Radix Astragali and Orthostatic Response: A Double-Masked Crossover Study

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Aim: Recent results from animal experiments have shown that radix astragali (RA), a traditional Chinese herbal tonic, alleviates muscle atrophy under simulated weightlessness conditions, rendering RA a candidate for human use as a countermeasure against muscular atrophy. Possible cardiovascular side effects have not yet been investigated. We analyzed the effects of RA on the orthostatic stability of healthy men.

Methods: There were 10 test subjects who were assigned to a double-blinded, randomized crossover design using RA or placebo (PL) for 14 d each, respectively. Test runs were separated by a 14-d ‘washout’ interval. At the beginning and the end of every 14-d test run, graded orthostatic stress (GOS) consisting of head-up tilt (HUT) combined with lower body negative pressure (LBNP) was used to achieve a presyncopal endpoint. Orthostatic effects on cardiac and vascular function were continuously monitored. Results: There were no significant differences between the RA vs. PL groups: mean arterial blood pressure dropped by 13 vs. 17%, pulse pressure 46 vs. 35%, heart rate increased 108 vs. 117%, and stroke volume index decreased 54 vs. 49% from supine control to pre-syncope. Neither did RA influence standing time compared to PL (18 ± 6 vs. 17 ± 6 min), nor did progression from the first to the fourth trial (15 ± 6 to 18 ± 7 min). Conclusion: RA does not influence resting cardiovascular variables and orthostatic capacity in humans. It can be expected that human studies of RA’s musculo-skeletal countermeasure potential will not be compromised by any cardiovascular side effects at the dosage employed in this study.

Keywords: orthostasis, cardiovascular, Chinese herbs, human, standing time.

Evidence from spaceflight missions and ground-based analogue experiments indicate that exposure to microgravity has multiple effects that occur in combination, like musculo-skeletal deterioration and reduced orthostatic tolerance. Naturally, it is important that any countermeasure to be applied should not present disadvantages in terms of any bodily systems not primarily targeted. Radix astragali (RA), or Huang Qi, is a traditional Chinese drug, derived from the root of astragalus membranaceus. It has been used as a tonic herb for thousands of years in China. Two RA species are in use as medicine and/or dietary supplement: Astragalus membranaceus and astragalus membranaceus mongolicus (18,23). RA has been observed to have ‘immune enhancing’ properties (3,9) and is used to treat numerous ailments, including heart, liver, and kidney diseases, as well as cancer, viral infections, and immune system disorders (8,12,14,16,22).

Generally, consumers appear to be attracted to traditional Chinese medicine for a variety of reasons, such as its emphasis on treating the whole person, emphasis on prevention, the attempt to stimulate the body’s inherent healing potential, few side effects, and its position within an alternative philosophical belief system (2,11). Indeed, RA sales in U.S. natural food stores ranked among the top 10 in 1997 and are expected to quadruple by 2015 (1,4).

The rationale for this study was the following: we have previously shown clear beneficial effects in terms of reduced muscle atrophy in a tail suspended rat model (7,24). Evidence for cardiovascular effects in healthy humans is absent, therefore, we investigated potential cardiovascular effects in terms of orthostatic tolerance before further work is performed in humans using RA as a countermeasure for muscle atrophy. Orthostatic stress as caused by head-up tilt (HUT) or lower body negative pressure (LBNP) induces cardiovascular and neuroendocrine changes in an intensity- and duration-dependent manner. To test the hypothesis that the ability to maintain cardiovascular resilience during increasing orthostatic stress remains unchanged with oral application of RA, we used graded orthostasis (GOS) in our experiments as it has been demonstrated that a combined HUT and graded LBNP protocol can reliably provoke orthostatic syncope in 100% of test subjects (15).

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METHODS

Test Design

There were 10 physically fit healthy men (75 ± 12 kg, 179 ± 6 cm, 25.3 ± 3.4 yr, supine rest heart rate 65 ± 10 bpm, maximum ergometric power output 4.1 ± 0.5 W · kg⁻¹), who received a medical examination before the test (inclusion: healthy, non-obese, non-medicated and nonsmoking men, ages 20-30 yr; exclusion: any pathological neurological, cardiovascular, or endocrine condition), and participated in a double-blinded, crossover, randomized fashion using RA or a placebo (PL), respectively. Subjects were familiarized with the test protocol, told about their right to exit the test at any point in time without being obliged to give any reason for such a decision, and gave their written informed consent. In the first 14-d trial, five of them started with RA and five with PL, respectively; the order was reversed in the second trial. A 14-d “washout” period followed the first trial. To compensate for possible climatic cardiovascular effects, every day two subjects entered the trial (one RA, one PL). The study was approved by the Graz University Ethics Board, and was performed in accordance with the 1989 WMA Declaration of Helsinki.

Before the first, and 1 h after the last drink in a series, respectively, orthostatic capacity was tested (GOS). Since salt intake influences baroreceptor sensitivity (5), and volume status may influence orthostatic regulation, test persons were advised to keep their fluid and salt intake according to their usual dietary habits. Additionally, none of the subjects exercised rigorously, or consumed alcohol or caffeenated drinks during the entire duration of the study.

Radix Astragali Purity and Dosage

We used a commercially available RA extract (Lot. No. 0,507,506, Tianjiang Pharmaceutical Co, Jiangyin, PR of China) that has been introduced to the European market. RA roots are extracted with boiling water as solvent (i.e., decoction according to the most common application form of traditional Chinese medicine herbal therapy) and the spray-dried native extract was processed to water-soluble granules with a herb-extract ratio of 5:1 (range 4:1 to 6:1). The pharmaceutical quality (heavy metals, microbiological quality) complies with the regulations of the European pharmacopoeia, and analysis of (by thin layer chromatography, microscopy of raw material) heavy metal content (by inductively coupled plasma mass spectroscopy) and microbiological contamination (Ph.EUR 5.1.4. category 3B) have been carried out at the production site as well as in laboratories in the EU (Sebastian Kneipp-Forschung Bad Wörishofen, BRD). The Dextrin used as adjuvant complies with the monograph of the Pharmacopoeia of the PRC (19).

The dosage of RA was chosen to be in the same range as in a previous tail suspension study (24). In that rodent study, raw RA in three dosages was chosen (100, 200, and 400 mg · kg⁻¹ · d⁻¹), all of which significantly reduced muscular deconditioning. It is conceivable that humans might respond to the same dosage with a similar decrease of muscle wasting during real or simulated (bed rest immobilization) weightlessness. In the present study, we therefore used a similar dosage: 4 g · d⁻¹ of a commercially available RA extract, which is equivalent to about 250 mg · kg⁻¹ · d⁻¹ raw substance.

RA or PL Preparation

RA or PL was provided as drinks which were taken twice a day between 0800–0900, and 1700–1800, respectively. The standard preparation was the following: 0.5 g hazelnut flakes were mixed with 1.5 g cane sugar in 50 ml hot water, and the solution was allowed to cool to room temperature. It was used unchanged for PL, or 2 g RA extracts were added per drink. There was no difference in flavor between drinks; a code was used (X, Y) to allow for double-blind test design. Subjective guesses as to which drink was taken were observed to be random.

GOS Test

The subjects were fasting and emptied the bladder before each study. Experiments were carried out in a semi-dark and quiet room maintained at 23–25°C and 50–60% humidity. A padded pair of tightly connected chains was used to stabilize and maintain an exact sealing position at hip level (spina iliaca anterior superior). Each experiment started with a 20-min supine rest to acquire cardiovascular steady state conditions. Continuous hemodynamic monitoring included blood pressure, heart rate (3-lead ECG), and thoracic impedance. Impedance cardiography was performed based on the original Kubicek approach but using an improved estimate of thoracic volume (Task Force Monitor®, CNSystems, Graz, Austria). Electrode strips were placed at the neck and thoracic regions, the latter specifically at the midclavicular line at the xiphoid process level (CNSystems standard electrode kits). The method has been described in detail elsewhere (6). In short, a constant sinusoidal alternating current is applied between outer ‘injection’ electrodes and the associated voltage sensed by the inner electrode pairs. Recorded and calculated data were stored real-time beat-to-beat throughout the entire experiment. From all variables, mean values from supine control and presyncopal GOS, respectively, were computed and used for further statistics.

At minute zero, the tilt table was brought to 70° head-up position. After 5 min, an additional −20 mmHg LBNP was provided. LBNP was then increased by 10 mmHg every 3 min. As soon as presyncopal signs or symptoms occurred, the table was brought back to 0° and LBNP was stopped at once, and the time in upright position recorded as “standing time” as a measure of orthostatic tolerance. Hemodynamic/thoracic impedance monitoring occurred continuously. The criteria for presyncope were 1) blood pressure drop below systolic 80 mmHg or by ≥ 20 mmHg · min⁻¹; diastolic by ≥ 10 mmHg · min⁻¹, and/or heart rate decrease by ≥ 15 bpm; and 2) lightheadedness, dizziness, visual disturbances,
nausea, stomach awareness, clammy skin, excessive sweating, or skin pallor.

The GOS tests—four per test subject—were carried out using the Institute of Adaptive and Spaceflight Physiology’s Automated Human Multi-Stimulation Test Device (www.meduni-graz.at/ia/b/VSIST.htm) (13). During LBNP the subjects were instructed to avoid un- due movements of the lower limbs and to breathe normally. The box was equipped with a footrest that was individually adjusted before LBNP was commenced. A pillow supported the head to avoid stimulation of the ototh organs, which has been reported to increase muscle sympathetic nerve activity and calf vascular resistance (10).

Test persons were secured and had access to an emer- gency shutdown (automatic return to supine and pres- sure neutralization) at all times. Transition from supine to upright was complete within 10 s, as well as pressure buildup in the LBNP box. A MatLab-based program managed the execution of the preprogrammed test proto- col and synchronous recording of all data from the cardiovascular monitoring system.

Treatment of Data

All values are presented as mean ± SD. Repeated-measures ANOVA for multiple hypotheses testing, with test condition and time as factors, and two-way ANOVA with Bonferroni post hoc test for multiple comparisons was used and significance assumed for an alpha error probability < 0.05.

RESULTS

RA, compared with PL, affected neither resting car- diovascular parameters, nor those observed during pre- syncopal orthostatic stress: two-way ANOVA did not in- dicate influences of treatment (RA, PL) or trial order on standing time and hemodynamic variables. Individual standing times ranged between 8.4 and 29 min; overall standing time was not different (P = 0.92) after 14 d RA application, compared to 14 d PL (18 ± 7 vs. 17 ± 6 min, breakdown in first and second trial given in Table I). There was no difference between tests at the respective beginning and end of the 14-d trials; a slight increase of standing time during progression from the first to the fourth trial (15 ± 6, 16 ± 6, 18 ± 6, and 18 ± 7 min) was not significant.

Data on hemodynamics after RA and after PL are pro- vided in Table II. Presyncopal orthostatic stress signifi- cantly reduced blood/pulse pressures and stroke vol- ume, and increased heart rate and thoracic impedance as expected. RA did not affect changes from supine control to presyncopal (values represent RA vs. PL treatment, respectively): systolic blood pressure decrease, 21 ± 15 vs. 22 ± 17% (P = 0.82); diastolic blood pressure decrease, 7 ± 17 vs. 10 ± 24% (P = 0.74); mean arterial pressure decrease, 12 ± 15 vs. 16 ± 28% (P = 0.56); pulse pressure decrease, 47 ± 24 vs. 34 ± 18% (P = 0.17); heart rate increase, 111 ± 29 vs. 119 ± 31% (P = 0.50); stroke volume index decrease, 48 ± 5 vs. 49 ± 7% (P = 0.86); and thoracic impedance increase, 15 ± 3 vs. 16 ± 3% (P = 0.40).

TABLE II. SBP, DBP, MAP AND PP, HR, SVI, AND TI BEFORE COMMENCING GOS, AFTER TREATMENTS, AND AT PRESYNCOPAL END POINT IN THE RA AND PL GROUPS.

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>PL</th>
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<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>118.5 ± 10.1</td>
<td>120.9 ± 10.0</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>74.7 ± 9.3</td>
<td>73.9 ± 8.8</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>87.9 ± 10.2</td>
<td>88.6 ± 9.4</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>45.8 ± 6.5</td>
<td>48.4 ± 11.2</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>67.2 ± 12.5</td>
<td>62.9 ± 9.1</td>
</tr>
<tr>
<td>SVI (mL/m²)</td>
<td>53.8 ± 9.4</td>
<td>53.3 ± 8.1</td>
</tr>
<tr>
<td>TI (Ohms)</td>
<td>27.9 ± 3.8</td>
<td>28.4 ± 3.0</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, PP = pulse pressure, HR = heart rate, SVI = stroke volume index, TI = thoracic impedance, GOS = graded orthostatic stress, RA = radix astragalii, and PL = placebo.

Changes from supine rest to presyncope were P < 0.05. There were no significant differences between RA and PL conditions.

DISCUSSION

The present study found no difference between ortho- static stability after RA and after placebo: there was no difference between tests at the respective beginning and end of 14-d trials, and the slight increase of standing time during progression from the first to the fourth trial was not significant. Our earlier research has shown that preparations of RA, in combination with ferulate, favorably alter changes of muscle fiber cross-sectional area and fiber type distribution (myosin ATPase activity) in rats under simulated weightlessness conditions (7,24). Transformation from slow-twitch to fast-twitch fiber type and the evolution of muscle atrophy was prevented.
to a considerable degree, opening perspectives to develop novel paradigms and drugs to prevent, and perhaps also treat, muscle atrophy. The beneficial effects in terms of reduced muscle atrophy have been discussed in detail elsewhere (8,12,14,16,17,20,21,25). In order to get a clear picture of possible cardiovascular action of RA without potentially confounding effects that might be caused by addition of ferulate, and to arrive at conclusions that apply to RA alone, we decided to use a preparation of pure RA in this study. Our data show that this herbal tonic influences neither resting cardiovascular parameters nor orthostatic stability in a sample of healthy persons.

The purpose of our investigation was to investigate whether RA exerts (unexpected) effects on cardiovascular (orthostatic) stability, an issue of considerable significance especially from a spaceflight medical point of view. We conclude that RA is safe to apply to other human experiments, particularly in connection to spaceflight medicine. Consecutive studies will need to investigate possible effects of ferulate, separately and in combination with RA.

There are some limitations in this study. Firstly, we could not directly study the effects of RA on the microvascular circulation. Secondly, as we only measured the effects following 2 wk of treatment, we do not know if cardiovascular RA effects emerge with longer (>2 wk) treatment in humans. Thirdly, our results do not provide information about safety aspects in terms of e.g., myocardial infarction or atherosclerosis. Fourthly, we do not know if higher doses of RA could have showed different effects, as the dosage for medicinal prescription is 8 g · d⁻¹. We used 4 g · d⁻¹—a relatively low and even safer dose—because this is equivalent to the range proven effective in the previous rodent study (24), and therefore provides a rational starting point for investigations of expected anti-deconditioning effects on the musculature in humans. Finally, while the conclusion that RA does not influence orthostatic capacity in any unfavorable way is clearly supported by the data, since test persons in this study were healthy and showed good orthostatic tolerance, this may have limited any potential improvement effect. Postflight, or in patients with impaired regulatory capacity, increased orthostatic tolerance with RA is still a possibility.

This opens an interesting area for further investigations, particularly in the target group of (deconditioned) astronauts. Further studies will have to specifically address the question of whether muscle wasting due to immobilization (actual spaceflight or simulated weightlessness) can be mitigated by oral application of RA. The exact mechanisms by which the anti-deconditioning effect of this Chinese herb occurs are still to be identified.

In conclusion, based on findings of the present study, 250-300 mg · kg⁻¹ · bodyweight · d⁻¹ RA applied orally for 2 wk seems to have no influence on circulatory stability as tested with increasing orthostatic stress up to syncopal levels (GOS paradigm) in healthy men, and therefore can be considered safe in terms of cardiovascular function. Our results do not indicate any deterioration—or any improvement—of cardiovascular function. Consecutive investigations using human deconditioning models will show if RA has the expected beneficial effects on the musculoskeletal system that are similar to those observed in rodents.

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