrations (pg/ml). *0* – pre exercise, *1* – post exercise, *2* – recovery. Data are given as the means (SD). Values pre-exercise control: 21.6 (9.2); ASA: 18.0 (4.8); 0/1, 0/2 $^{*}p<0.02$, $^{**}p<0.01$, $^{***}p<0.001$; 1/2 ♦$p<0.01$; Con1/ASA1 #$p<0.05$

Discussion

ACTH and cortisol

Endogenic PGs can have both a stimulating and a restrictive influence on the secretion of many hormones including ACTH and cortisol. ASA and other NSAIDs, which inhibit the synthesis of PGs by blocking COX, exert opposite effects to PGs (Berine and Jubiz 1978; Cavagnini et al. 1979; Halter and Metz 1982; Hockings et al. 1993).

To help interpret this work, we refer to the results of our preceding work (Przybyłowski et al. 1999). This

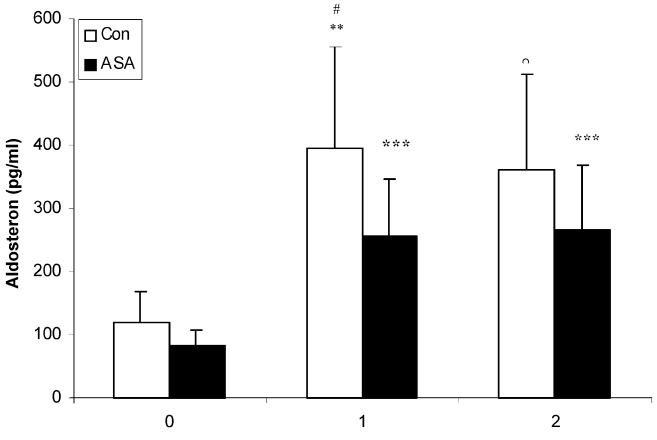

Fig. 3 Aldosterone concentrations (pg/ml). Values pre-exercise control: 118.9 (50.0); ASA: 83.1 (25.0). 0/1, 0/2 °$p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$. Con1/ASA1 #$p<0.05$

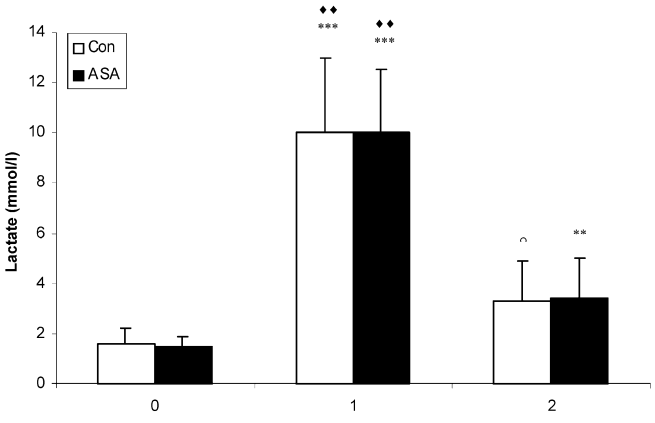

Fig. 4 Lactate concentration (mmol/l). Values pre-exercise control: 1.6 (0.6); ASA: 1.5 (0.4). 0/1, 0/2 °$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; 1/2 ♦♦$p < 0.001$

study showed that administration of 0.5 g ASA about 30 h before exercise (that was more intensive but of shorter duration than in the current study) did not lower basal ALD concentrations, but rather significantly decreased the ALD concentration and insignificantly decreased the cortisol concentration after 30 min of recovery ($p < 0.1$).

The present subjects received 1.0 g ASA on the day before the test and 0.5 g on the day of exercise about 3–4 h before the test. The load was increased every 4 min by 30 W until exhaustion, which, compared to Przybyłowski et al. 1999, was a lower exercise intensity but about twice as long a duration. The determined exercise parameters (exercise duration, maximal heart rate, lactate concentration) were similar in the control and ASA groups.

No effect of PG inhibitors on basal ACTH and cortisol levels was found (Cavagnini et al. 1979; Hockings et al. 1993). The reaction to insulin-induced hypoglycaemia is similar to that caused by intensive physical effort. It results in increased secretion of adrenaline, noradrenaline, corticotrophin-releasing hormone (CRH), arginine vasopressin (AVP), ACTH and cortisol (Viru et al. 1996; Nye et al. 1997). ASA (Cavagnini et al. 1979), INDO (Berine and Jubiz 1978; Cavagnini et al. 1979) and sodium salicylate (Halter and Metz 1982) were used as COX inhibitors. These investigations produced contradictory results.

Administration of 1.0 g ASA to our subjects on the day before exercise and 0.5 g on the day of exercise caused a significant increase in post-exercise ACTH compared to the control group.

Halter and Metz (1982) observed that infusion of sodium salicylate in dose of 40 mg/h for 2 h increased the ACTH and cortisol response to hypoglycaemia. Cavagnini et al. (1979) stated that pre-treatment with INDO in doses of 300 mg daily for 4 days increased the hypoglycaemic ACTH response, delayed it onset, and moderately decreased the cortisol response. Instead, ASA in doses of 3.2 g daily given for 4 days significantly decreased the ACTH response and did not alter the cortisol response. A similar effect of INDO given in small doses for 13 days was observed by Berine and Jubiz (1978). The effect of COX inhibition and the increase or decrease of ACTH secretion depend on the kind of drug given, the magnitude of the dose, the administration route as well as the magnitude and duration of hypoglycaemia (Cavaginini et al. 1979).

The effect of PGs inhibitors also depends on the prevailing functional state of the HPA axis (Nye et al. 1997). It is reasonable to presume that, in our subjects, the increase of ACTH in the ASA group was due to both the intensity and duration of the effort made as well as the magnitude of the ASA dose.

The intravenous administration of PGE_2 increases ACTH secretion in humans after CRH administration (Zacharieva et al. 1992). Nye et al. (1997) stated that the increase of cortisol and ACTH that occurs after intravenous AVP administration is lowered after a previous administration of 600 mg ASA. These results suggest that PGs stimulates the secretion of ACTH at the pituitary level.

Hockings et al. (1993) stated that administering 600 mg ASA before naloxone induced an increase of ACTH concentration. It is possible that, in humans, PGs exert a stimulating effect at the pituitary gland level, and an inhibitory effect at the level of the hypothalamus. In the case of ASA administration prior to naloxone, its effect of blocking PGs synthesis within the hypothalamus may increase the amount of CRH released by naloxone and cause a further ACTH increase (Nye et al. 1997). This may explain our observed further increase of ACTH in the ASA group.

Maximal cortisol secretion appears at submaximal ACTH concentrations. The ACTH increases or decreases that occur in proper dynamic systems after the application of PGs inhibitors do not always cause similar changes in the cortisol concentration (DeBold el al. 1984). A decrease in the control group's ACTH concentration may be sufficient to induce cortisol secretion approaching a maximal level. Therefore, the cortisol concentration should be similar in both groups. Indeed, Cavagnini et al. (1979) gave ASA for 3 days and found that it blunted the hypoglycaemia-induced increase of ACTH concentration, leading to similar rises in the cortisol concentration in the investigated and control groups. Hockings et al. (1993) reported a similar increase of cortisol in the investigated and control groups instead of a greater ACTH increase after giving 600 mg ASA before naloxone injection in the investigated group.

The above data indicate that our observation of similar cortisol levels in the ASA and control groups is probably caused by a rise in ACTH in both groups that was enough to stimulate maximal cortisol secretion.

Aldosterone

ALD is synthesized in the zona glomerulosa of the adrenal cortex. ALD synthesis has also been found to occur in other tissues. Other factors that regulate ALD synthesis include: the RAA system, ACTH, the sympathetic nervous system and prostaglandins. The main regulator of ALD synthesis is angiotensin II (AII) (Kokot 1986; Foster et al. 1997; Szczepańska-Sadowska 2000). All of these factors mentioned also increase the tissue secretion of PGI_2. This process is inhibited by previous administration of ASA or INDO (Gryglewski et al. 1980).

The influence of PGs on renin secretion is beyond doubt. PGs induce renin release from isolated renal cells (Drew and Michelakis 1974). The application of PGE_2 increases renin secretion probably through an action on cells of the juxtaglomerular apparatus, which activates adenyl cyclase and increases the cAMP concentration (Franco-Saenz et al. 1980). PGs also increase ALD secretion through a direct action on adrenal glands (Saruta and Kaplan 1972).

The ALD threshold of sensitivity to physiological and pharmacological stimuli seems to be lower than that of ACTH.

Chalmers et al. (1984) reported that, contrary to ACTH, ASA, INDO and other NSAIDs may decrease the basal concentration of ALD and plasma renin activity (PRA). Thus, a decrease of basal and exercise-induced ALD concentrations may be an earlier sign of diminishing PGs synthesis than the ACTH concentration.

In our previous study (Przybyłowski et al. 1999), giving 0.5 g ASA 30 h before intensive exercise did not decrease the basal concentration of ALD. However, 30 min after recovery, the increase in the ALD concentrations was significantly smaller in the ASA group. In the present study we observed an insignificant decrease in the basal ALD concentration and a significantly smaller increase in the ALD concentration in the ASA group after exercise compared to the control group.

Mittelman and Zambraski (1992) found that 150 mg INDO daily significantly diminished basal ALD and PRA values as well as those found after exercise of 75% maximal oxygen consumption, and after the recovery period.

Likewise, Staessen et al. (1984) observed that INDO given in a similar dose for 3 days, and 50 mg on the day of the test, causes a decrease of the basal ALD concentration. Exercise on a cycle ergometer, similar to that in our study, caused a high, fourfold increase of ALD and PRA concentrations in both the experimental and control groups, although these parameters were significantly lower in the former compared to the latter group. Similar concentrations of adrenaline and noradrenaline allowed the authors to conclude that the exercise-induced increase of ALD and PRA is due to the adrenergic mechanism, and that the prostaglandin mechanism plays a less important role. However, exercise did not completely inhibit the influence of PGs on ALD secretion.

It is possible that the threefold ALD increase post-exercise and post-recovery in both groups of our subjects was caused by stimulation of the adrenergic system. However, the lack of a significant decrease of basal ALD concentration and the occurrence of a significantly lower ALD concentration only after exercise is probably caused by the low dose of ASA given (1.5 g for 2 days), which did not completely inhibit the prostaglandin mechanism.

ASA at a dose of 3.0 g for 2 days caused a decrease in ALD concentration in subjects in the supine position and a lower ALD increase in subjects in the upright position. A similar effect was observed after the administration of 50 mg diclofenac for 3 days (Norbiato et al. 1978) and after the administration of 200 mg INDO (Pedrinelli et al. 1982). INDO is a stronger COX inhibitor than ASA, and, in the study of Mittelman and Zambraski (1992) and Staessen et al. (1984), the INDO dose was close to the maximal treatment dose in humans (Rane et al. 1978).

The data of our previous study (Przybyłowski et al. 1999) suggest that the ASA dose that decreases the exercise-induced ALD release is considerably lower than the dose that lowers the basal ALD concentration. To date, neither the lowest ASA dose to diminish the exercise-induced increase in ALD concentration nor the duration of its effect has been determined.

ASA given daily at 0.45 mg/kg for 4 days inhibits 95% of the platelet synthesis of TXA_2. After 30 days of treatment no statistically significant changes in urinary excretion of PGE_2, $PGF_{2\alpha}$ and $PGF_{1\alpha}$ were observed (Patrigniani et al. 1982). PGs exert their effects mainly at the site of synthesis (Wilson and Kapoor 1993) and have a very short half life (less than 3 min). Their production rate is tissue dependent (Guazzi et al. 1999). It is not possible to exclude the possibility that treatment with a low ASA dose may diminish the synthesis of PGs and may decrease the exercise-induced increase of ALD concentration and other hormones.

An exact understanding of the influence of low ASA doses on PGs synthesis is greatly relevant to reports of the diminution by ASA of the favorable actions of enalapril and other angiotensin-converting enzyme inhibitors in diseases of the cardiovascular system. These drugs diminish the degradation of bradykinin, which is a strong stimulator of prostaglandin synthesis. Prostaglandins have a variety of favorable effects in diseases of the cardiovascular system, and ASA administration may inhibit these actions (Guazzi et al. 1999; Harjai et al. 2001). To date there has been no agreement about the magnitude of a safe ASA dose. It is recommended that the ASA dose should not exceed 200 mg daily (Meune et al. 2000), or even be 100 mg or less (Nawarskas and Spinler 2000).

Conclusion

1 Administration of ASA for 2 days, to give a total dose of 1.5 g, before intensive graded exercise until exhaustion causes a greater ACTH increase after exercise compared to the control group. However, the ACTH increase in the control group is sufficient to give rise to near-maximal cortisol secretion, resulting in similar cortisol levels in both groups.
2 The tendency for the ASA group to have lower basic ALD concentrations and a significantly lower ALD concentration after exercise is probably because ASA diminishes the effects of PGs on ALD secretion.
3 The influence of ASA on basal and exercise-induced ALD concentrations depends on the magnitude of the ASA dose.
4 Less ASA is needed to lower the exercise-induced ALD concentration than to lower the basal concentration.
5 Further studies are needed to clarify the effects of low ASA doses on PG synthesis and the hormonal changes induced by exercise.

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