Dietary soy exerts an antihypertensive effect in spontaneously hypertensive female rats

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Martin, D. S., N. P. Breitkopf, K. M. Eyster, and J. L. Williams. Dietary soy exerts an antihypertensive effect in spontaneously hypertensive female rats. Am J Physiol Regulatory Integrative Comp Physiol 281: R553–R560, 2001.—This study tested the hypothesis that dietary soy would attenuate the development of hypertension in female spontaneously hypertensive rats (SHR). Female SHR and control Wistar-Kyoto rats were obtained at 4 wk of age, randomly assigned to either an ovariectomized (OVX) group or a sham-operated group, and placed on a soy diet or control casein diet. After a minimum of 8 wk on their respective diets, mean arterial pressure (MAP) and heart rate (HR) were recorded before and after inhibition of nitric oxide synthase, air-jet stress, or ganglionic blockade. The major finding of this study is that MAP was reduced in the OVX SHR consuming soy diet compared with the casein-fed controls (150 ± 4 vs. 164 ± 3 mmHg). Plasma genistein concentrations were increased in the soy-fed OVX SHR (1.23 ± 0.31 μM) compared with the casein-fed OVX SHR (nondetectable). However, there was no difference in plasma genistein concentrations between sham-operated and OVX SHR (1.37 ± 0.42 vs. 1.23 ± 0.31 μM). Inhibition of nitric oxide synthase increased MAP and decreased HR in all groups; diet did not affect this response. Air-jet stress increased MAP and HR in all groups. However, these responses were exaggerated in the soy-fed SHR. Finally, ganglionic blockade abolished the antihypertensive effect of soy diet in the OVX SHR. These findings indicate that dietary soy exerts an antihypertensive effect in OVX SHR. This effect does not involve the nitric oxide system but may be related to an as yet undefined interaction with the autonomic nervous system.

PHOTOESTROGENS, particularly those found in soybeans, are plant-derived compounds that have recently attracted a great deal of public attention (41, 42). The major phytostrogens found in soybeans are the isoflavones, genistein and daidzein. These compounds possess a variety of physiological effects including regulation of cell growth, bone density, and plasma lipids (2, 21, 41, 42).

However, one area of soy isoflavone research that has received relatively little attention is the area of vascular function and blood pressure (BP) control. There is good reason to believe that soy isoflavones such as genistein may have effects on BP regulation. Genistein acts as an estrogen-receptor agonist (32), and estrogen appears to exert protective effects on the cardiovascular system, both by modulating plasma lipid concentrations and via direct vascular and/or neural effects (3, 4, 7, 8, 11). In addition, genistein is also an inhibitor of tyrosine kinase. Recent data suggest that tyrosine kinases may be involved in the control of vascular tone (9) and the generation of hypertension (40). Nevertheless, comparatively few studies have examined effects of soy isoflavones on BP and vascular function. Genistein caused a direct vasodilator effect in isolated mesenteric arteries (35) and rat aorta (33). Moreover, genistein dilated coronary arteries in vivo following intra-arterial injection (19). In addition, previous work indicated that soy or soy isoflavones may also have a protective effect on the development of hypertension. Hayashi et al. (18) reported that consumption of natto, a fermented soy food, decreased systolic BP in male spontaneously hypertensive rats (SHR). Similarly, Kimura et al. (22) obtained lower levels of systolic BP in male SHR that were fed a diet containing a soy protein isolate than those fed casein. More recently, genistein supplementation of a standard rat chow was reported to decrease systolic pressure in male but not female SHR (36). In contrast, others showed that BP was similar in SHR fed a soy protein isolate compared with casein-fed rats (26, 48). These disparate findings may be related to isoflavone content of isolates that varies with processing methods, the use of fermented soy products (natto) that contain high concentrations of isoflavones, or the direct addition of unconjugated genistein to the diet. The present study tested the hypothesis that unmodified dietary soy would attenuate the development of arterial hypertension in the female SHR.

MATERIALS AND METHODS

Animals. Female SHR or Wistar-Kyoto rats (WKY) were obtained from Taconic Farms (Germantown, NY) at 4 wk of age. Immediately on arrival, the rats were placed on custom diets (ICN Biochemicals) consisting of 19% whole soy meal...
(Soy) or a control diet in which protein was derived from casein. One week after arrival, some rats were subjected to bilateral oophorectomy via a retroperitoneal approach. Sham-operated rats underwent the same surgery, but the ovaries were not removed. All rats consumed the diet throughout the study. Rats were allowed to eat the diets a minimum of 8 weeks before experimentation.

Protocols. Two days before experimentation, the rats were anesthetized with isoflurane, and catheters were placed in the femoral artery and vein for arterial BP recording and drug administration, respectively. On the experimental days, the rats were brought to the laboratory and remained in their home cages. The arterial catheter was interfaced with a computerized data-acquisition system. Mean arterial pressure (MAP) and heart rate (HR) were recorded for a baseline period of at least 60 min. The rats were then randomly assigned to groups subjected to inhibition of nitric oxide synthase (NOS) \([\text{N}^\text{G}-\text{nitro-L-arginine methyl ester (l-NNAME)}] 25 \mu\text{mol/kg}, \text{ganglionic blockade (chlorisondamine 10 mg/kg, OXV, or a 2-min exposure to air-jet stress. Trunk blood was collected at the end of the experiments for the measurement of plasma genistein levels.}

Measurement of plasma genistein concentrations. After collection, the blood was centrifuged, and the plasma was collected and stored frozen at \(-80^\circ\text{C}\) until the time of assay. For the assay, 50 \mu l of rat plasma were aliquoted in duplicate with 5 \mu l (515 U) of \(\beta\)-glucoronidase sulfatase Type H (Sigma). All aliquots were incubated in conical tubes at 37°C for 17 h. After incubation, 50 \mu l of absolute methanol were added to each tube; the tubes were vortexed for 20 min at 2,500 g. Fifty microliters were removed and placed in a micro autosampler vial. An HPLC system was used for the quantitative analysis. The samples were manually injected onto Nova Pak Waters C18 60A 4-\mu l (3.9 \times 150 mm) column with a Rheodyne injector. An isocratic system was used: solvent A 20% (acetonitrile); solvent B 80% (10% acetic acid in water). Flow rate was set at 1.2 ml/min. The detecting UV wavelength was 280 nm. Sample concentration was calculated on a standard curve and corrected for recovery of 91 \pm 0.01% per 50 \mu l rat plasma sample.

Data analysis. All values are means \pm SE. The data were analyzed using ANOVA. The factors were diet (2 levels: soy and casein), strain (2 levels: SHR and WKY), and gender (2 levels: sham and ovariectomized (OVX)). Differences between means were assessed by Student’s t-test using Bonferroni’s correction for multiple comparisons. Differences were considered significant at \(P < 0.05\).

RESULTS

Effect of dietary soy on MAP and HR. Figure 1 illustrates the absolute values for MAP (A) and heart rate (B) in female sham-operated and OVX SHR and WKY rats fed casein or soy diet. In OVX WKY, MAP averaged 114 \pm 2 mmHg on the casein diet and 115 \pm 5 mmHg on the soy diet. OVX SHR fed the casein diet had a baseline MAP of 164 \pm 3 mmHg. In contrast, OVX SHR fed the soy diet had a MAP of 150 \pm 4 mmHg. This value was significantly lower than that observed in the casein-fed OVX SHR. This antihypertensive effect was not observed in the sham-operated rats, which exhibited only a small trend toward lower BP in the soy-fed animals. In WKY, MAP averaged 113 \pm 4 mmHg, whereas MAP was 108 \pm 3 mmHg in the soy-fed WKY. This difference was not statistically significant. Similarly, whereas MAP was significantly elevated in SHR compared with WKY, the dietary treatment did not significantly influence MAP (casein 170 \pm 5 mmHg vs. soy 163 \pm 5 mmHg). A similar pattern was observed with respect to HR. HR was somewhat elevated in SHR compared with WKY; however, there were no significant differences between dietary treatments.

Thus dietary soy exerted an antihypertensive effect selectively in OVX SHR. In contrast, ANOVA indicated a significant main effect of surgery (\(P = 0.0001\)) and strain (\(P = 0.0004\)) on HR. HR was lower in OVX compared with sham-operated rats. HR was also lower in WKY compared with SHR. There was no main effect of diet (\(P = 0.38\)) on HR.

Role of NO. NO is known to contribute to the control of BP, and soy isoflavones may stimulate production of NO by virtue of their estrogen-agonist properties (17, 41). Accordingly, this series of experiments was undertaken to assess whether dietary isoflavones enhanced the contribution of NO to MAP. Figure 2 illustrates the MAP and HR responses to a blockade of NO. l-NNAME administration was associated with an increase in MAP and a decrease in HR in all groups. In the sham-operated WKY, MAP increased by 22 \pm 3 mmHg in the casein-fed group and by 22 \pm 4 mmHg in the soy-fed group. Similarly, in sham-operated SHR, blockade of NO caused MAP to increase by 28 \pm 4 and 28 \pm 4 mmHg in the casein- and soy-fed animals, respectively. In OVX WKY on the casein and soy diets, l-NNAME treatment increased MAP by 29 \pm 3 and 23 \pm 5 mmHg.
OVX rats. This dietary effect was not evident in WKY. The greater in the soy-fed compared with the casein-fed SHR compared with WKY. Moreover, in OVX SHR, responses to air-jet stress were significantly higher in SHR. This effect of diet was not apparent in WKY. HR greater in the soy-fed SHR compared with casein-fed to air-jet stress. MAP responses were significantly \( (P < 0.0001) \) and \( (P = 0.02) \) on the MAP responses to air-jet stress. MAP responses were significantly greater in the soy-fed SHR compared with casein-fed SHR. This effect of diet was not apparent in WKY. HR responses to air-jet stress were significantly higher in SHR compared with WKY. Moreover, in OVX SHR, air-jet stress-induced HR responses were significantly greater in the soy-fed compared with the casein-fed rats. This dietary effect was not evident in WKY. The OVX SHR on the soy diet also appeared to exhibit greater tachycardic responses than the sham-operated SHR on soy, however, this effect only reached significance at one time point (60 s). Overall, these findings confirm that cardiovascular responsiveness to stress is enhanced in the hypertensive rats. However, contrary to our expectations, dietary soy did not attenuate but, in fact, appeared to potentiate these exaggerated responses to stress.

**Effects of ganglionic blockade.** The autonomic nervous system is thought to play a role in the development of hypertension in SHR. A second approach to assess the possibility that dietary soy interacted with the autonomic nervous system was to treat the animals with a ganglionic blocking agent to interrupt autonomic function. Figure 4 illustrates the MAP and HR values obtained in each of the groups after treatment with the ganglion-blocking agent chlorisondamine. Ganglionic blockade produced a marked decrease in both MAP and HR in all animals.

In sham-operated WKY fed casein, MAP and HR were reduced to 71 ± 4 mmHg and 302 ± 8 beats/min, respectively. In the soy-fed sham-operated WKY, MAP and HR averaged 74 ± 6 mmHg and 332 ± 11 beats/min. In sham-operated SHR, the corresponding values were 104 ± 7 mmHg and 329 ± 14 beats/min for the casein-fed rats and 101 ± 5 mmHg and 302 ± 8 beats/min for SHR on soy diet. Although MAP was reduced significantly from control in both strains after ganglionic blockade, MAP in SHR remained significantly higher compared with WKY. There were no differences in the MAP or HR values between the dietary treatments in the sham-operated rats subjected to chlorisondamine treatment.

In OVX rats, ganglionic blockade lowered MAP and HR to 73 ± 3 mmHg and 314 ± 9 beats/min in the casein-fed WKY and to 73 ± 2 mmHg and 311 ± 9 beats/min in the soy-fed WKY. Ganglionic blockade also produced a significant fall in MAP and HR in OVX SHR. In the casein-fed group, MAP and HR decreased by 62 ± 4 mmHg and 60 ± 12 beats/min, respectively, whereas the soy-fed OVX SHR exhibited a reduction in MAP of 47 ± 5 mmHg and a decrease in HR of 58 ± 10 beats/min. The chlorisondamine-induced fall in MAP was significantly greater \( (P = 0.02) \) in the casein- vs. soy-fed OVX SHR. Indeed, after ganglionic blockade, the absolute value of MAP observed in the casein-fed OVX SHR (102 ± 5 mmHg) was not significantly different \( (P = 0.62) \) from that recorded in the soy-fed OVX SHR (106 ± 4 mmHg). Thus ganglionic blockade abolished the difference in MAP between the OVX SHR fed casein or soy shown in Fig. 1.

**Plasma genistein levels.** Plasma was collected from a subset of rats in each group at the end of the protocols for the measurement of plasma genistein levels. Figure 5 illustrates the plasma genistein concentration achieved in each of the groups. In the casein-fed animals, regardless of strain or surgery, genistein levels remained below the level of detection. In contrast, genistein levels in the soy-fed animals were in the low micromolar range. In the sham-operated WKY, plasma...
genistein averaged 0.9 ± 0.18 μM, whereas in OVX WKY the value was 1.07 ± 0.16 μM. Similar levels were observed in SHR (1.37 ± 0.42 in sham-operated SHR and 1.23 ± 0.31 μM in OVX rats). There were no statistically significant differences between the plasma genistein levels recorded in the rats fed the soy diet. Thus differences in plasma genistein concentrations cannot account for the differential effect of the soy diet in the various groups.

DISCUSSION

Interest in the potential health benefits of soy and soy isoflavones has increased dramatically in recent years (41, 42). In terms of cardiovascular health, there has been considerable research effort directed at analyzing the effects of soy and soy isoflavones on plasma lipids. Although early studies suggested an effect of soy on BP, this possibility has received relatively little attention. The current study was undertaken to assess the effects of dietary soy on BP in female SHR. We observed that dietary soy produced an antihypertensive effect selectively in OVX female SHR. This effect may be related to an effect on the autonomic nervous system, however, it does not appear to involve any change in NO function.

Comparatively few studies have examined effects of soy-derived foods on BP and vascular function. In hypertensive rats, Hayashi et al. (18) reported that consumption of natto, a fermented soy food, decreased BP. Similarly, Kimura et al. (22) obtained lower levels of BP in hypertensive rats that were fed a diet containing a soy protein isolate than those fed casein. More recently, Kimura et al. (22) obtained lower levels of BP in hypertensive rats that were fed a diet containing a soy protein isolate than those fed casein. More recently, Kimura et al. (22) obtained lower levels of BP in hypertensive rats that were fed a diet containing a soy protein isolate than those fed casein. More recently, Kimura et al. (22) obtained lower levels of BP in hypertensive rats that were fed a diet containing a soy protein isolate than those fed casein. More recently, Kimura et al. (22) obtained lower levels of BP in hypertensive rats that were fed a diet containing a soy protein isolate than those fed casein.

The current study confirms these findings by demonstrating that dietary soy did not significantly lower MAP in sham-operated SHR, and it extends...
previous work by demonstrating that dietary soy does exert an antihypertensive effect in female OVX SHR. We observed an overall reduction in MAP of $14 \text{ mmHg}$, which was statistically significant compared with the casein-fed animals. The magnitude of this antihypertensive effect is in the range previously reported in other studies. A soy protein diet reduced systolic BP by $17 \text{ mmHg}$ in male stroke-prone SHR (22), whereas a somewhat larger response was observed by Hayashi et al. (18), who reported that SHR fed natto (a fermented soy product containing elevated isoflavone levels) exhibited a decrease in systolic BP of $20–30 \text{ mmHg}$. Moreover, the coronary vasodilator effect of dietary isoflavones was mimicked by direct injection of genistein into a coronary artery (19). Similarly, a vasodilatory effect of genistein has been previously reported in rat mesenteric arteries in vitro (35). Genistein has also been reported to exert a vasodilator effect in the isolated kidney (14, 30). Thus genistein appears to be a prime candidate for mediating the effects of dietary soy on BP.

In the present study, we measured plasma genistein concentrations in each of the treatment groups. Not surprisingly, genistein levels were below detection limits in animals fed the casein diet. In contrast, rats fed the soy diet exhibited plasma concentrations of genistein in the micromolar range ($0.9–1.37 \text{ mM}$). In comparison, humans consuming an isoflavone-containing soy drink for 2 wk had a plasma genistein concentration of $0.55$ to $0.86 \text{ mmol/l}$ (2). Similarly, Sprague-Dawley rats consuming a diet supplemented with genistein (250 mg/kg) demonstrated plasma genistein concentrations of $0.418 \text{ mmol/l}$ (13). Rats given an isoflavone-rich soy extract by gavage were found to have genistein plasma levels of $\sim 5 \text{ mmol/l}$ (23, 24). Thus dietary intake of soy- or genistein-containing substances produced plasma genistein concentrations in the range of $0.5$ and $5 \text{ mmol/l}$. Therefore, the plasma whole ground soy in our diet and measured plasma genistein levels in our study. Thus, at least in our hands, dietary soy exerts a significant antihypertensive effect in female OVX SHR.

Although soybeans contain a variety of bioactive substances, the isoflavones have attracted considerable interest. The primary isoflavones in soy are genistein (an estrogen-receptor agonist and tyrosine kinase inhibitor) and daidzein (an estrogen-receptor agonist) (41, 42). Previous studies suggested that genistein may be the active compound responsible for the effects of soy on BP. Preliminary work indicated that direct injection of genistein lowered MAP in male and OVX female SHR (34) and intact female borderline hypertensive rats (5). Moreover, the coronary vasodilator effect of dietary isoflavones was mimicked by direct injection of genistein into a coronary artery (19). Similarly, a vasodilatory effect of genistein has been previously reported in rat mesenteric arteries in vitro (35). Genistein has also been reported to exert a vasodilator effect in the isolated kidney (14, 30). Thus genistein appears to be a prime candidate for mediating the effects of dietary soy on BP.
genistein concentrations obtained in the present study were within the range previously described during dietary intake of soy products. Moreover, there were no significant differences in plasma genistein concentrations between the sham-operated and OVX rats nor between WKY and SHR, suggesting that there were no substantive pharmacokinetic differences for genistein between WKY and SHR nor between intact and OVX rats. Therefore, the differences in BP responses to dietary soy between the various groups were not the result of differences in the pharmacokinetics of genistein.

Alternatively, the differences between groups may lie in the pharmacodynamic effects of the active compounds found in the soy diet. These effects may be complex. Indeed, although we observed a significant fall in BP in OVX SHR fed soy, there was only a smaller nonsignificant antihypertensive effect in the sham-operated SHR fed soy. The reasons for this difference are not immediately clear. Nevertheless, it is possible to speculate that the complex pharmacological profile of the isoflavones found in soy may account for this difference. One of the recognized actions of genistein is its ability to bind to and activate estrogen receptors (27). However, genistein has differential effects on estrogen-receptor subtypes reportedly having a higher affinity at estrogen receptor beta than at estrogen receptor alpha (41). In addition, genistein and daidzein (two isoflavones found in soy) behave as partial agonists at estrogen receptors and may exhibit both agonist properties and antagonist properties depending on the tissue and prevailing conditions (41). Thus the different effect of the soy diet in sham-operated vs. OVX SHR may reflect a different response to the isoflavones in the presence or absence of background estrogen. Indeed, preliminary studies by our group (data not shown) indicate that the effect of combination replacement therapy with estrogen + genistein in OVX rats on gene expression is not predictable based on results obtained in OVX rats that received either estrogen or genistein alone. Thus there appears to be unique interactions between estrogen and genistein when these agents are present concurrently. It is possible that these interactive effects account for the lack of BP lowering in sham-operated SHR consuming the soy diet.

The mechanisms underlying the effects of soy or genistein on vascular function and BP remain to be determined. Because estrogen increased the activity of NOS (17), genistein may activate antihypertensive mechanisms such as increased synthesis of NO. Indeed, genistein injection was reported to increase endothelial NOS activity in rat lung (43), and inhibition of NOS attenuated genistein-induced vasodilation in isolated rat aorta (33). We assessed the role of NOS in the antihypertensive effect of dietary soy by treating the animals with an NOS inhibitor. The rationale was that if a soy diet enhanced NO synthesis, inhibition of NOS would produce a greater pressor response in the soy-fed groups than in the casein-fed SHR. In fact, we observed no significant differences between strain or diet treatments with respect to the pressor response elicited by NOS inhibition, suggesting that dietary soy does not lower MAP by enhancing NO vasodilator function in female SHR.

Alternatively, the sympathetic nervous system is thought to play an important role in the development of spontaneous hypertension, because early sympathectomy attenuated the final level of MAP in adult SHR (6, 39). Soy isoflavones such as genistein may interact with the autonomic nervous system through either estrogen receptor-related mechanisms or through inhibition of tyrosine kinase. Treatment with estrogen decreased norepinephrine (NE) efflux from the adrenal medulla and from the portal vein (4). In humans, estrogen replacement therapy decreased NE spillover in perimenopausal women (44). On the other hand, other studies showed that tyrosine kinase inhibitors such as genistein and tyrphostins can attenuate the vasoconstrictor activity of NE and other α-adrenergic agonists (1, 10, 12, 45). Moreover, tyrphostin attenuated the exaggerated constrictor response of SHR aortic rings to NE (50). Thus dietary soy may have exerted an antihypertensive effect by virtue of the ability of genistein to stimulate estrogen receptors and/or inhibit tyrosine kinase to reduce sympathetic tone in SHR. We assessed this possibility using two approaches. Because SHR reportedly exhibit an exaggerated sympathetic response to environmental stress (28) and enhanced BP reactivity to stress is a predictor of future hypertension (31), the first approach was to challenge the animals with air-jet stress to activate the sympathetic nervous system. We predicted that if dietary soy reduced the development of hypertension by attenuating responsiveness to stress, SHR fed soy should exhibit a smaller pressor response. In contrast to our prediction, we observed that soy-fed SHR actually exhibited somewhat greater pressor responses to air-jet stress than the casein-treated SHR. Thus it seems unlikely that dietary soy acts to reduce overall sympathetic responsiveness in SHR. The second approach used to assess the role of the sympathetic nervous system was to treat the animals with a ganglion-blocking agent to interrupt sympathetic function. Not surprisingly, ganglionic blockade was associated with a marked decrease in MAP in all groups of rats. Consistent with our previous findings (29), MAP in SHR remained significantly elevated compared with WKY irrespective of dietary treatment. This suggests the involvement of nonneural factors (humoral or structural) in the maintenance of elevated MAP in SHR.

Interestingly, MAP was not significantly different in the soy-fed OVX SHR and the casein-fed OVX SHR after ganglionic blockade. Thus interruption of autonomic function abolished the effect of dietary soy on BP in OVX SHR, suggesting a potential interaction between dietary soy and autonomic function that requires further study.

There is a number of other potential mechanisms, which were beyond the scope of this study, that may contribute to the antihypertensive effect of soy isoflavones. Genistein may inhibit influx of calcium...
through voltage-gated calcium channels (1, 12, 15, 46). Genistein also reportedly enhances flux through calcium-activated potassium (47). Alternatively, genistein has been reported to increase renal excretion of sodium and water (14, 30) and also caused vasodilation in an isolated perfused kidney preparation (14, 30), suggesting that a diuretic effect may contribute to the long-term BP effects of soy isoflavones. Finally, considerable evidence supports the involvement of the renin-angiotensin system in the development and maintenance of high BP in several forms of hypertension. It has been reported that soy-derived foods contain angiotensin-converting enzyme inhibitory activity (25, 37, 38). Thus there are several potential mechanisms that may underlie the antihypertensive effect of soy and that need to be addressed in future studies.

In summary, the present study demonstrated that dietary soy, producing plasma genistein concentrations in the micromolar range, reduced the development of hypertension in OVX SHR. This effect did not appear to involve the NO system but may be related to an effect on the autonomic nervous system.

Perspectives

There is an increasing interest in alternative or natural remedies for a variety of clinical conditions despite a paucity of hypothesis-driven research on their biological effects (49). Compounds that have received considerable interest of late are the soy isoflavones. The majority of this interest has focused on the ability of these agents to reduce osteoporosis, inhibit cell growth, and reduce plasma lipids. Because of the unique pharmacological profile of these agents, they have been suggested as an alternative to estrogen replacement therapy in postmenopausal women; a time when the incidence of hypertension increases greatly. The current study indicates that dietary soy reduces the development of hypertension in OVX SHR, one model of postmenopausal hypertension. The BP lowering effect of soy diet was modest. However, because of the beneficial effects of dietary soy on bone density and plasma lipids, the mild antihypertensive effect of dietary soy may nonetheless produce a significant reduction in cardiovascular risk and offer other positive benefits in the postmenopausal state. Verification of this possibility awaits the outcome of long-term BP effects of soy isoflavones. Multiple effects of tyrosine kinase inhibitors on vascular smooth muscle contraction. Eur J Pharmacol 281: 29–35, 1995.


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