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Treatment of hypertension with oral taurine: experimental and clinical studies

Review Article

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Summary. Oral taurine treatment has been studied extensively as a hypotensive agent. Several rat models of hypertension have been used to prove that dietary taurine supplementation can alleviate high blood pressure, among other cardiovascular problems. Experimental models mentioned in this review are the spontaneously hypertensive rat, the DOCA-salt rat, the Dahl-S rat, the renovascular hypertensive rat, the hyperinsulinemic rat and the ethanol-treated rat. The beneficial effects of taurine were also demonstrated in studies involving human subjects suffering essential hypertension. Taurine supplementation of 6 g/day for as little as 7 days resulted in measurable decreases in blood pressure in these patients. In both rat and human studies, the effects of taurine appeared to be dependent on the modulation of an overactive sympathetic system. However, taurine has positive effects on other types of cardiovascular problems and thus may act through more than one mechanism.

Keywords: Hypertension – Taurine supplementation – Experimental models – Modulation of overactive sympathetic system

Introduction

It has been scientifically established for nearly a century that patients with elevated arterial blood pressure tend to die prematurely. Thus, genetic predisposition to or disease conditions that involve hypertension are considered serious health concerns that demand immediate, sometimes aggressive, treatment and vigilant medical supervision. Today, the pharmaceutical marketplace is awash with numerous drugs for hypotensive therapy aimed at controlling high blood pressure. Various forms of alternative non-pharmaceutical regimen are also extremely popular, like stress management, exercise, yoga and diet modification.

Hypertension has been studied using various experimental models of hypertension, most of which employ the use of rats (Pinto et al., 1998). While the most common model is the spontaneously hypertensive rat, other models are also used like the DOCA-salt rat, the salt-sensitive Dahl-S rat and the renovascular hypertensive rat, among others (Table 1). In all of these experimental models, the use of taurine supplementation has been effective in controlling hypertension.

For more than 3 decades, taurine has been studied as a possible agent for the control of hypertension. Most of the work has been done in Japan and made use of subjects exhibiting essential hypertension. The interest in taurine came from correlative studies in which it was demonstrated that food rich in sulfur amino acids, like fish, seemed to prevent hypertension and stroke (Yamori et al., 1996). Taurine is a very attractive option for hypertension therapy because, as a natural substance, it is relatively cheap, non-toxic and easily available.

The use of taurine supplementation is potentially a very safe and convenient regimen for the control of high blood pressure. It is unfortunate that use of taurine has yet to achieve any level of recognition as a dietary option in the treatment of hypertension, given the strong experimental data and consistent clinical findings supporting its efficacy. This review article aims to describe the beneficial effects of taurine on hypertension both in rat experimental models and in cases of human hypertension. Other aspects of taurine

Table 1. Models of hypertension and the anti-hypertensive effects of oral taurine treatment

Experimental model	Description	Reference
Spontaneously hypertensive rat (SHR)	hypertensive Wistar substrain; genetic; age-related	Nara et al., 1978; Abe et al., 1987; Trachtman et al., 1989
SHR model	stress evoked hypertension	Yamamoto et al., 1985
DOCA-salt (Sprague-Dawley) rats	hypertension induced with deoxycorticosterone acetate	Inoue et al., 1988; Fujita and Sato, 1984, 1986, 1988; Fujita et al., 1986; Sato et al., 1991
Salt-sensitive Dahl rats (Dahl-S)	hypertension induced by high-salt diet	Ideishi et al., 1994
Renovascular hypertensive rats (RHR)	two-kidney, one-clip hypertension; simultaneous treatment with enalapril	Ji et al., 1995; Tao and Rao, 1996
Hyperinsulinemic (Wistar) rat	hypertension induced by fructose-rich diet	Anuradha and Balakrishnan, 1999
Ethanol treated (Wistar-Kyoto) rat	ethanol-induced hypertension	Harada et al., 2000
Clinical setting: human	essential hypertension	Kohashi et al., 1983; Fujita et al., 1987; Yamori et al., 1996

physiology relevant to the hypotensive effects of taurine are also discussed.

The effect of taurine on hypertension in SHR rats

In 1963, Okamoto and Aoki reported the creation of a special strain of Wistar-Kyoto (WKY) rats that developed spontaneous hypertension with age without exception. The strain has since been known as the spontaneously hypertensive rat (SHR) strain. The genetic line was started with a male rat which showed elevated systolic blood pressure (BP) of 145–175 mm Hg and a female rat with blood pressure of 130–140 mm Hg, a value slightly higher than average. It is with the SHR model that the hypotensive effects of taurine have been studied the most.

The male SHR rats appeared to have a slightly higher blood pressure than female rats (reviewed in Okamoto et al., 1966). The rat model presented with age-dependent resting hypertension, with 100% incidence of hypertension occurring between 10–25 weeks of age in studies covering the F1 to the F16 generation (Okamoto, 1969). In later studies, Nara and colleagues (1978) reported that BP increased to the highest values at ~50–60 days of age and leveled off after that. The different scientific reports involving the SHR rat model have exhibited variability in both the onset and severity of hypertension through the years.

The SHR rat model exhibited various hypertension-linked lesions. Cerebral lesions, myocardial infarction and fibrosis, nephrosclerosis, periarteritis nodosa and arterionecrosis without nephrosclerosis, and malignant hypertension were some of the lesions observed (Okamoto, 1969). In the hypertensive stage, a significant increase in cardiac weight was observed, while hardly any difference was observed in the body weight. Other organs, like the thyroid and adrenals all exhibited slight increases in weight, however, the pituitary organ became markedly enlarged as the hypertension progressed. Pneumonia was the most common cause of death in the SHR (74%). Death due to malignant hypertension (8%) and cerebral hemorrhage (3%) were also observed. The SHR rats have since been established as a useful animal model for essential hypertension in humans.

The mechanism behind the increase in blood pressure appears to involve the hypothalamic-autonomic axis or the hypothalamohypophyseoadrenocortical system (Okamoto, 1969). Hypophysectomy, radiothyroidectomy and bilateral adrenalectomy, but not gonadectomy, each prevented the development of hypertension in the prehypertensive rats and lowered the blood pressure in the hypertensive rats. The hypertension may also involve the hypothalamic dysregulation of adrenocorticotropic (ACTH) and thyroid-stimulating (TSH) hormone secretion from the pituitary. Histologic studies of the hypothalamus and the brainstem, as well as plasma measurements of TSH, T3, T4 and prolactin (Kojima et al., 1975a,b) appear to support these concepts. While it was postulated that the regulation of the pressor and depressor mechanisms in the CNS is abnormal, and that periph-

eral lesions result from this abnormality, clearly the genesis of hypertension in the SHR is multifactorial and complex.

Hypertension at rest

Nara and colleagues (1978) reported that oral administration of taurine (3% in drinking water for ~10 weeks) was effective in lowering resting blood pressure in SHR rats and in a specific stroke-prone substrain of SHR rats (SHRSP). In one experiment in this study, the SHRSP substrain exhibited blood pressures of ~227 mm-Hg at three months of age, while the non-stroke-prone group (SHR) exhibited blood pressures of ~189 mm-Hg (control BP = ~129 mm-Hg). In another experiment, BP measurements were ~196, ~178 and ~127 mm Hg for SHRSP, SHR and control rats, respectively, clearly indicating a variability in the severity of the developed hypertension in the SHR rat model.

Taurine lowered blood pressure in SHR and SHRSP rats, but did not affect blood pressure in the non-hypertensive control WKY rats. Specifically, taurine attenuated the increase in BP from ages 4- to 10-weeks. Oral taurine was more effective as an antihypertensive drug with the SHR-SP group than with the SHR group, equalizing BP in these two strains. Taurine did not reduce blood pressure to control levels. The data suggest that taurine acts to stabilize blood pressure to a certain level rather than to produce the same relative effect in all rats.

Very similar results were observed in experiments performed more than 10 years later with SHR rats. The rats were treated with 1% taurine (in drinking water) for 16 weeks (Trachtman et al., 1989). Taurine treatment was hypotensive after 4 weeks of treatment until the end of the experiment at 16 weeks. Under this regimen, taurine levels increased in the plasma >200%, in contrast to the study by Nara and colleagues (1978) which demonstrated no changes in plasma taurine levels after taurine treatment. The difference may be due to the longer treatment duration or to a difference in the method of plasma isolation.

Prenatal effects of dietary taurine

Another study demonstrated the hypotensive effect of maternal taurine on the rat fetus. In experiments with SHRSP rats, taurine was administered in drinking water to the female rats before and during pregnancy, and at certain cases, during the time the rats fed on maternal milk (Horie et al., 1987). At 2 and 3 months after birth, exposure to taurine correlated to a decrease in developed hypertension. Exposure to taurine after birth produced an even greater hypotensive effect.

Stress-induced hypertension

Yamamoto et al. (1985) report hypotensive effects with taurine treatment in SHR rats that have been subjected to stress. Various hemodynamic parameters were measured in SHR and control WKY rats at rest and during short-term shaker stress. Taurine (1.5% in drinking water for 8 weeks) was given to half of the rats and was found to be effective in attenuating the rise in mean arterial pressure, heart rate and total peripheral resistance in SHR rats during shaker stress. Similar hypotensive effects were observed in control WKY rats, albeit to a much less significant degree. The effects of taurine were, thus, attributed to the attenuation of hemodynamic and plasma catecholamine changes during stress.

Salt-induced hypertension

Increased salt intake is an important factor in the development of hypertension. A high-salt diet was associated with increased fluid intake and urine output in the SHR rats (Dawson et al., 2000). However, no changes in body weight or serum taurine levels were observed. Increased salt intake accelerated the development of hypertension in SHRSP rats and exhibited slightly higher BP levels during the hypertensive stage. Taurine was administered in the drinking water (1.5% for ~21 weeks) and did not antagonize the effect of high-salt diet to accelerate the development of hypertension. However, mean blood pressure during the hypertensive stage was slightly lower compared to rats that did not receive taurine. In general, taurine administration showed certain cardio- and renoprotective effects.

The effect of taurine on hypertension in DOCA-salt rats

Another animal model used for the study of hypertension is the DOCA-salt rat. Normal rats given deoxycorticosterone acetate (DOCA) were found to exhibit hypertension with a high salt-diet (Fujita and Sato,

1984). Succeeding work described increases in cardiac, hypothalamic and splenic turnover of norepinephrine (NorE), in the levels of NorE and epinephrine (Epi) in the plasma, and in Epi levels in the adrenal glands (Fujita and Sato, 1984, 1988; Fujita et al., 1986a; Sato et al., 1991). The same group also described the increased depressor response to ganglionic blockade (Fujita et al., 1986a). Another research group reported that in these rats, urinary NorE and Epi excretion were also increased (Inoue et al., 1988). These data are consistent with prior data on this specific model system, and along with early findings that immunosympathectomy inhibited hypertension (Ayitey-Smith and Varma, 1970), suggested that the rise in blood pressure in these rats involved increased sympathetic activity.

Dietary taurine was found to be effective in inhibiting the development of hypertension in DOCA-salt rats. The effect was dose-dependent as 3% taurine in drinking water produced greater hypotensive effects than 1% (Fujita et al., 1986b). Another group used 2% taurine in drinking water with similar success (Inoue et al., 1988). Clearly, taurine serves to reverse the changes in the sympathetic system of the rats. Taurine (1% in drinking water) could normalize the increased turnover rate of NorE in the heart, spleen and hypothalamus of these rats (Fujita and Sato, 1984, 1988; Fujita et al., 1986a). The levels of NorE and Epi in the plasma and adrenal glands were also normalized with taurine supplementation (Fujita and Sato, 1988; Sato et al., 1991). Overactivity of the sympathetic system in response to cold stress was also attenuated by taurine supplementation (Fujita et al., 1986a). However, taurine supplementation did not affect NorE turnover in the control rat (Fujita and Sato, 1988). The pressor response and sympathetic nerve response to electrical stimulation of the hypothalamus were also decreased with taurine treatment (Inoue et al., 1988). Interestingly, while taurine supplementation increased taurine levels in the heart and hypothalamus, no change was observed in the adrenal glands (Fujita et al., 1986a; Fujita and Sato, 1988; Sato et al., 1991). Hypertension is usually associated with increased extracellular fluid (ECF), but, paradoxically, taurine treatment increased the ECF volume in the course of its hypotensive effects (Fujita et al., 1986b). Taurine treatment was also associated with increased natriuresis (Inoue et al., 1988). The suppression of the sympathetic system was also associated with the action of endogenous opiates. It was found that the effects of taurine may have involved the activation of opiate receptors as naloxone, an opiate antagonist, was found to inhibit the hypotensive action of taurine (Fujita and Sato, 1988). Naloxone, however, did not exhibit any effect on blood pressure in control or in any other experimental conditions. Taurine levels increased in the hypothalamus with taurine treatment, and were associated with increased β-endorphin-like immunoreactivity in the hypothalamus. Thus, in addition to the normalization of catecholamine metabolism, the overproduction of β-endorphin in the hypothalamus was considered to be an important factor in the hypotensive effects of taurine in the DOCA-salt rat model.

The effects of taurine on hypertension in Dahl-S rats

A specific strain of Dahl rats (Dahl-S) is prone to hypertension and is particularly sensitive to the effects of a high salt diet (Ideishi et al., 1994). Blood pressure was found to be higher at all ages compared to control salt-resistant rats (Dahl-R). Moreover, Dahl-S rats exhibited increased systolic BP with a high salt diet while Dahl-R rats showed no changes at all. The data suggested that the hypertension is due to decreased renal kallikrein gene expression, a factor that may be crucial in the development of human essential hypertension. When taurine was administered (3% in drinking water) at the same time as the high-salt diet, the development of hypertension was retarded significantly. Taurine treatment was also associated with greater urinary volume and increased kallikrein excretion.

The effect of taurine with renovascular hypertensive rats

Goldblatt hypertension is surgically induced in normal rats by clipping the renal artery, thereby reducing blood flow to the kidney, and eliciting a renin-dependent hypertensive feedback response (Pinto et al., 1998). This model of hypertension usually presents with left ventricular hypertrophy and calcium overload, and is also known as the renovascular hypertensive rat (RHR) model or the two-kidney, one-clip rat model. Taurine was described to produce hypotensive effects in RHR (Ji et al., 1995; Tao and Rao, 1996). Renin antagonism with enalapril and simultaneous taurine treatment reduced BP to control levels and reversed ventricular hypertrophy and normalized cal-

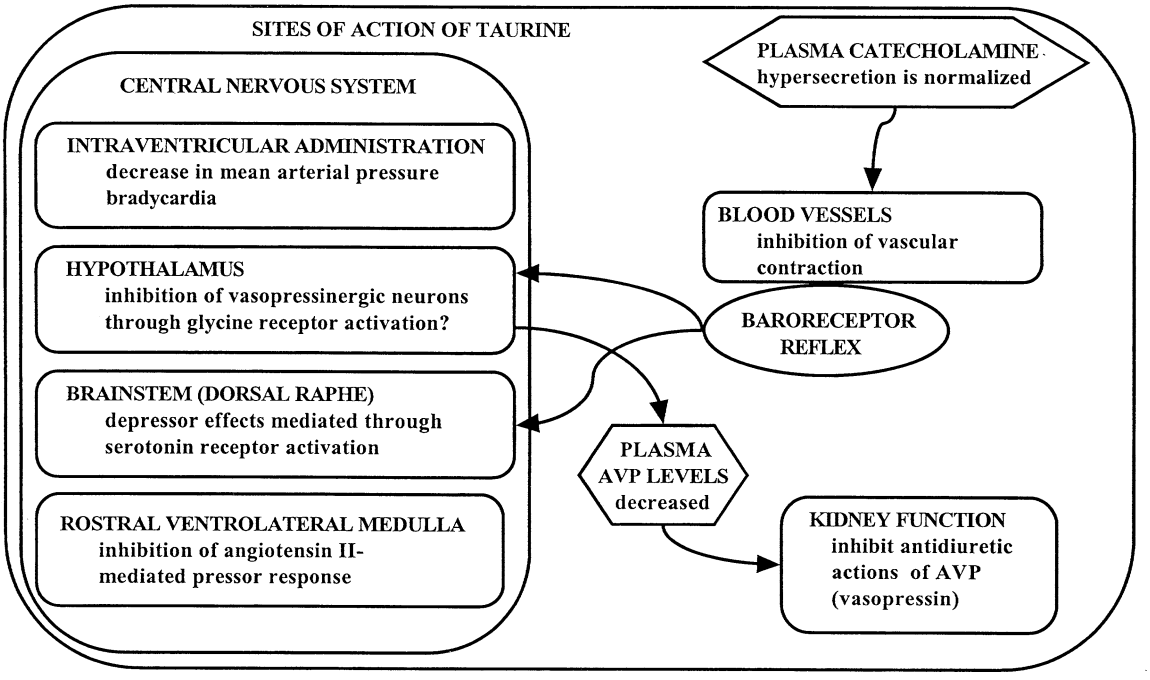

Fig. 1. Schematic diagram of the possible sites of action of taurine as a hypotensive agent. Please refer to the text for details

cium metabolism. Combination treatment was more effective than treatment with each drug alone.

The effect of taurine on other experimental models of hypertension

Increased insulin levels has been associated with hypertension, and this pathology has been studied in an experimental rat model. Moderate hypertension could be induced in normal Wistar rats with fructose feeding, along with hyperinsulinemia, insulin resistance and impaired glucose tolerance (Anuradha and Balakrishnan, 1999). Fructose feeding (6 weeks duration) did not appear to affect food and fluid intake, urinary output, body weight gain and final body weight in the rats. Plasma glucose and insulin were increased as expected, while plasma sodium and taurine were increased and decreased, respectively. The mechanism behind the decrease in taurine is unclear. Treatment with taurine (2% in drinking water concomitant with fructose feeding) inhibited the rise in BP and plasma insulin, suggesting the possible use of taurine in cases of hypertension induced by hyperinsulinemia.

Hypertension can also be induced in normal rats with ethanol treatment, hypothetically due to the formation of acetaldehyde which is the primary metabolite of ethanol (Harada et al., 2000). At around 4 weeks of ethanol treatment (5% or 15% in drinking water) of control Wistar-Kyoto rats, systolic BP rose in an apparent dose-dependent manner. No significant difference was observed in body weight with ethanol treatment but increases in hemoglobin-bound acetaldehyde levels (HbAA) were evident. The hypertension was also associated with decreased urinary output, sodium retention and abnormal intracellular cation levels. Simultaneous treatment with taurine (1% in drinking water) prevented the hypertensive effects of ethanol, an effect that involved the normalization of HbAA levels and of cation metabolism. Thus, it was suggested that ethanol caused hypertension through an acetaldehyde-dependent mechanism and that taurine prevented ethanol-induced hypertension by modulating acetaldehyde dehydrogenase activity and cation transport.

The effects of taurine on human hypertension

Oral taurine treatment has been an effective antihypertensive regimen in human subjects as well. A clinical study reported that taurine supplementation of eight patients with essential hypertension under a strict 10-g salt diet alleviated the symptoms of hypertension (Kohashi et al., 1983). After 6 weeks of taurine treatment (6 g/day), significant reductions in systolic

BP, diastolic BP and mean BP were observed (N = 8). The authors later went on to suggest that taurine acts through the enhancement of the kallikrein-kinin and prostaglandin system in the kidney.

These findings were validated in a separate double-blind placebo-controlled study performed several years later. Fujita and colleagues (1987) report similar findings with patients who were either given taurine (6 g/day for 7 days) or a placebo. Normotensive and borderline hypertensive patients were treated on an out-patient basis. Among hypertensive patients, systolic, diastolic and mean BP decreased with taurine treatment ($p < 0.05$, N = 10 paired t-test), whereas with the placebo (N = 9), no changes were observed. Among normotensive patients, taurine produced no effects on blood pressure.

More recently, a similar study on the hypotensive effects of taurine was done with Tibetans living at the foot of Mt. Everest (Yamori et al., 1996). Mild hypertensive and borderline hypertensive men were given 3 g of taurine per day for 2 months. Both systolic and diastolic BP decreased significantly in 11 out of 17 men who took taurine regularly. No effect was observed with less than 10 days of taurine treatment. The report suggested that taurine is not only a positive factor in the treatment of hypertension but in cardiovascular disease treatment in general.

Plasma taurine levels and taurine excretion in hypertension

In producing its hypotensive effects, taurine supplementation may have acted to reverse taurine deficiency, among other possible mechanisms of action. Taurine levels in the plasma and liver were not significantly different in the SHR rats as compared to control rats, but were significantly decreased in the SHR-SP rats (Nara et al., 1978). However, there was a decreasing trend observed through the three experimental groups (controls > SHR > SHRSP, N = 6–8), corresponding roughly to the increasing severity of the hypertension across the rat strains. With higher N values, the difference in plasma taurine may be significant through the 3 groups. Strangely enough, taurine treatment did not significantly change plasma taurine levels in any of the rat groups. While no exact mechanism has been proposed for the change in taurine levels, it is assumed that the lesion is genetic in origin in the same way the hypertension of the SHR.

In the above studies (Nara et al., 1978), a significant increase was observed in the taurine levels in the cerebellum (9%), diencephalon (25%) and lower brainstem (33%) of the SHRSP rats after taurine supplementation even if no increase in plasma taurine was observed. Unfortunately, no similar measurements were done with the control and SHR rat groups. The data are significant because these brain areas have been associated with the pathogenesis of hypertension in this specific experimental model (reviewed in Okamoto, 1969). Whether this effect on the brain levels of taurine is pertinent to the anti-hypertensive effects of taurine is, however, unclear. In a separate experiment, no differences were observed in the taurine content of these brain areas across the three experimental groups. Moreover, absolute values of taurine levels were slightly lower in the studies with taurine treatment of SHRSP rats compared to the baseline study involving all rat groups.

In the study by Nara and colleagues (1978), it is interesting to note that serum taurine concentration decreased across the SHR substrains in relation to the severity of the hypertension, for it suggests a dose-dependent function for taurine in preventing hypertension, however unknown the mechanism behind the decrease may be. Moreover, the decrease is also observed in other studies on hypertension. For example, in the rat model of hyperinsulinemic hypertension, taurine is also decreased in the plasma (Anuradha and Balakrishnan, 1999). Similarly, in a study of 12 patients with essential hypertension, plasma taurine was found to be significantly lower compared to 12 normotensive patients under similar dietary control, and the decrease correlated inversely with systolic blood pressure (Ogawa et al., 1985). These patients were under nutritional control for 10 days or more. Thus, on the surface, the antihypertensive effect of taurine supplementation appears to be a simple compensation for a deficiency of taurine in the blood. In fact, a training regimen that improves blood pressure in patients with essential hypertension also results in increased taurine levels in the blood (Tanabe et al., 1989).

However, Yamamoto and colleagues (1985) report only a slight but non-significant decrease in plasma taurine in SHR, age 15 weeks. Jones (1988) reported no difference in plasma taurine levels in SHR at ages 3.5, 6 and 28 weeks, and moreover, described an increase at age 8 weeks. Similarly, in studies involving a larger group of patients, it was reported that there were no differences in plasma taurine levels between

normotensive subjects and hypertensive subjects (Kohashi and Katori, 1983; Fujita et al., 1987). All the subjects, however, were studied in an outpatient basis and their diets were not controlled. Perhaps, the relative lack of diet control makes comparisons between these clinical studies inappropriate. Unfortunately, the discrepancies are still without explanation.

There also appears to be a negative correlation between decreased taurine excretion and essential hypertension. Essential hypertension presents with decreased urinary excretion of taurine (Kohashi and Katori, 1983), a most interesting observation in that the same study showed no difference in the plasma levels of taurine between the two groups. It was hypothesized that the decreased excretion may be due to some hypertension-linked renal dysfunction. However, the decrease did not correlate with diminished renal function, and so it was suggested that in essential hypertension, there is a depression of taurine formation the mechanism of which is yet unknown.

A correlation between taurine excretion and hypertension was also observed in later population studies. Mizushima and colleagues (1997) report that middle-aged Japanese immigrants in Brazil showed greater incidence of hypertension and obesity compared to similar subjects in Japan. The study suggests strong environmental influence on the development of hypertension as the subjects were of the same geo-ethnic background. Increased taurine excretion was observed in the groups that exhibited lesser frequency of hypertension. Another study involved the comparison of 4 ethnic groups in China (Liu et al., 2001). In this study, subjects randomly selected from the Han and Uygur ethnic groups presented with lower prevalence of hypertension than subjects from the Kazak and Tibetan groups. An inverse association between blood pressure and taurine excretion was observed in all 4 ethnic groups. For these 2 studies, the difference in taurine excretion was attributed to higher seafood intake, however, the earlier study of Kohashi and Katori (1983) suggest that the mechanism may be genetic and not diet-dependent. Again, there are exceptions to this hypothesis. The study by Fujita and colleagues (1987) demonstrated no differences in taurine excretion between normotensive and borderline hypertensive clinical subjects. The discrepancy is still unexplained.

The effects of taurine in the central nervous system to reduce hypertension

There is strong evidence that taurine acts in the central nervous system (CNS) to produce its hypotensive effects. Sgaragli and Pavan (1972) injected various amino acid compounds into the cerebrospinal fluid space of control Sprague-Dawley rats and measured changes in arterial BP. Taurine, glycine, GABA, L(α)-alanine and L-serine were effective in lowering arterial BP acutely (<3 minutes), with taurine producing the greatest effect. The effects were observed with both intracisternal (4th ventricle) and intraventricular administration (lateral ventricles). All the amino acids also caused CNS depression in general and a reduction in body temperature, and thus, it is unclear what is the primary effect of injected taurine. Significantly, similar administration of taurine into the ventricles of the brain has alleviated hypertension in studies using the SHR and RHR models (Petty and Di Francesco, 1989; Takemoto, 1991).

Hypertension and the hypothalamus

Hypertension has been linked to many functional changes in the hypothalamus, a central component of the limbic system (reviewed in De Wardener, 2001). The hypothalamus acts as a neuroendocrine control center for body functions such as water conservation, blood pressure, heart rate, satiety, thirst and hunger, among others. Changes in the release of neurotransmitters are more easily observed in the rostral hypothalamus and mostly lead to an increase in sympathetic nervous activity. It was suggested that the changes are secondary to renal and intrathoracic cardiopulmonary afferent stimulation, and were mainly compensatory natriuretic response to decreased sodium excretion. Notably, the role of taurine and glial cells in the modulation of hypothalamic activity has also been well studied. While neurons also exhibited taurine immunoreactivity, glial cells possessed the highest taurine signal in the hypothalamus (Decavel and Hatton, 1995). It was hypothesized that glial cells contribute to the regulation of neuronal function in the hypothalamus through a mechanism involving the release of taurine upon hypoosmotic stimulation or through some receptor-mediated mechanism, and through the subsequent inhibition of neuronal activity by taurine (reviewed in Hussy et al., 2000).

Taurine may specifically inhibit the activity of hypothalamic neurons that secrete arginine vaso-

pressin (AVP), a potent vasocontrictor hormone also known as the anti-diuretic hormone (ADH) (Engelmann et al., 2001). AVP and oxytocin are hormones that are released into the bloodstream at the pituitary anastomosis by nerve terminals emanating from the supraoptic (SON) and paraventricuiar (PVN) nuclei of the hypothalamus as an acute response to a drop in arterial pressure. AVP also acts in a chronic manner to maintain blood pressure levels by modulating renal function and stimulating water-retention. Engelmann and colleagues (2001) described the possible inhibition of hypothalamic release of AVP by taurine in control Wistar rats. Taurine release was increased in the SON during stress, while AVP levels within the SON and in the plasma remained the same. However, AVP levels increased after a taurine antagonist was dialyzed directly into the SON. GABA release was not increased during stress and GABA inhibition had no effect on plasma AVP levels, supporting the primary if not solitary inhibitory role of taurine.

Moreover, taurine appears to selectively modulate AVP secretion. Oxytocin levels in the plasma increased with stress and, expectedly, were not affected by taurine antagonism. The data suggest taurine functions as a specific endogenous inhibitor of AVP release from the hypothalamus at moments of stress. Indeed, extracellular single-unit recordings in the SON revealed that the taurine antagonist inhibited the firing of vasopressinergic neurons but not of oxytocinergic neurons. Taurine may be acting on glycine receptors in these experiments. Taurine is thought to act as a major natural agonist on glycine receptors on SON neurons (Hussy et al., 1997), and in turn, the activation of these receptors appear to inhibit the release of AVP (Hussy et al., 2001).

The regulation of AVP secretion by taurine has also been studied in rats either supplemented with taurine in their diet or depleted of taurine (Mozaffari and Schaffer, 2001). Control Wistar rats were given taurine (3% in drinking water), or were depleted of taurine through β-alanine treatment (3% in drinking water), for 3 weeks. Fluid excretion and sodium excretion were decreased and increased in taurine-depleted and taurine-supplemented rats, respectively. The opposite trend was observed with potassium excretion. The effects of taurine-depletion were effectively neutralized by either AVP antagonist treatment or repletion with taurine, and were associated with increased levels of AVP in plasma. Indeed, the effects of taurine-depletion were consistent with increased effects of AVP on the kidney (Carney et al., 1993). The study, thus, documented the regulation of body-fluid homeostasis by taurine through an AVP-dependent mechanism.

Modulation of the baroreflex

Yang and Lin (1983) also report similar hypotensive effects with the injection of taurine into the CNS, and in addition, have demonstrated the possible modulation of the baroreflex by taurine. The baroreflex involves an acute CNS-mediated reflex response to signals from baroreceptors in peripheral blood vessels that detect positive and negative changes in blood pressure. Taurine, GABA and glycine were administered into the lateral ventricles and mean arterial pressure (MAP) and heart rate almost immediately decreased. Moreover, the same treatment facilitated adrenaline (Epi)-induced reflex bradycardia, suggesting that taurine may modulate the baroreflex response.

Another report by the same group described the use of the microinjection of excitatory and inhibitory amino acids into the dorsal raphe region of the brainstem to study the central modulation of cardiovascular function (Yang et al., 1992). Intraraphe administration of taurine, GABA or glycine lowered mean arterial pressure and the heart rate. These effects were antagonized by a serotonergic receptor antagonist cyproheptadine. As expected, the same microinjection treatment enhanced the baroreflex response to intravenous epinephrine. The reflex hypotension and bradycardia induced by intravenous adrenaline (Epi) were greater with taurine, GABA or glycine treatment. These effects were again antagonized by cyproheptadine, suggesting that taurine acts through a mechanism that is serotonergic receptor-dependent. The authors thus concluded that bulbospinal serotonergic nerve activity inhibits hypotensive baroreceptor reflexes and that taurine can suppress this effect.

In addition to its effects at the brainstem level, taurine also appears to be involved in the baroreflex at the level of the limbic system. Changes in peripheral BP affect the release of taurine in the hypothalamus, a limbic structure discussed in the previous section. It is known that hypervolemia or a pressor response elicited by intravenous levarterenol treatment can produce an increase in taurine release in the posterior hypothalamus, and that the opposite is induced by

controlled hemorrhagic hypotension or by hypotension elicited by nitroprusside infusion (Guo and Athineos, 1995). In similar studies that used rats after bilateral aortic denervation (AD) (Singewald et al., 1997), hypothalamic superfusate levels of taurine and GABA were measured after an intravenous infusion of phenylephrine produced a pressor response. Taurine and GABA release were increased in control rats but not in AD rats. Conversely, baroreceptor unloading elicited by nitroprusside treatment or by controlled hemorrhage attenuated amino acid release. The data strongly suggest that the baroreflex pathway modulated amino acid release. Indeed, direct electrical stimulation of the afferent aortic nerve increased amino acid release in the posterior hypothalamic nucleus.

However, taurine depletion exhibited no effect on the baroreflex. Mozaffari and Abebe (2000) used β-alanine to interfere with the transport of taurine in control Wistar rats, and reported no changes in the baroresponse to either phenylephrine or sodium nitroprusside. The findings were surprising as taurine depletion was expected to impair the baroreflex response. It is possible that taurine levels were not decreased to a sufficient level by the β-alanine treatment, or that taurine may act only as a permissive or secondary factor.

Modulation of brain RAS function

Other studies suggested that taurine may also act on the local renin-angiotensin system (RAS) in the brain to reduce hypertension (Muratani et al., 1996). Renin catalyzes the production of AngII from precursor molecules. The importance of renin in the development of hypertension in the SHR was demonstrated with the use of renin antisense oligodeoxynucleotides (Kubo et al., 2001). Renin antisense inhibits the expression of the renin protein and was used in SHR. Intraventricular, but not intraarterial, administration of the renin antisense produced a significant and prolonged decrease in systolic BP. The data demonstrated how crucial the RAS is in the development of hypertension.

The involvement of local brain RAS in hypertension has been demonstrated in other rat experimental models. In one study, salt-sensitive Dahl rats were infused with CV-11974, an AngII antagonist, through an intraventricular cannula (Teruya et al., 1995). The treatment attenuated the rise in mean arterial pressure that was elicited by a high-salt diet, implicating the activation of AngII receptors in the development of hypertension. Similarly, in the DOCA-salt rat model, the administration of losartan, an angiotensin receptor antagonist, into the lateral ventricle, normalized mean arterial pressure (Park and Leenen, 2001). These effects were not observed in control rats.

In studies with the SHR model, the rostral ventrolateral medulla (RVLM) was implicated in the pressor response in both control (Wistar) and hypertensive rats. Angiotensin blockade with microinjection of AngII antagonist into the RVLM caused a depressor response in rats (Muratani et al., 1993). Conversely, administration of AngII into the RVLM caused an increase in spontaneously neuronal firing of RVLM cardiovascular neurons and an ensuing pressor response (Chan et al., 1996; Zhu et al., 1998). The data suggested that AngII activates the vasomotor neurons of the RVLM to increase blood pressure. Reticulospinal neurons emanating from the RVLM are thought to mediate the vasomotor sympathetic signal from the RVLM, and interestingly, electrophysiological studies have demonstrated that these putative cardiovascular neurons are inhibited by iontophoretic application of taurine or glycine (Sun and Guyenet, 1985). No studies have been performed on the effects of oral taurine treatment on these cardiovascular neurons.

Other data suggest, however, that oral treatment with taurine may modulate the activity of local RAS in the brain. It was demonstrated that renin injected into the preoptic area increased salt and water intake in the rats, while AngII increased water intake but not salt intake in both SHR and control WKY rats (Abet et al., 1987). The effect of renin to increase salt intake was specifically potentiated in the SHR rats compared to control. Thus, the authors suggest that the activity of the RAS for the local production of AngII in the brain contributes to the hypertension in SHR rats through the stimulation of salt intake. Treatment with taurine (3% in drinking water for ~13 weeks) inhibited the development of hypertension, as expected. Moreover, taurine inhibited the specific effect of renin injected into the preoptic area to induce salt intake.

The peripheral effects of taurine

Taurine may also act on sites outside the CNS. An important factor in the effects of taurine on hypertension is its effects on plasma catecholamine levels. In the SHR model, the hyperactivity of the adrenal glands

was documented (reviewed in Okamoto, 1969). The adrenal glands contained twice as much NorE as controls; Epi content was unchanged, however. Yamamoto and colleagues (1985) reported that SHR rats exhibited slightly higher levels of plasma norepinephrine (NorE) and epinephrine (Epi) compared to control WKY rats both at rest and during stress (N = 11), albeit only plasma Epi changes during stress were statistically significant. No changes were observed with plasma renin and corticosterone levels. Taurine treatment (1.5% in drinking water for 8 weeks) lowered plasma catecholamine levels at rest and during stress in both SHR and control WKY rats, but again only plasma Epi levels in the stressed SHR rats decreased enough to be statistically significant. The study provided evidence that taurine may act to lower blood pressure in the SHR rat through a mechanism involving the modification of catecholamine metabolism during stress, but in resting or baseline hypertension. Another study by Trachtman and colleagues (1989) echoed these results. Taurine (1% in drinking water) for 8 weeks had no effect on plasma NorE and Epi levels in SHR rats at rest. Curiously, the treatment appeared to increase plasma NorE after 16 weeks, while at the same time causing hypotensive effects. The study suggested that the effects of taurine on resting hypertension might be catecholamine-independent.

In addition to its effects on catecholamine levels, oral taurine treatment also inhibited the vasoconstrictor effects of catecholamines. In studies with SHRSP rats, oral taurine treatment (3% in drinking for 5 weeks) inhibited the contractile response of mesenteric artery to direct NorE stimulation *in vitro* (Li et al., 1996). On the other hand, there was no effect observed on the contractile response to KCl or AngII, or on the vasorelaxant effects of acetylcholine. Similarly, oral taurine treatment of control WKY rats (1% in drinking water for 7–8 weeks) inhibited NorE-induced contractions of aortic rings, apparently in an endothelium-dependent manner (Abebe and Mozaffari, 2000). In this study, however, taurine treatment also facilitated the relaxant effects of acetylcholine.

In human studies, Fujita and colleagues (1987) described the hypotensive effects of oral taurine treatment as the attenuation of the increase in sympathoadrenal tone found in hypertensive patients. Similar to the aforementioned experiments with rat models of hypertension, taurine supplementation served to lower plasma catecholamine levels, specifically plasma Epi levels. Plasma NorE measurements exhibited an apparent 10% decrease also, but standard errors were too high and no statistical significance was associated with the decrease.

Paradoxical nature of taurine therapy

Oral taurine treatment of hypertensive patients clearly involves an increase in plasma taurine, regardless of the exact mechanism of action (Kohashi et al., 1983; Fujita et al., 1987). Taurine treatment may produce increases as much as 400% above plasma taurine levels in control patients. Given this fact, the regimen can be said to provide an interesting if not paradoxical antihypertensive option because of the increased taurine levels found in the hypertensive heart. In many reports, an increase in cardiac taurine levels has been associated with various models of hypertension. The physiological and pathological consequences of this increase have not been adequately addressed in the literature, although the various effects of taurine on the function of the heart have been described (Chapman et al., 1993). Interestingly, other cardiomyopathic conditions also exhibit increased taurine levels in the cardiac and paradoxical benefits from oral taurine therapy (Militante and Lombardini, 2001).

Left ventricle weight has been reported by Paasonen and colleagues (1978) to be increased in SHR over control Wistar rats (~61%), a change which correlated significantly with the increase in blood pressure. Yamamoto et al. reported similar findings in 1985. After correcting for this increase in weight, taurine concentration was found to be increased in the SHR hypertension model. Huxtable and Bressler (1974a) reported that taurine concentration was increased in the hearts of this strain of rats (~115%). Similarly, it was reported that in SHR, taurine concentration (μmol/g protein) was increased, specifically, in the left ventricle (~21%) (Paasonen et al., 1978). Chau et al. (1983) measured cardiac taurine in SHR and found that cardiac taurine increased over control at the same time systolic BP also increased. However, contrasting data were presented by Nara et al. (1978) which demonstrated no significant difference in cardiac taurine levels between control rats and SHR.

That there is a positive correlation between the taurine content of the heart and hypertension is supported by data from control rats exhibiting stress-induced hypertension (Huxtable and Bressler, 1974a). The data demonstrated a 35% increase in cardiac taurine levels with rats made hypertensive with the use of

environmental stress (loud noises, flashing lights, cage oscillation) (systolic pressure = 161 ± 3 mm-Hg). The increase did not appear in non-stressed rats (systolic pressure = 122 ± 2 mm-Hg) nor in rats that became only mildly hypertensive (systolic pressure 138 ± 2 mm-Hg).

The link between cardiac taurine and hypertension could also be observed with human autopsy data and the corresponding clinical data. Among patients with no cardiac pathology, taurine levels were found to be significantly increased (~68–70%) in the heart when either systolic (>125 mm-Hg) or diastolic pressure (>80 mm-Hg) was significantly elevated as compared to control (Huxtable and Bressler, 1974b). Interestingly, no such correlation could be found in patients who suffered CHF. Similar findings were reported by Bohles et al. in 1987.

Conclusion

Oral taurine therapy is effective in most all experimental models of hypertension currently in general use. Furthermore, clinical and epidemiologic data support the safety and sense of taurine use in human hypertension. There is strong evidence that taurine acts on the sympathetic system to lower blood pressure, but other mechanisms of action may also apply. All the data, however, are limited to studies that involved taurine treatment for a few weeks at the most. This is a severe scientific handicap in the proposed use of taurine as a hypotensive agent, for the chronic effects or taurine treatment are unknown. More long-term studies are thus necessary.

More important to remember, the hypotensive effects of taurine in the rat model has been associated with the alleviation of other cardiovascular problems like stroke, hypercholesterolemia, atherogenesis and cardiac hypertrophy (Yamori et al., 1996; Dawson et al., 2000). Available data suggest that taurine does not act through one specific mechanism, but rather through the simultaneous modulation of several physiologically interrelated cardiovascular processes. Perhaps, taurine is better compared to sodium or calcium, which figure in many different cellular processes and which must be replenished if depleted in any way, than to a drug which acts specifically at its own receptor. Much in the same way that hypertension cannot be studied separate from other cardiovascular lesions, the effects of taurine on hypertension cannot be studied in isolation.

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