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Interaction between the actions of taurine and angiotensin II*

Review Article

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Summary. The amino acid, taurine, is an important nutrient found in very high concentration in excitable tissue. Cellular depletion of taurine has been linked to developmental defects, retinal damage, immundeficiency, impaired cellular growth and the development of a cardiomyopathy. These findings have encouraged the use of taurine in infant formula, nutritional supplements and energy promoting drinks. Nonetheless, the use of taurine as a drug to treat specific diseases has been limited. One disease that responds favorably to taurine therapy is congestive heart failure. In this review, we discuss three mechanisms that might underlie the beneficial effect of taurine in heart failure. First, taurine promotes natriuresis and diuresis, presumably through its osmoregulatory activity in the kidney, its modulation of atrial natriuretic factor secretion and its putative regulation of vasopressin release. However, it remains to be determined whether taurine treatment promotes salt and water excretion in humans with heart failure. Second, taurine mediates a modest positive inotropic effect by regulating $[Na^+]_i$ and Na^+/Ca^{2+} exchanger flux. Although this effect of taurine has not been examined in human tissue, it is significant that it bypasses the major calcium transport defects found in the failing human heart. Third, taurine attenuates the actions of angiotensin II on Ca^{2+} transport, protein synthesis and angiotensin II signaling. Through this mechanism taurine would be expected to minimize many of the adverse actions of angiotensin II, including the induction of cardiac hypertrophy, volume overload and myocardial remodeling. Since the ACE inhibitors are the mainstay in the treatment of congestive heart failure, this action of taurine is probably very important.

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Cardiac hypertrophy is considered a major facet of congestive heart disease. Two of the primary mechanisms involved in the acceleration of myocyte growth and the development of cardiac hypertrophy are excessive hemodynamic overload and neurohumoral stimulation by factors, such as angiotensin II (Morgan and Baker, 1991; Yamazaki et al., 1995b). Although it is difficult to quantitate the contribution of each mechanism towards the development of heart failure, the possible means by which these factors affect the failing heart has been the focus of numerous studies. It is now accepted that angiotensin II can affect heart function by regulating blood pressure and vascular tone, increasing salt and water retention, stimulating myocyte protein biosynthesis, promoting ventricular remodeling and enhancing cardiac fibrosis (Lindpaintner and Ganten, 1991; Holtz, 1993). Parallel studies have revealed that hemodynamic overload and mechanical distortion activate a signaling pathway that culminates in myocyte proliferation, cardiac hypertrophy and a remodeled ventricle (Sadoshima et al., 1992; Komuro and Yazaki, 1994). Since angiotensin II is released in attached, arrested myocytes that are mechanically subjected to a unidirectional stretch of 10–20%, it was initially thought that the promotion of cardiac hypertrophy by mechanical overload might be mediated solely by angiotensin II. However, use of angiotensin II receptor antagonists confirmed the existence of both angiotensin II-dependent and -independent mechanisms of cardiac hypertrophy (Yamazaki et al., 1995a).

Another factor proposed to influence the development of heart failure is the amino acid, taurine. The normal concentration of taurine in the mammalian heart varies from 2–3 mM in the cat and cow to 25 mM in the rat (Huxtable, 1978). Nonetheless, when the intracellular concentration of taurine is decreased about 13 fold in the cat heart (from 13 to 1 μmol/g wet wt) through dietary manipulation, the animal develops a cardiomyopathy (Fox and Sturman, 1992; Novotny et al., 1991; Pion et al., 1987). Although these studies support a role for intracellular taurine in the maintenance of normal contractile function, elevations in the extracellular content of taurine also improves contractile function (Schaffer et al., 1994). Therefore, it is not surprising that taurine can favorably influence the course of heart failure caused by events independent of taurine deficiency. Azuma et al. (1984) and Elizarova et al. (1993) have convincingly demonstrated that the mortality rate of rabbits with experimental heart failure is significantly reduced in animals maintained on a diet containing 100 mg/kg taurine. More importantly, Azuma et al. (1983) have found that patients maintained on a daily oral dose of 4 g taurine exhibit an improvement in their congestive symptoms.

Three theories have been proposed to account for the cardioprotective activity of taurine. First, taurine may function by reducing the salt and fluid load of the patient. Second, it may relieve congestive symptoms by improving

contractile function. Third, taurine may act by inhibiting the actions of angiotensin II. The present review discusses these three putative actions of taurine.

Diuretic effects of taurine

For many years, the classical treatment regimen for congestive heart failure consisted of a diuretic in combination with a positive inotropic agent. The positive inotropic agent was thought to partially reverse the sequence of events leading to the accumulation of salt and fluid while the diuretic was used to prevent excessive fluid accumulation. More recent therapy has focused on the prevention of the adverse cardiovascular effects of angiotensin II, including its promotion of sodium and fluid retention. Three mechanisms contribute to the accumulation of sodium by angiotensin II (Lonn et al., 1994; Jackson and Garrison, 1996). First, angiotensin II stimulates Na^+/H^+ exchanger activity in the proximal tubules of the kidney, causing increased reabsorption of sodium. Second, it elevates aldosterone secretion from the adrenal cortex. The released aldosterone acts on the distal and collecting tubules of the kidney to enhance sodium retention. Third, it reduces renal blood flow, thereby exerting a negative effect on both water and sodium excretion.

In contrast to angiotensin II, acute taurine administration significantly enhances sodium excretion (Mozaffari et al., 1997). The natriuretic activity of taurine has been attributed to its osmoregulatory activity in the kidney, its modulation of atrial natriuretic factor secretion, and its putative regulation of vasopressin release (Dlouha and McBroom, 1986; Miyata et al., 1997; Mozaffari et al., 1997). It can also be attributed to the excretion of taurine, resulting in less reabsorption of Na^+ and Cl^- across the renal epithelium (Zelikovic et al., 1989; Jones et al., 1995). Thus, taurine can cause a net loss of sodium without eliciting an extracellular volume expansion. However, taurine is also capable of directly blocking some of the actions of angiotensin II. Therefore, a portion of its natriuretic activity may involve reversal of the effects of angiotensin II on renal Na^+/H^+ exchanger activity, aldosterone secretion and renal blood flow. Although Mozaffari et al. (1997) have suggested that the natriuretic and diuretic activity of taurine may contribute to the improvement in the symptoms of congestive heart failure following taurine therapy, it remains to be established whether taurine treatment is capable of increasing either sodium or fluid excretion in patients suffering from heart failure.

Effect of taurine on myocardial contractility and calcium movement

Positive inotropic agents have been used for centuries to alleviate the symptoms of heart failure. Since taurine exerts a modest positive inotropic effect in the hemodynamically depressed heart (Schaffer and Azuma, 1992), it has been proposed that taurine therapy benefits patients with heart failure by

improving contractile function. This conclusion is supported by evidence that dP/dt is elevated in taurine-treated animals suffering from congestive heart failure (Takihara et al., 1986; Awata et al., 1987).

The inotropic effect of taurine in the failing heart is most likely an action of extracellular taurine for several reasons: (1) The effect is noted soon after exposure of the heart to medium containing taurine. Yet, the transport of taurine into the heart proceeds slowly. (2) While taurine supplementation can restore contractile function in taurine deficient cats, there is no evidence that a form of human idiopathic congestive heart failure is caused by a loss of myocyte taurine. Indeed, patients with congestive heart failure appear to contain elevated levels of myocardial taurine (Huxtable and Bressler, 1974).

The inotropic effect of taurine has largely been linked to changes in the activity of several prominent membrane transporters which elevate $[Ca^{2+}]_i$. Sperelakis et al. (1989) have suggested that the enhancement of the slow, tetrodotoxin-insensitive sodium current by extracellular taurine may lead to an increase in $[Na^-]_i$, which in turn may elevate $[Ca^{2+}]_i$ through the actions of the Na^+/Ca^{2+} exchanger. Similar effects of extracellular taurine on the tetrodotoxin-sensitive sodium channel have been described, which could also elevate both $[Na^+]_i$ and $[Ca^{2+}]_i$ (Satoh and Sperelakis, 1998). Schaffer et al. (1994) have proposed that these sodium-linked effects of taurine dominate in the hypodynamic myocardium.

Yet, another putative scenario maintains that taurine raises $[Ca^{2+}]_i$ by either reducing calcium efflux via the Na^+/Ca^{2+} exchanger or by enhancing calcium influx via the L-type calcium channel (Satoh and Sperelakis, 1998). In support of this hypothesis, Satoh and Sperelakis (1993) found that taurine enhances L-type calcium channel flux at $[Ca^{2+}]_i$ commonly observed during diastole. However, this hypothesis is inconsistent with the finding that taurine enhances cellular calcium efflux via the Na^+/Ca^{2+} exchanger, presumably by promoting the release of calcium from intracellular stores (Earm et al., 1993). Irrespective of which mechanism dominates, the advantage of both mechanisms is that they bypass the major calcium transport defect found in the failing human heart, namely, the impairment of calcium handling by the sarcoplasmic reticulum (Gwathmey et al., 1987). Taurine has the added advantage that it does not exhibit toxicity commonly associated with other positive inotropic agents that share its ability to elevate $[Ca^{2+}]_i$.

Interaction between taurine and angiotensin II

Effect of taurine on angiotensin II-induced cell proliferation

The American Heart Association has recommended that angiotensin converting enzyme (ACE) inhibitors be used as frontline drugs in the treatment of congestive heart failure. Although the ACE inhibitors block bradykinin metabolism, their primary function is the prevention of the adverse effects of angiotensin II. Surprisingly, taurine therapy mimics some of the actions of the ACE inhibitors.

Takahashi et al. (1997) and Rao and Tao (1998) have shown that treatment of rat cardiac cardiomyocytes with 20 mM taurine prevents angiotensin II-induced stimulation of [^{3}H]-phenylalanine incorporation. Moreover, taurine abolishes both angiotensin II-induced cell proliferation and the stimulation of [^{3}H]-thymidine uptake by rat cardiac nonmyocytes (primarily fibroblasts). These effects of taurine are important because angiotensin II-induced stimulation of DNA and protein synthesis in the heart can culminate in the development of the hypertrophic cardiomyocyte (Lindpaintner and Ganten, 1991; Miyata and Haneda, 1994; Dostal et al., 1997).

Another important factor implicated in angiotensin II-induced myocyte hypertrophy is altered calcium homeostasis. Since both taurine and angiotensin II affect $[Ca^{2+}]_i$, interest has been spurred regarding the interaction of taurine and angiotensin II at the level of cardiomyocyte calcium transport. The first report describing an effect of angiotensin II on calcium transport was reported by Allen et al. (1988), who found that angiotensin II increased calcium influx into neonatal cardiomyocytes through the activation of the L-type calcium channel. Although at the time it was assumed that the increase in calcium influx should elevate $[Ca^{2+}]_i$, subsequent studies revealed that angiotensin II often lowers, rather than increases, the amplitude of the calcium transient (Kohmoto et al., 1993; Sempe et al., 1994; Kinugawa et al., 1995). One explanation for this apparent dichotomy is that although calcium influx is enhanced by angiotensin II, calcium efflux via the Na^+/Ca^{2+} exchanger is stimulated even more, causing a net loss of calcium from the cell (Ballard and Schaffer, 1996; Iwamoto et al., 1996; Fukuta et al., 1998). Support for this scenario comes from the study of Kem et al. (1991), who found that the angiotensin II-induced decline in $[Ca^{2+}]_i$ is preceded by a rise in the calcium transient. Moreover, angiotensin II has been shown to stimulate Na^+/Ca^{2+} exchanger activity (Ballard and Schaffer, 1996; Fukuta et al., 1998). However, the response to angiotensin II is highly species dependent (Wikman-Coffelt et al., 1991; Kohmoto et al., 1993; Ikenouchi et al., 1994), suggesting that angiotensin II regulates several calcium transporters, including transporters having opposite effects on $[Ca^{2+}]_i$. Thus, angiotensin II can either increase or decrease $[Ca^{2+}]_i$, with the final outcome dependent upon the importance of the key transporters affected in a particular species.

Despite these species variations, investigators have consistently observed an antagonistic interaction between taurine and angiotensin II. In 1997, Takahashi et al. (1997) found that angiotensin II induces a slight rise in the amplitude of the calcium transient, an effect blocked by preincubation of the neonatal rat cardiomyocytes for 24 hours with 20 mM taurine. Taurine also blocks the angiotensin II-induced elevation in $[Ca^{2+}]_i$ seen in nonmyocyte cultures containing primarily fibroblasts (Takahashi et al., 1997). Since angiotensin II-induced calcium accumulation has been attributed to the activation of the L-type calcium channel (Allen et al., 1988), it is likely that taurine interferes with the ability of angiotensin II to stimulate L-type calcium current (I_{Ca}). Indeed, Satoh and Sperelakis (1993) have shown that addition of 10–20 mM taurine to the extracellular medium reduces I_{Ca} provided that

$[Ca^{2+}]_i$ is in the range commonly seen during systole. In addition to their competing effects on I_{Ca}, a direct interaction between taurine and angiotensin II also seems possible. Ballard-Croft et al. (1997) have shown that while angiotensin II stimulates Na^+/Ca^{2+} exchanger activity, taurine reverses this effect. Since taurine alone has no effect on Na^+/Ca^{2+} exchanger activity (Ballard-Croft et al., 1997), the amino acid must be capable of directly blocking the actions of angiotensin II on the exchanger. This raises the possibility that taurine may inhibit several other actions of angiotensin II through the regulation of an early step in the signaling pathway of angiotensin II.

Effect of taurine on angiotensin II signaling pathway

The signaling pathway of angiotensin II is very complex and is subject to regulation at several reaction steps. The initial event in the hypertrophic response of angiotensin II is the interaction of the peptide with the AT_1 receptor (Schunker et al., 1990). When activated, the AT_1 receptor becomes coupled to phospholipase C, which generates two cellular messengers, 1,2 diacylglycerol and inositol 1,4,5 triphosphate. In the neonatal cardiomyocyte, diacylglycerol appears to be the more important effector, causing the activation and translocation of certain protein kinase C isozymes. Although protein kinase C is considered a potent mitogen, Booz et al. (1994) found that phorbol ester-induced downregulation of protein kinase C does not affect the normal stimulation of [^{3}H]-thymidine incorporation by angiotensin II. On the other hand, protein kinase C downregulation appears to suppress the induction of c-fos by angiotensin II, an observation consistent with the presence of a protein kinase C response element on the c-fos promoter (Sadoshima and Izumo, 1993). These data suggest that multiple pathways are initiated by angiotensin II stimulation.

To define the steps involved in angiotensin II signaling, recent research has focused on the identity of specific protein kinases involved in the actions of angiotensin II (Fig. 1). In the intact myocardium, increased perfusion pressure promotes PKC-epsilon translocation and elevates c-fos expression, both of which are blocked by AT_1 antagonists (Kang et al., 1996; Paul et al., 1997). Nonetheless, there is some debate as to whether angiotensin II alone is capable of promoting PKC translocation in the isolated rat heart (Kang et al., 1996; Paul et al., 1997). Another protein kinase C isozyme implicated in angiotensin II action is PKC-zeta, a form insensitive to both calcium and the phorbol esters (Dostal et al., 1996). PKC-zeta is of interest because it translocates to the nucleus in response to angiotensin II treatment. In the nucleus, PKC-zeta activates NF-KB, a transcription factor involved in the initiation of DNA synthesis. Another important action of PKC-zeta is the activation of the MAP kinases, ERK 1 and 2, an enzyme system capable of phosphorylating the nuclear transcription factors, $p62^{TCF}$ and AP-1 (Activator protein 1). These transcription factors regulate the expression of immediate early genes, such as c-fos and c-jun (Gille et al., 1992; Sadoshima and Izumo,

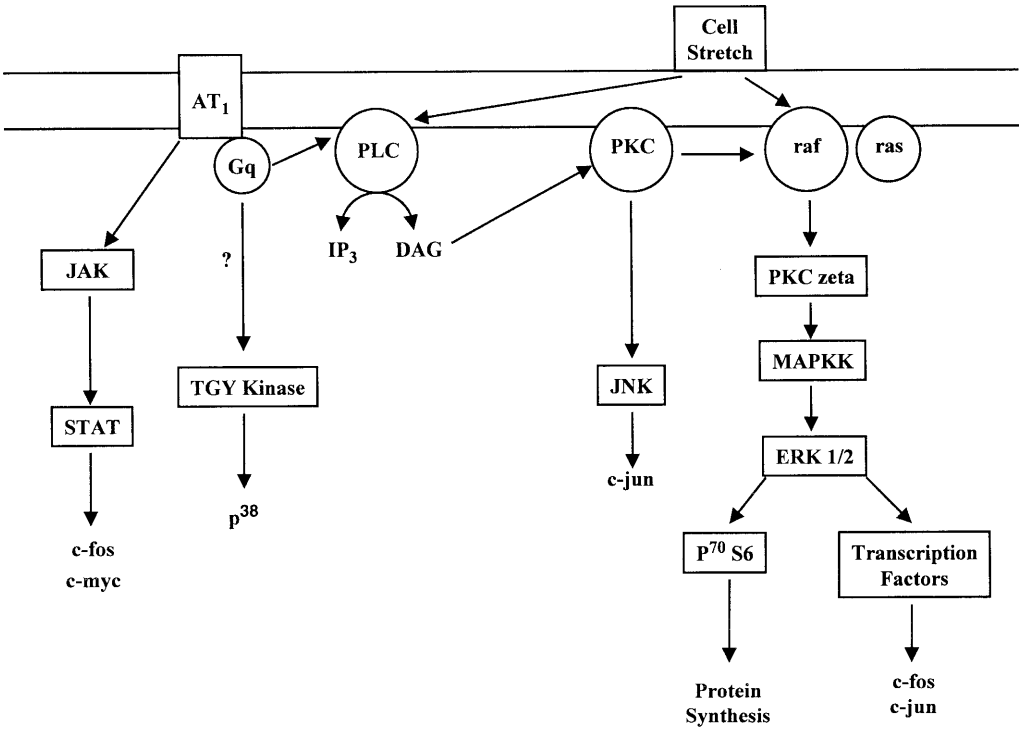

Fig. 1. Signal transduction pathway of angiotensin II. The abbreviations used are as follows: AT_1, angiotensin II type 1 receptor; *Gq*, Gq alpha subunit of heterotrimeric G-proteins; *JAK*, janus kinase; *STAT*, signal transducer and activator of transcription; *TGY kinase*, a kinase with a phosphorylation sequence of TGY; *PLC*, phospholipase C; IP_3, inositol triphosphate; *DAG*, diacylglycerol; *PKC*, protein kinase D; *JNK*, c-jun N-terminal kinase; *PKCzeta*, protein kinase C-zeta isoform; *MAPKK*, mitogen-activated protein kinase kinase; *ERK*, extracellular regulated kinase; p^{70} *S6*, 70 or 85 kD form of S6 kinase. Shown are the signaling pathways for the activation of JAK-STAT, p38, JNK and ERK 1 & 2 by the angiotensin II type 1 receptor. Also shown are the pathways activated by cell stretching

1993). The ERK 1 and 2 MAP kinases also phosphorylate p^{70} S6 kinase, whose activation is considered an obligatory step in the stimulation of protein synthesis by angiotensin II (Takano et al., 1996; Sadoshima and Izumo, 1995). However, the role of the ERK MAP kinases in the induction of cardiac hypertrophy has been challenged by Post et al. (1996), who found that inhibition of the ERK MAP kinases do not block phenylephrine-stimulated atrial natriuretic factor expression. Thus, further studies are required to clarify the role of the ERK MAP kinases.

Besides the ERK 1 and 2 family of MAP kinases, the heart also contains two other families of MAP kinases, the stress related kinases, also known as JNK or SAPK, and the p38 MAP kinases. Exposure of the cardiomyocyte to angiotensin II stimulates c-jun NH_2-terminal kinase (JNK), a process which is both calcium and protein kinase C dependent (Kudoh et al., 1997). It has been proposed that JNK may regulate gene expression by activating Jun protein.

However, the JNK family has also been implicated in the process of apoptosis (Schmitz and Berk, 1997) and is the likely mechanism by which angiotensin II promotes apoptosis in the heart (Cigola et al., 1997).

Much less information is available on the p38 MAP kinase family. p38 is activated by proinflammatory cytokines, such as IL-1 and tumor necrosis factor, and by environmental stresses, such as osmotic shock (Han et al., 1994; Rouse et al., 1994). Since it is also activated by Gq coupled hypertrophic agonists, such as endothelin-1 and phenylephrine, it is likely that it will also be activated by angiotensin II (Nemoto et al., 1998). Although the signaling pathway for p38 is poorly defined, it is clear that activation of p38 induces atrial natriuretic peptide expression and plays a central role in the development of cardiomyocyte hypertrophy (Nemoto et al., 1998).

The angiotensin II receptor lacks tyrosine kinase activity; nonetheless, a number of proteins are very rapidly phosphorylated on tyrosine residues following exposure of cardiac myocytes or fibroblasts to medium containing angiotensin II (Sadoshima et al., 1995; Schieffer et al., 1996). One of the tyrosine kinases activated by angiotensin II is Jak2 kinase (McWhinney et al., 1997). Its substrate, Jak2, belongs to a family of kinases that phosphorylate and activate STAT (Signal transducers and activators of transcription) proteins (Kodama et al., 1998). Activation of the JAK-STAT pathway is also believed to regulate early response genes, c-jun and junB, and the process of cardiac hypertrophy (Dostal et al., 1997).

Because the angiotensin II signaling pathway consists of a cascade of reactions, involving several branch points and protein kinase steps, a logical site of taurine action would be an early phosphorylation step. In this context, Lombardini and coworkers have reported that taurine inhibits the phosphorylation of several specific proteins in a number of different rat tissues, such as the retina (Lombardini et al., 1985, 1996; Lombardini and Props, 1997), brain cortex (Li and Lombardini, 1991), and heart (Lombardini, 1996a,b, 1997). However, whether the effect of taurine, that is, inhibition of protein phosphorylation, has any direct significance with respect to its antagonistic effects on the actions of angiotensin II remains to be demonstated.

In the rat retina, there is an inverse relationship between the effects of taurine on ATP-dependent Ca^{2+} uptake (stimulatory) and protein phosphorylation (inhibitory) (Lombardini 1985). This inverse relationship appears to hold for a wide number of taurine analogues. However, there are also some taurine analogues which demonstrate opposite effects, such as inhibiting ATP dependent Ca^{2+} uptake and stimulating protein phosphorylation. Finally, certain modifications of the taurine molecule completely eliminate any effects on both Ca^{2+} uptake and phosphorylation. It would be of interest to test these taurine analogues for their interaction with angiotensin II in the various models and test systems previously discussed.

Recently, Lombardini and coworkers (Lombardini 1996b; Lombardini et al., 1996b) discovered that drug-induced taurine depletion increases the

phosphorylation of at least two proteins. When guanidinoethansulfonate (1.5%) was administered to rats in their drinking water for up to 6 weeks, an ~20kDa protein present in a retinal membrane preparation, whose phosphorylation was previously demonstrated to be inhibited by taurine, was now shown to have its phosphorylation increased by approximately 94% (Lombardini et al., 1996). The increased phosphorylation of the ~20kDa protein observed after guanidinoethanesulfonate treatment was reversed when the animals were treated with taurine (1.5%) in the drinking water for an additional 6 weeks. Similar results (an increase of 85%) were observed in rat heart mitochondrial preparations with an ~44kDa protein (Lombardini 1996b). These results suggest that taurine has a regulatory role in the phosphorylation of a specific protein in retina and cardiac tissue.

Sequence analyses of the protein bands with approximate molecular weights of 20k (retina) and 44k (heart) when isolated from the SDS polyacrylamide gels indicate that the affected phosphoproteins are probably histone H2B (Lombardini 1998) and pyruvate dehydrogenase (Lombardini 1997). These data raise the possibility that taurine might influence the trophic actions of angiotensin II by modulating the phosphorylation of proteins.

The other mechanism by which taurine can prevent the actions of angiotensin II is by modulating cell size and the status of cellular stretch receptors located on the cell membrane (Schaffer et al., 1998). When activated, these stretch receptors promote the release of angiotensin II, with the amount released dependent upon the extent of cell stretching (Sadoshima et al., 1993; Paul et al., 1997). This release mechanism provides another logical link to taurine. Since a loss of taurine from the cardiomyocyte occurs in response to an osmotic imbalance and cell swelling (Rasmusson et al., 1993; Song et al., 1998), taurine efflux from the cell can dramatically reduce the degree of cell swelling. Through this action, taurine loss minimizes the extent to which the stretch receptors can be activated. This in turn will decrease the amount of swelling-induced angiotensin II release.

Another important consequence of taurine-induced cell volume regulation is the modulation of the stretch-dependent, angiotensin II-independent receptor (Kent and McDermott, 1996; Nyui et al., 1997; Thienault et al., 1997). The signaling cascade activated by this stretch receptor includes the activation of a phospholipase that promotes the accumulation of inositol phosphates and the translocation of PKC-epsilon (Paul et al., 1997). The stretch-activated pathway also activates MAP kinase, which increases S6 kinase-linked protein synthesis and the expression of c-fos. Another downstream target of the stretch receptors are the “fetal genes”, such as skeletal alpha-actin, atrial natriuretic factor and beta-myosin heavy chain, whose upregulation by mechanical stretching is an important step in ventricular remodeling (Sadoshima et al., 1992). Thus, taurine may regulate both angiotensin II-dependent and -independent signaling pathways that contribute to the development of cardiomyocyte hypertrophy and ventricular remodeling. The mechanisms involved in taurine action await further investigation.

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