Hypotensive effect of taurine. Possible involvement of the sympathetic nervous system and endogenous opiates.

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Research Article

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Hypotensive Effect of Taurine

Possible Involvement of the Sympathetic Nervous System and Endogenous Opiates

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Abstract

We studied the role of diminished sympathetic nervous system (SNS) activity and endogenous opiate activation in the hypotensive action of taurine, a sulfur amino acid, in deoxycorticosterone acetate (DOCA)-salt hypertensive rats. Supplementation of taurine could prevent the development of DOCA-salt hypertension in rats, but failed to change blood pressure in vehicle-treated control rats. Cardiac NE turnover, which was determined from the rate of decline of tissue NE concentration after the administration of α-methyl-*p*-tyrosine, was markedly accelerated in DOCA-salt rats, but 1% taurine supplement restored it to normal. Moreover, naloxone (2 mg/kg), the specific opiate antagonist, increased blood pressure in taurine-treated DOCA-salt rats, restoring it to levels similar to those in the DOCA-salt rats. In contrast, taurine did not decrease cardiac NE turnover in the control rats, nor did naloxone increase blood pressure in the taurine-treated control rats. Moreover, supplementation of taurine increased both β-endorphin-like immunoreactive material and taurine contents in the hypothalamus of DOCA-salt rats, whereas it did not increase β-endorphin in that of control rats despite increased taurine contents. Thus, taurine not only normalized the increased cardiac SNS activity but also elicited an opiate-mediated vasodepressor response only in DOCA-salt rats. It is suggested, therefore, that endogenous opiate activation, which is intimately related to SNS suppression, may contribute to the antihypertensive effect of taurine in sodium chloride hypertension.

Introduction

Recently, there has been increased concern about ascertaining the importance of nutrients in the regulation of blood pressure and pathogenesis of hypertension (1, 2). It is well known that dietary nutrients such as sodium, potassium, calcium, and magnesium influence blood pressure (3–6). Moreover, several investigators have suggested that dietary protein and amino acids could also influence blood pressure and thus affect the development of hypertension (7, 8). Recently, emphasis has been focused on the relationship between taurine, a sulfur amino acid, and cardiovascular disease (9). Our recent studies have indicated that supplementation of the diet with taurine could attenuate the development of deoxycorticosterone acetate (DOCA)[1]-salt–induced hypertension in rats (10). Based upon the result of tissue NE turnover rate, moreover, the antihypertensive action of taurine could be attributed mainly to the suppression of increased sympathetic nervous system (SNS) activity in DOCA-salt rats (11). Furthermore, taurine could exert its antihypertensive action in man in a similar fashion, since oral administration of taurine (6 g/d) not only decreased mean blood pressure by 9 mmHg but also normalized the increased sympathoadrenomedullary tone in young patients with borderline hypertension (12).

Several investigators suggest that taurine might suppress the depolarization-induced release of NE or acetylcholine from a variety of neuronal tissues (13). It has been reported that this compound significantly decreased the electrical stimulation–or high potassium–induced release of NE in the cerebral cortical slices (14). Moreover, evidence such as the presence of taurine in relatively high concentrations in the central nervous system (CNS) (15) suggests that taurine may act as a neurotransmitter or as a neuromodulator in the CNS and thus influence sympathetic activity. Accordingly, we have demonstrated that the hypothalamic noradrenergic system might be involved in the hypotensive action of taurine in DOCA-salt rats (16).

Recently, a growing body of evidence has suggested an intricate relationship between taurine and endogenous opiates such as β-endorphin and enkephalins in the CNS; pellet implantation of morphine in rats increased taurine content in the spinal cord, which produced tolerance to analgesia of morphine and β-endorphin (17), and intraventricular administration of taurine not only inhibited the occurrence of tolerance (18, 19), but also promoted a recovery from akinesia and analgesia caused by [D-Ala^2, Met^5] enkephalinamide, an enkephalin analogue (20). In addition, activation of central opiate receptors can decrease sympathetic tone and blood pressure. In both animals and humans the administration of β-endorphin and morphine has been reported to decrease blood pressure and SNS activity (21–23). Moreover, endogenous opiates appear to participate in the antihypertensive response of hypertensive animals and patients to clonidine and α-methyldopa, which diminish central sympathetic outflow (24–26). These observations led us to test the possibility that endogenous opiates might contribute not only to the suppression of SNS activity but also to the lowering of blood pressure with the supplementation of taurine in DOCA-salt rats. We also report here further studies that address the role of diminished SNS activity and endogenous opiate activation in the hypotensive action of taurine in DOCA-salt rats.

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1. *Abbreviations used in this paper:* ANOVA, analysis of variance; DOCA, deoxycorticosterone acetate; SBP, systolic blood pressure; SNS, sympathetic nervous system.

Methods

Animal preparation. Male Sprague-Dawley rats weighing 120–130 g were subjected to unilateral left nephrectomy at 5 wk of age. After 10–14 d they were randomly divided into four groups as follows. The DOCA-salt group received weekly subcutaneous injections of 0.4 ml of a suspension containing, per milliliter of water, 25 mg DOCA, 10.5 mg methyl cellulose, 3 mg carboxymethyl cellulose, 1 mg polysorbate 80, and 8 mg NaCl, and this group was given 1% NaCl solution in tap water ad lib. The DOCA-taurine group received injections of DOCA suspension and was given a mixed solution of 1% NaCl and 1% taurine as drinking water ad lib. The control group received weekly injections of the vehicle suspension without DOCA and was given tap water to drink. The taurine group received weekly injections of the vehicle suspension without DOCA and was given 1% taurine solution to drink. Throughout the study, the animals were housed in a room with constant temperature (23±1°C) and humidity (60±5%) and light from 6 a.m. to 6 p.m. Systolic blood pressure (SBP) was measured by the tail-cuff method (10, 11) without anesthesia over a 4-wk period preceding the experiment.

Cardiac NE turnover. NE turnover is an in vivo measure of SNS activity in sympathetically innervated organs of unanesthetized, unrestrained animals (27). After the blockade of NE synthesis, tissue NE contents decrease exponentially in accord with the release of NE in response to incoming nerve impulses. The rate of disappearance of NE thus reflects SNS activity in an individual tissue. For the blockade of NE synthesis, α-methyl-*p*-tyrosine methyl ester hydrochloride was given intraperitoneally in the four groups. After the first injection of 300 mg α-methyl-*p*-tyrosine, six to eight animals from each group were killed at 3 h, and the remaining animals were reinjected with the same dose of α-methyl-*p*-tyrosine every 3 h and killed at 6 and 9 h. Also, eight animals from each group were not injected and served as t_0 references. At preselected times, six to eight rats from each group were killed and their hearts were removed for analysis of endogenous NE. The tissues were stored at −40°C until analyzed. After the tissues were homogenized in ice-cold 0.4 N perchloric acid (Wako), the homogenates were centrifuged at 40,000 *g* for 10 min. The NE was isolated with activated alumina (Woelm, FRG), and the eluates were analyzed fluorimetrically (model PF-500LC; Shimadzu, Kyoto, Japan) as described previously (11, 16).

Data are plotted as means±SE for endogenous NE in each group at each time. The line representing the decline in endogenous NE with time was calculated by the method of least squares. The slope, or rate constant of decline, represents the fractional turnover rate of NE or the percentage of the pool declining per hour (27).

Effect of naloxone on SBP in taurine-treated DOCA-salt rats. The animals were gently heated with a warming plate and heat lamp to a rectal temperature 39°C, a procedure to which the animals had been acclimated over a 4-wk period preceding the experiment.

To address the question of opiate involvement in the hypotensive response to taurine, we measured SBP in the taurine-treated DOCA-salt rats before and after intraperitoneal injection of naloxone, the specific opiate antagonist. Baseline SBP values in 10 DOCA-salt rats and 10 taurine-treated DOCA-salt rats were obtained as a mean of six to eight measurements. After the measurements, each animal was injected intraperitoneally with 2 mg/kg naloxone or an equal volume of saline. After a 1-d interval, the rats of respective groups were given the opposite treatments. The effect of naloxone on SBP was assessed from readings (mean of three) done at 5-min intervals until 30 min after the administration.

To assess whether the pressor response to naloxone was specific to taurine-treated DOCA-salt rats, we measured maximum changes in SBP after administration of 2 mg/kg naloxone or saline in DOCA-salt rats and vehicle-injected control rats with and without the supplementation of taurine, and compared the results. The experiment was repeated in accordance with a crossover design. For example, the rats in each group that received naloxone in the first experiment were given saline in the second experiment. The data are means±SE for maximum changes in SBP over 30 min after drug administration in eight rats per group.

Hypothalamic β-endorphin and taurine contents. Rats were decapitated and the brains were quickly removed, leaving the pituitary behind in the sella. The hypothalamus was dissected from the brain according to the method of Glowinski and Iversen (28). Tissues were quickly frozen on dry ice and stored at −40°C until analyzed. When the tissue samples were ready for assay, they were weighed, and placed in 1 M acetic acid preheated to 95°C. After 15 min in the hot bath, samples were chilled in ice, homogenized, and centrifuged (1,000 *g*, 1 h). The supernatant was frozen overnight, neutralized to pH 7.5 with 1 M NaOH supplemented with 0.2 M Na_2HPO_4, and refrozen overnight. Centrifugation (1,000 *g*, 1 h) after thawing yielded a clear supernatant that was then used in the RIA (29). The concentration of β-endorphin-like immunoreactive material in the supernatant was measured by RIA with ^{125}I-labeled human β-endorphin as tracer (New England Nuclear, Boston, MA) and a rabbit antibody to human β-endorphin, which was a gift of Dr. M. Matsumura. It showed 100% cross-reactivity with rat β-endorphin but only 4.5% cross-reactivity with rat β-lipotropin on a mass basis, and did not react with other peptides, including enkephalins, endorphins (α, γ, and δ), γ-lipotropin, and $^{1\text{-}39}$ACTH (30). The standards (2–512 pg human β-endorphin/tube) and samples were made up to a total volume of 0.3 ml by the addition of an assay buffer. Anti-β-endorphin antiserum (final dilution 1:20,000) with assay buffer was added, and the mixture was incubated for 24 h at 4°C. Then ^{125}I-β-endorphin (10,000 cpm/100 μl) was added and the tubes were incubated for 24 h at 4°C. All incubations were done in siliconized test tubes. The antibody-bound antigen was precipitated by the addition of goat anti-rabbit γ-globulin serum (diluted 1:100) and was incubated at 4°C for 24 h. Then the supernatant was decanted, and the radioactivity of the precipitate was counted. The average rate of binding was 42% in tubes without standard. A dose-related response in RIA was observed in a range of 4–256 pg/tube. The concentration of β-endorphin in the hypothalamus was expressed as picograms per milligrams protein (31).

For the measurement of hypothalamic taurine content, tissues were deproteinized with sulfosalicylic acid, and the deproteinized samples were analyzed on an amino acid analyzer (model D-502; Dionex, CA) (11). The tissue taurine content was expressed as micromolars per gram of wet weight.

Statistical analysis. Group values are expressed as means±SE. Results were analyzed by two-way analysis of variance (ANOVA) for the differences between the control and DOCA salt lines (F_A), the effects of taurine supplementation (F_B), and the differential effects of taurine supplementation on each of the two lines (interaction: F_{AB}), and the Bonferroni method was used for comparisons between individual means (32). A P value of $< 5\%$ was considered significant.

Results

Blood pressure. The effect of taurine on SBP was assessed in DOCA-salt rats and control rats. SBP of DOCA-salt rats at week 4 (154±4 mmHg) was significantly ($P < 0.001$) increased compared with those of control rats (111±4 mmHg). In contrast, 1% taurine supplementation inhibited the elevation of SBP in DOCA-salt rats (118±4 mmHg), whereas taurine did not change SBP in control rats (112±3 mmHg).

Cardiac NE turnover. The effect of taurine on the turnover of NE in cardiac tissue was measured simultaneously in DOCA-salt rats and control rats (Fig. 1). In DOCA-salt rats, fractional and calculated turnover rates were significantly greater as compared with vehicle-treated control rats. With the supplementation of taurine, however, fractional and calculated turnover rates in DOCA-salt rats were significantly decreased, restoring them to normal, whereas those of control

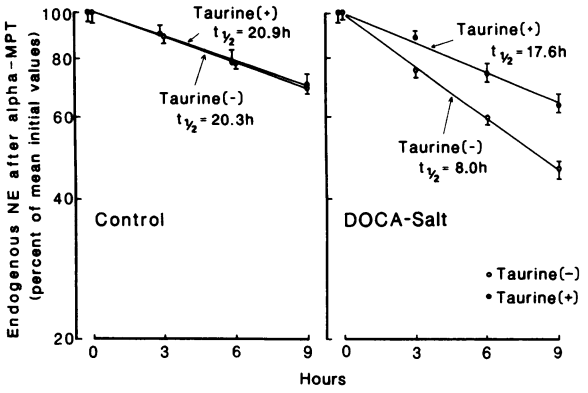

Figure 1. Effect of taurine on turnover of NE in the hearts of DOCA-salt rats and vehicle-injected control rats. The slopes of the lines (fractional turnover rates) are 3.33±0.45 and 3.41±0.50%/h for taurine-treated and taurine-untreated vehicle-injected control rats, respectively (NS); 3.94±0.52 and 8.66±0.67%/h for taurine-treated and taurine-untreated DOCA-salt rats ($P < 0.001$). The content of endogenous cardiac NE was 499±38 and 495±35 ng/g in taurine-treated and taurine-untreated control rats; 426±37 and 415±44 ng/g in taurine-treated and taurine-untreated DOCA-salt rats, respectively. No statistically significant variation was observed by two-way ANOVA. Calculated cardiac NE turnover was 16.6±2.2 and 16.5±2.5 ng/g per h (NS) in taurine-treated and taurine-untreated control rats; 16.8±2.2 and 35.1±2.7 ng/g per h ($P < 0.001$) in taurine-treated and taurine-untreated DOCA-salt rats, respectively. At both fractional and calculated turnover rates, main effects for line (control and DOCA-salt), taurine supplementation, and line times taurine interaction were revealed. Thus, taurine supplementation resulted in the attenuation of cardiac NE turnover only in DOCA-salt rats.

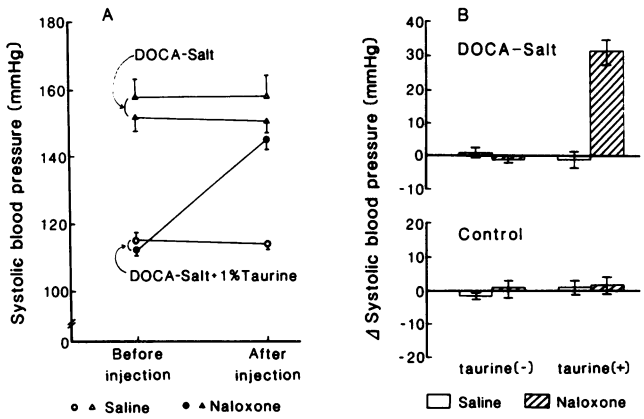

Figure 2. (*A*) Effect of 2 mg/kg naloxone on SBP in 10 DOCA-salt rats and 10 taurine-treated DOCA-salt rats. Naloxone increased SBP significantly in taurine-treated DOCA-salt rats ($P < 0.001$, by paired *t* test) whereas saline did not. In contrast, neither naloxone nor saline changed SBP in DOCA-salt rats. The postnaloxone SBP levels in taurine-treated DOCA-salt rats were significantly ($P < 0.01$) higher than the postsaline SBP levels, and then reached those in DOCA-salt rats. (*B*) Change in SBP in DOCA-salt rats and vehicle-treated control rats with and without supplementation of taurine before and after injection of 2 mg/kg naloxone or saline. In DOCA-salt rats, two-way ANOVA revealed significant effects for naloxone (F 3,28 = 41.91, $P < 0.001$), taurine (F 3,28 = 41.91, $P < 0.001$), and interaction (F 3,28 = 49.90, $P < 0.001$). Thus, the elevation in SBP after naloxone was injected into taurine-treated DOCA-salt rats (+31.3±3.5 mmHg) was significantly different from the responses in the other groups of DOCA-salt ($P < 0.001$). In control rats the between-group variation in SBP was not statistically significant.

rats remained unchanged with taurine. Taurine thus suppressed cardiac SNS activity only in DOCA-salt rats with increased SNS activity, which resulted in the prevention of the development of DOCA-salt hypertension.

Effect of naloxone on SBP. SBP in taurine-treated DOCA-salt rats was significantly lower than in DOCA-salt rats (112±1 vs. 151±4 mmHg, $P < 0.001$). Naloxone increased SBP by 31.3±3.5 mmHg over the ensuing 30 min in taurine-treated DOCA-salt rats ($P < 0.001$); in contrast, no significant change was observed after saline treatment (Fig. 2 *A*). In taurine-untreated DOCA-salt rats, however, neither naloxone nor saline changed SBP. Thus, naloxone increased SBP only in taurine-treated DOCA-salt rats, and restored it to levels similar to those in the DOCA-salt rats. As shown in Fig. 2 *B*, moreover, SBP in naloxone-treated, taurine-treated DOCA-salt rats increased significantly compared with SBP in the other three DOCA-salt rats ($P < 0.001$). In vehicle-injected control rats, on the other hand, no significant variation was noted among the four groups. The pressor effect of naloxone was specific to taurine-treated DOCA-salt rats.

Hypothalamic β-endorphin and taurine contents (Table I). Supplementation of taurine increased β-endorphin-like immunoreactive material content in the hypothalamus of DOCA-salt rats (218±20 vs. 132±18 pg/mg protein [$P < 0.01$]), whereas its content did not increase with taurine in that of control rats (159±19 vs. 166±15 pg/mg protein [NS]). In contrast, taurine supplementation produced a significant increase in taurine content of the hypothalamus in both DOCA-salt rats (3.18±0.20 vs. 2.32±0.20 μmol/g, $P < 0.01$) or control rats (3.08±0.12 vs. 2.43±0.08 μmol/g, $P < 0.05$).

Discussion

Our first relevant observation, in keeping with our previous studies (10, 11, 16), is that 1% taurine supplementation in DOCA-salt rats effectively prevented the development of hypertension. Concomitant with the antihypertensive effect of taurine is that the increased cardiac NE turnover in DOCA-salt rats was normalized by taurine supplementation. In contrast, 1% taurine supplementation in normotensive control rats affected neither blood pressure levels nor cardiac NE turnover. Thus, these results strongly suggest that the factor that most likely accounts for the antihypertensive effect of taurine is the normalization of the increased SNS activity observed only in sodium chloride hypertensive animals. However, the

Table I. Effects of Taurine Supplementation on β-Endorphin and Taurine Contents in the Hypothalamus of DOCA-Salt Rats

	β-Endorphin		Taurine	
	n	*pg/mg protein*	*n*	*μmol/g wet weight*
Control	8	159±19	8	2.43±0.08
Control + 1% taurine	9	166±15	9	3.08±0.12*
DOCA-salt	8	132±18	8	2.32±0.20
DOCA-salt + 1% taurine	9	218±20‡§	9	3.18±0.20‡§

Data are presented as mean±SE. *n*, number of animals per group; * $P < 0.05$, compared with control group; ‡ $P < 0.01$, compared with the control group; § $P < 0.01$ compared with DOCA-salt group.

precise mechanism of the hypotensive effect of taurine is still unknown.

With regard to the causal relationship between endogenous taurine and SNS activity, one might speculate that abnormal taurine metabolism in the CNS was able to increase central sympathetic outflow, resulting in the development of DOCA-salt hypertension. The evidence does not support such a suggestion, however, since there was no significant difference in hypothalamic taurine content between DOCA-salt hypertensive rats and control normotensive rats. However, until taurine content in the hypothalamus increased with the supplementation of taurine, neither SNS activity nor blood pressure were normalized in DOCA-salt rats. These data provide evidence for a "protective" or "secondary" role rather than a "primary" role in the prevention of sodium chloride hypertension by taurine.

The second important finding in this study is that naloxone, the specific opiate antagonist, could reverse the hypotension produced by taurine supplementation. These data provide indirect evidence that endogenous opiates contribute to the reduction in SBP observed in these animals treated with taurine. However, naloxone failed to increase blood pressure in taurine-untreated DOCA-salt rats and vehicle-injected control rats with and without taurine supplementation. These data imply that the opiate-induced hypotension occurred only in sodium chloride hypertensive animals and only in response to taurine.

Taurine may act as a neurotransmitter or as a neuromodulator in the CNS and may influence SNS activity (13, 14, 33). Opiates are also known to modulate autonomic outflow by action at central sites (34, 35). According to the central action of taurine, our previous studies showed that taurine supplementation could attenuate the cold stress-induced augmentation of noradrenergic activity in the hypothalamus as in the hearts of DOCA-salt hypertensive rats, which suggests the possible role of the hypothalamic noradrenergic system in the hypotensive action of taurine (16). In the present study, moreover, taurine content in the hypothalamus was markedly increased in the taurine-treated DOCA-salt rats. Concurrently, supplementation of taurine increased β-endorphin-like immunoreactive material content in the hypothalamus of DOCA-salt rats. The evidence strongly suggests that overproduction of a β-endorphin-like material in the hypothalamus contributes to the antihypertensive action of taurine in DOCA-salt rats, since it has been reported that opiates administered into the anterior hypothalamus produce bradycardia and hypotension (22, 23). Thus, the inhibition of the hypotensive action of taurine by naloxone is accordingly due to the blocking of the effect of this opiate on central opiate receptors that inhibit to SNS activity. Moreover, it is suggested that endogenous opiates in the hypothalamus might contribute to the taurine-induced reduction in the increased SNS activity in DOCA-salt rats, but such an effect was not evident in control rats under the same condition in which it was observed in DOCA-salt rats.

The failure of naloxone to influence blood pressure in control rats correlates with the failure of taurine to increase hypothalamic β-endorphin content in these animals, and also agrees with the failure of taurine to suppress cardiac NE turnover and to decrease blood pressure in control rats. Consistently, our previous studies have showed that taurine was effective in suppressing SNS activity and decreasing blood pressure only in hypertensive animals and patients with increased SNS activity, but failed to do so in normotensive rats and subjects with normal SNS activity (11, 12, 16). Thus, we were led to the speculation that the antihypertensive effect of taurine exerts its influence only under the conditions of increased SNS activity, through the normalization of SNS overactivity. Supporting this possibility are reports demonstrating that the addition of taurine in vitro significantly attenuates the Ca-dependent, K-evoked release of [^{3}H]NE from a variety of neuronal tissues without affecting uptake or unstimulated (spontaneous) release (14).

As a putative neuromodulator, taurine is believed to modulate Ca transport across biomembranes; taurine has been shown to inhibit Ca release from synaptosomal fractions of brain tissue and to attenuate Ca influx in neuronal tissues, which leads to a decrease in availability of intracellular Ca in the sympathetic nerve (13, 33). Thus, taurine might modulate the release of NE in neuronal tissues. Similarly, β-endorphin may inhibit the release of neurotransmitters by inhibition of Ca influx, whereas naloxone inhibits its action (36–39). Therefore, it seems reasonable to assume that a possible taurine-induced alteration of Ca transport, which may modulate neurotransmission in the CNS, could be partially restored by treatment with naloxone, which would result in the elevation of blood pressure due to the increased SNS activity. In support of this hypothesis, several investigators have demonstrated the interaction between taurine and endogenous opiates such as β-endorphin and enkephalins; morphine-treated rats had increased taurine content in their spinal cords (17), which might cause the inhibition of the development of tolerance to morphine and β-endorphin in rats (18, 19). It is suggested, therefore, that brain taurine and β-endorphin are interdependent and may function together in a common system by regulating each other and the release of neurotransmitters.

Evidence suggests that the combination of SNS suppression with opiate activation is not unique to the taurine-treated DOCA-salt rats. Diminished SNS tone and increased opiate activity have been demonstrated in clonidine-treated SHR (24, 25), fasted SHR (40), and animals suffering from experimentally induced hypotension (hemorrhagic or endotoxin shock) (41–43). In all these situations, which are analogous to forms of hypotension associated with SNS suppression, endogenous opiates might play a role in the central regulation of SNS tone and blood pressure. Thus, reciprocal changes in the activity of both systems may be important in the taurine-induced hypotension, since opiates and the SNS act antagonistically on blood pressure.

Finally, the evidence presented here suggests that endogenous opiate activation, which is intimately related to SNS suppression, may contribute to the antihypertensive effect of taurine in sodium chloride hypertension.

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