Activation of Renal Dopamine System by Physical Exercise

Kikuo Arakawa, Shin-ichiro Miura, Manabu Koga, Akio Kinoshita, Hidenori Urata *, and Akira Kiyonaga

Physical exercise is one of the life-style modifications used for lowering blood pressure. Except for diminished norepinephrine spill over, the mechanism by which physical exercise exerts its effects was not known. Based on our preliminary finding that the reduction of blood pressure was inversely correlated to the baseline plasma renin activity, we have consequently revealed that mild exercise reduces plasma volume and hence the cardiac index. In order to elucidate the mechanism, we have investigated all possible parameters relevant to plasma volume regulation. Among them, urinary free dopamine and urinary active kallikrein increased in the early stages (weeks 2-4) while atrio-natriuretic factor (week 4) and endogenous ouabain-like substance (EOLS) consequently (weeks 7-10) decreased. Serum taurine increased and plasma norepinephrine decreased in the late stages. The conclusion reached is that mild exercise seems to first activate the renal dopamine and kallikrein systems and second trigger other mechanism, such as an increase in taurine and decreases in EOLS and norepinephrine. (Hypertens Res 1995; 18 Suppl. I: 573-577)

Key Words: dopamine, renin, taurine, ouabain, norepinephrine

Thanks to advances in antihypertensive drug development, lowering blood pressure is now becoming an easier task, and hypertensive cardiovascular complications are being reduced. However, hypertension, in particular mild hypertension, is still so common that the decision whether or not to treat all patients pharmacologically is difficult to make. This problem becomes even more serious if other accompanying risk factors, such as hyperlipidemia, hyperglycemia and low insulin sensibility, are to be treated by drugs simultaneously.

In looking for an alternative way of lowering blood pressure, one should first consider the etiology of hypertension. It is generally believed that hypertension is a polygenic disease. That is, the genes responsible for regulating blood pressure have inherent irregularities. Additionally, patient lifestyle is a major factor in promoting their expression. One example is the relationship between an inborn error of kallikrein and excess salt intake. As with Dahl’s salt-sensitive rats, salt-sensitive human hypertensives are also characterized by a low renal-kallikrein system and because of this, excess salt intake readily causes elevation of blood pressure in those patients (1). The best type of treatment for this type of hypertension is naturally to minimize salt intake.

In addition to salt, it is now known that several other lifestyle factors contribute to the development of hypertension: obesity; excessive intake of alcohol; mental stress; and physical inactivity (2). That the latter, a sedentary lifestyle, causes hypertension in some individuals has been demonstrated in both cross-sectional (3) and longitudinal studies (4). Initiation of some form of physical exercise should, therefore, reverse the hypertension and, in fact, this has been proven in many studies including our own (5-16).

The mechanism by which physical exercise lowers blood pressure is not perfectly understood, but the results from our studies, reviewed below, show that renal dopamine seems to have a role.

Method

We carried out and reported on nine studies (6-14), all of which followed nearly an identical protocol; in principle, 20 Japanese subjects, age range 40 to 60 years, having mild to moderate hypertension were enrolled to each study, exceptly the first preliminary study in which 10 subjects without control group. The subjects were randomly divided into two groups: 10 for exercise group A, and 10 for non-exercising controls in group B. After a 4-week run-in period, exercise was initiated in the group A subjects only; group B was still constantly monitored.

The intensity of exercise required to attain the lactate threshold, corresponding to 40-60% VO₂max, was determined for each individual using a graded submaximal exercise test by cycle ergometer. With this lactate threshold intensity which was...
individually determined, exercise was begun. Duration of exercise was 60 min, three times a week (every other day), for 10 weeks in our air-conditioned laboratory.

All the patients were well informed of the nature of the study, and their consent was obtained prior to the start of the study. The patients were instructed not to change their normal lifestyle, especially with regard to other physical activity, and their intake of both alcohol and salt.

Results

1. Blood Pressure

A typical result is shown in Fig. 1 (7). There was a significant reduction in both systolic and mean blood pressures in group A, but not in group B. There was no significant change in body weight and 24 h urine sodium excretion in patients from either group, suggesting that the blood pressure reduction seen only in exercising group were solely due to exercise.

2. Biochemicals

(a) Endogenous vasoconstrictives

There was a significant decrease in plasma nor-epinephrine. This was demonstrated in our first non-comparative study (5, 6), without a control group, and was almost simultaneously proven by Australian (17) and American (18) studies.

Plasma renin activity (PRA) did not change. Rather, Kiyonaga et al. observed that the lower the baseline PRA, the greater the reduction in blood pressure (Fig. 2) (6).

(b) Endogenous vasodilatives

Prostaglandin E was significantly increased (6), but atrial natriuretic factor (ANF) decreased in early phase (Week 4) (9). The urine kallikrein system did not change after 10 weeks of exercise (6), but in more recent study it was found increased in early stages of Week 1-2 (14).

(c) Endogenous diuretic factors

In accordance with the theory, baseline ANF levels correlated well with the baseline plasma volume (9). ANF significantly decreased in the early stages (Week 4) of exercise, and returned to the baseline level by the end (Week 10) of exercise (9). This decrease of ANF in week 4 correlated well with the urinary sodium excretion, as well as with systolic blood pressure reduction; this suggested that some other diuretic factor was active prior to change in ANF.

Like ANF, an endogenous ouabain-like substance (EOLS) also decreased significantly, but in the later phases after Week 7 of the 10-week exercise period (11).

In contrast, urine total dopamine (t-DA) excretion significantly increased at week 4 (9). In a separate, more recent study by Miura et al., the change in urine free DA (f-DA) excretion at week 2 correlated well with the change in urine sodium excretion, as well with the change in diastolic blood pressure (14).

Urine kallikrein also increased only in the early stages (Week 1-2) in association with the systolic blood pressure reduction (14), but not later stages.
at Week 10 which we first reported (6, 14).
By week 10, there was a gradual 26% increase in
levels of serum taurine, another substance known
for its diuretic actions as well as its sympatholytic
actions (10).
(d) Plasma volume and hemodynamics
As blood pressure in those patients with a low PRA
responded better to exercise, as shown (Fig. 2) in
our preliminary study, it was considered that plasma
volume must have played some role in the mecha-
nism (6). This was addressed in our second study by
Urata et al.; plasma volume did decrease signifi-
cantly only in exercising group but not in the control
group (7). However, the decrease in cardiac index
was not significant, probably because of the small
number of patients; and it did become significant
when the number of patients was increased from 10
to 21 (Fig. 3) (8). In addition, the hematocrit and
the mean corpuscular volume (MCV) significantly
decreased (7, 8).

Discussion
Since an identical protocol was employed through-
out the nine studies, it may be assumed that a near-
identical, if not identical, mechanism was at work
throughout.

Our series of studies, as well as others have now
proven that physical exercise lowers blood pressure
by $-11/-6$ mmHg in systole/diastole (19). The
decrease in blood pressure is not so great as with anti-
hypertensive drug therapy, and so one may doubt
that it really works; but, the associated biochemical
changes support that it must have worked.

Decrease in plasma NE by exercise has now been
confirmed by many, and the extent of this decrease
in plasma NE was comparable with that induced by
clonidine, a central $\alpha_2$-agonist according to Jennings.
et al. who also proved that it was associated with a decrease in renal NE spillover in the kidney (20). They, as well as other investigators, have reported that a reduction in blood pressure was due to the decrease in total peripheral resistance (TPR) (19). Ours has been the only exception. Despite a significant reduction of NE, in our Japanese subjects a decrease in TPR was not the principle hemodynamic change recorded. In contrast, the principle hemodynamic change we recorded was a decrease in plasma volume with or without a decrease in the cardiac index (Fig. 3) (7, 8).


Among the many plasma volume regulatory factors, our major target hormones, ANF (9) and EOLS (11) did not seem to have played any role, but instead they decreased after an increase in other factors such as u-DA and u-active kallikrein (9). Taurine, another volume regulatory substance is known to lower blood pressure by dual actions. On the one hand it activates kallikrein system and, on the other, it suppresses NE release from nerve endings. Ideishi et al. recently proved that taurine helps promote expression of renal kallikrein mRNA in Dahl rats (21). However, in human exercise studies, increase in serum taurine level did not correlate with sodium excretion or plasma volume change, but it did correlate with the decrease in plasma NE (10). In addition, the increase in plasma taurine was gradual, as was the plasma NE decrease, suggesting that the increase in taurine is not an initiative factor.

On the other hand, DA, which is known to cause natriuresis by itself and also by activating renal kallikrein system, increased in the early phases of exercise(Fig. 4) (9, 14). Therefore, it seems that DA was first activated, and then it triggered all the other regulatory mechanisms involved with plasma volume and the sympathetic nervous system (Fig. 5) (14). Just how renal DA is activated by exercise is not known and this needs further investigation.

References


