AT$_2$ receptor: Its role in obesity associated hypertension

Review Article

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Abstract

The renin-angiotensin system (RAS) is a hormonal cascade that acts together to regulate blood pressure. Angiotensin II (Ang II) is the major octapeptide of RAS and mediates its cellular and physiological actions by acting on AT$_1$ and AT$_2$ receptor. Most of the cellular and physiological actions of Ang II such as cellular growth and proliferation, vasoconstriction, antinatriuresis and increase in blood pressure are mediated via AT$_1$ receptor. The functions associated with the AT$_2$ receptors are less studied, in part, due to its lower expression in adult tissues. However, AT$_2$ receptor has been suggested as functional antagonist of AT$_1$ receptors and thereby opposes the actions of Ang II mediated via AT$_1$ receptor. Thus, the activation of AT$_2$ receptors has been shown to cause vasodilatation, natriuresis and decrease in blood pressure.

After the discovery of the AT$_2$ receptor in various parts of the kidney, including in proximal tubules, there has been an interest in establishing a link between the renal AT$_2$ receptor, renal Na-excretion and blood pressure regulation. Earlier, we have reported that activation of renal AT$_2$ receptors increases urinary Na excretion in obese Zucker rats, in part via inhibiting Na$^+$/K$^+$-ATPase (NKA) activity and stimulating nitric oxide/cGMP pathway in the proximal tubules. An impaired pressure natriuresis and increased AT$_1$ receptor function is believed to be the cause of hypertension in obese Zucker rats and other animal models of obesity. In this review, we are focussing on the role of renin angiotensin system especially AT$_2$ receptors in obesity associated hypertension.

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Introduction

Obesity is defined as having a very high amount of body fat in relation to lean body mass, or body mass index (BMI). Person having BMI of >30 is considered obese. It is one of the most important nutritional disorders worldwide. It has become a global epidemic and is particularly true for the United States, where approximately 300 000 deaths each year are associated with being overweight and obese.

Prevalence

There is a dramatic increase in the prevalence of obesity in the United States within the last decade. In 1996 no states had obesity prevalence rates above 18%, whereas in 2008, almost all the states had obesity prevalence rates of 29% and 23 states are already in obese category (Source: Center for Disease Control and Prevention). Obesity is associated with an increased risk of hypertension and diabetes.

Pathological triad of obesity, diabetes and hypertension

Obesity leads to endothelial dysfunction and impairment of renal function that contribute to the maintenance and development of hypertension (20). Obesity also increases fat mass in the body. These fat cells release a novel protein called PEDF (pigment epithelium-derived factor). PEDF is released into the bloodstream and causes the muscle and liver to become desensitized to insulin (22). This results in increase in glucose because the pancreas then produces more insulin to counteract these negative effects. This is one of the mechanism by which obesity leads to diabetes. Moreover, adipose tissue also secretes a large number of cytokines in addition to leptin that modulate glucose metabolism and insulin action. These cytokines also induce suppressor of cytokine signaling-3 (SOCS-3), an intracellular signaling molecule that impairs the signaling of both leptin and insulin and are elevated in obesity (21). This increased glucose in obesity doubles the risk of mortality in hypertensive patients by affecting renal cellular functions including increase in sodium-glucose transport, cellular hypertrophy (78), synthesis of transforming growth factor-β (63) and matrix accumulation (78). High glucose also directly affects the cardiovascular functions, vasculature, and neuron damage and also increases sympathetic activation, increased Na absorption which eventually causes hypertension. This pathological triad of obesity, diabetes and hypertension is becoming an economic burden on USA. According to the Center for Disease Control and Prevention, it's costing more than $187 billion dollar each year to treat obesity associated hypertension. Since renin angiotensin system regulates blood pressure so it is the major therapeutic target to treat hypertension. Although, current available drugs like ACE inhibitors and AT$_1$ blockers improve renal/cardiovascular functions in hypertensive patients but they remain ineffective in treating obesity/diabetes related hypertension where desirable blood pressure levels is below 120 mmHg. It is very difficult to achieve lower pressure in obese/diabetic patients and requires combination of three or more drugs.

Mechanism of obesity associated hypertension

There has been a strong positive correlation between weight gain and blood pressure. These obesity related hypertension affects several organs in the body such as heart, vasculature and kidney. The kidney is one such important organ whose function is severely affected by hypertension (30). The mechanism by which obesity causes hypertension can be attributed to the enhanced sympathetic and renin angiotensin system activity, alteration of intrarenal physical forces, and hyperinsulinemia (37, 38). Obesity leads to excessive tubular absorption of Na and alters kidney function. This leads to increased extracellular blood volume and hence a shift in pressure natriuresis which is believed to be an important mechanism by which obese person develops hypertension (36). It has also been postulated that increased renal interstitial pressure due to accumulation of subcapsular fat might lead to tubular compression which further leads to more sodium absorption in the proximal tubules thus raising the blood pressure.

Obesity associated hypertension

Role of sympathetic nervous system

Sympathetic nervous system (SNS) plays an important role in cardio-renal function. Activation of SNS especially renal sympathetic nerve activity has been linked to the pathogenesis of obesity associated hypertension (39). Activation of SNS is partly mediated by hyperinsulinemia, angiotensin II, melanocortin 4 receptors and adipokines such as leptin, tumor necrosis factor α and interleukin-6. Binding of leptin to its receptors in the brain regions activates neuronal pathways that reduces appetite and increases SNS activity leading to an increase in blood pressure. Mutation in the leptin receptor leads to exaggerated plasma leptin which causes early onset of obesity. Several studies suggest a link between adipose tissue and exaggerated SNS activity in muscles and kidneys of normotensive humans (39). Pharmacological blockade of α and β adrenergic receptors lowers the blood pressure in obese subjects by at least 50-60%. Moreover, renal denervation cause natriuresis and decrease in blood pressure. These observations suggest that increased SNS activity contributes to the development of hypertension in obesity. Hyperinsulinemia in obesity contribute to overactivation of SNS in dif-ferent tissues including kidney (62). However the role of insulin resistance in the development of hypertension is somewhat controversial.

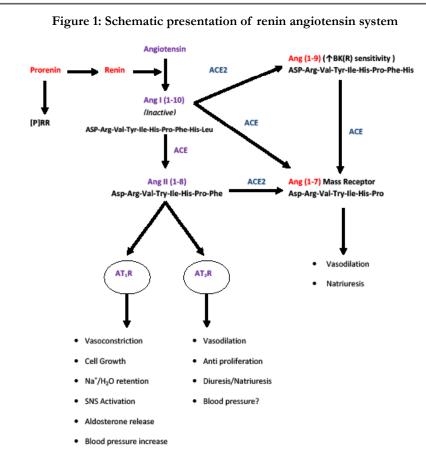### Role of atrial natriuretic peptide

Renal glomeruli contains peptides called atrial natriuretic factor (ANP) that plays an important role in regulating sodium homeostasis (11), fluid balance, vasodilatation and blood pressure. In the kidney, ANP opposes the actions of Ang II via AT$_1$R and causes natriuresis. Low levels of ANP have been observed in obese people and are suggested as one of the mechanisms for obesity-related hypertension (73). The mechanism associated with the decreased ANP levels in obesity is attributed to up-regulated natriuretic peptide clearance receptors (NPR-C) which basically removes natriuretic peptides from the circulation (16). Reduced ANP function on natriuresis has been reported in obese Zucker rats (5).

Role of renin angiotensin system

Renin angiotensin system (RAS) is a very important hormonal regulator of sodium homeostasis in the kidney (13). RAS was believed to be an antinatriuretic but recent data suggest that it has both natriuretic and antinatriuretic components. However, during obesity associated hypertension there is an increased RAS activity which shifts the sodium balance from pronatriuretic to an antinatriuretic direction resulting in increased sodium absorption leading to increase in blood pressure. Moreover increased RAS also elevates plasma aldosterone (60) which again leads to an abnormal Na-reabsorption and elevation of arterial pressure. Increased RAS activity has been implicated in the etiology of obesity associated hypertension because blockade of RAS has been implicated as a therapeutic strategy in the management of obesity associated hypertension. Here increased RAS activity is mostly taken in terms of increased renin and/or AT$_1$R function.

Overview of renin angiotensin system

According to Guyton's theory, RAS was considered as circulating endocrine system that regulates blood pressure and Na-homeostasis. The discovery of RAS components in different tissues including brain, heart, vasculature, adipose tissue, gonads, pancreas, placenta, and kidney demonstrates the local/tissue production of Ang II (58). The tissue RAS plays an important role in normal physiological processes and has been

Figure 1: Schematic presentation of renin angiotensin system

implicated in pathophysiological conditions such as hypertension, congestive heart failure and cardiovascular hypertrophy (19, 47). The present view of RAS is very complex and is a group of related hormones that act together to regulate blood pressure (68). When the blood pressure drops for any reasons, special cells in the kidney called juxta-glomerular cells detect those changes and release renin into the blood stream. Renin floats around and converts inactive forms of angiotensinogen into angiotensin I. Angiotensin converting enzyme (ACE) converts inactive angiotensin I into angiotensin II. Ang I and Ang II are further converted into Ang 1-9 and Ang 1-7 by ACE2. Ang 1-9 gets converted to Ang 1-7 by ACE and acts on Mas receptors. Angiotensin II is the most important peptide of RAS and produces its effect by binding onto AT_1 and AT_2 receptors (15). Ang II via AT_1 receptors causes vasoconstriction, salt and water retention, promotes cell growth, releases aldosterone, activates SNS and all these altogether leads to an increase in blood pressure. The effects of AT_2 receptor activation are the opposite of those mediated through AT_1 receptors (10, 25). Ang II via AT_2 receptor promotes vasodilatation and inhibits cellular growth (figure 1). Numerous studies indicate that AT_2 receptor has a potential role in blood pressure and natriuresis (32, 34, 69).

Components of kidney renin angiotensin system

Angiotensinogen (AGT)

AGT is a glycoprotein consisting of 452 aminoacids. AGT is synthesized in several tissues including liver, heart, blood vessels, adipose tissues and kidney. Renin converts this inactive angiotensinogen into angiotensin I. Increased expression of angiotensinogen gene is observed in plasma samples of hypertensive rats. The increased activity of this gene might lead to more Ang II formation and may cause more renal and cardiovascular damage (61).

Renin and (pro) renin receptor [P] RR

Renin is a key enzyme of RAS and is produced from the juxtaglomerular apparatus of the kidney. Renin is considered as a rate limiting enzyme in Ang II production as it converts inactive angiotensinogen into angiotensin I. In addition to enzymatic action, renin and pro-renin also acts as ligands for two receptors leading to cellular responses. The first is the mannose-6-phosphate (M6P) receptor which binds and internalizes both renin and prorenin and hence is called a clearance receptor. The second receptor is the specific (pro) renin receptor ([P]RR), the activation of which initiates downstream signaling cascades (55). [P]RR is made up of 350 amino acids and consists of single transmembrane domain. Since prorenin is an inactive form of renin, it undergoes proteolytic and non proteolytic activation which leads to the increased activity of the receptor. The binding of this active form of renin to [P]RR decreases its activation energy and leads to the phosphorylation of mitogen-activated protein kinases (MAP kinase p44/42 and extracellular regulated kinases 1/2 (ERK1/2). The phosphorylation of these kinases leads to an increase in plasminogen activator inhibitor 1 and enhanced expression of transforming growth factor (TGF) β1. This result in synthesis of fibronectin and collagen 1 which is important in regulating actin filament dynamics, maintenance of cell structure, growth, movement and cell death (54). Several studies suggest that overexpression of [P]RR leads to increased blood pressure and aldosterone secretion. As a result of which prorenin receptor inhibitors like allikskerin are used as a therapeutic target to treat high blood pressure (54).

Angiotensin II

Angiotensin II (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe) is the most important hormone of RAS and produces its effect by binding onto AT_1 and AT_2 receptor (75). Most of the actions of Ang II are mediated via AT_1 receptors because these are abundant as compared to AT_2 receptor. Ang II via AT_1 receptor increases peripheral vascular resistance and increased blood pressure.

ACE/ACE2

ACE is an important enzyme of RAS as it converts Ang I to Ang II. ACE also converts Ang 1-7 into smaller angiotensin fragments thereby reversing the vasodilatory effect of Ang 1-7. ACE is considered a pro-hypertensive enzyme because it generates Ang II and also inhibits the peptides such as bradykinin, responsible for vasodilatation (24, 61). ACE2 is a recently discovered enzyme which has 42% structural resemblance to ACE but implicated in reducing the actions of ACE. ACE2 converts Ang II to Ang 1-7 which acts on Mas receptor and causes vasodilation and natriuresis (17). This enzyme also converts Ang I to Ang 1-9, however the affinity for ACE2 for Ang II is 400-fold higher than Ang I. Since ACE and ACE2 leads to the generation of peptides which has nearly opposite function, a novel concept has been proposed wherein imbalance between ACE/ACE2 could result in different functions. For example increased ACE activity concomitant with reduced ACE2 activity would lead to generation of peptides which would cause more vasoconstriction and vice versa. This balance of ACE/ACE2 in the regulation of different components of RAS is novel target to treat hypertension and renal damage (46).

Mas receptor

Ang 1-7 (Asp-Arg-Val-Tyr-Ile-His-Pro) is formed from Ang II by the action of ACE2 and is the agonist for Mas receptor. The association of Ang 1-7, ACE2 and Mas receptor forms a separate branch of renin-angiotensin system called the ACE2/Ang 1-7/Mas axis (23). The physiological effects mediated by Ang 1-7 is opposite to that of Ang II acting via AT_1 receptor. Ang 1-7 by acting on Mas receptor causes vasodilatation and antiproliferation. Several studies suggest that ACE2/Ang 1-7/Mas axis interacts with the AT_1 and AT_2 receptor stimulation. For example, it has been shown that stimulation of Mas receptor inhibits the AT_1 mediated regulation of ERK1/2 activity which was reversed by Mas receptor antagonist (46). However, the interaction between AT_2 receptor mediated signaling cascade and the ACE2/Ang 1-7/Mas axis is still not known.

Angiotensin III

Ang III (Arg-Val-Tyr-Ile-His-Pro-Phe) is formed from Ang II by the action of aminopeptidase A. The physiological effects of Ang III are similar to that of Ang II but are less potent. Infusion of Ang III is known to increase BP and intracerebroventricular injection of Ang III is known to increase thirst, vasopressin release and hypertension in animal models (61). Recent studies suggest that Ang III might be the preferred agonist for AT_2 receptor. Infusion of Ang III produces natriuresis via AT_2 receptor in AT_1 blocked rats (57).

Angiotensin IV/AT4 receptor

The receptor for Ang IV (Val-Tyr-Ile-His-Pro-Phe) is known as insulin-regulated aminopeptidase (IRAP) or AT4 receptor. IRAP/AT4 is a zinc-bound metalloenzyme attached to the transmembrane domain and their translocation to the cytosol is regulated by insulin. It has a molecular mass of 165 kDa and is made up of 1025 amino acid (2). Since IRAP is an endopeptidase, it cleaves substrates at the N-terminal of cysteine and leucine amino acids. Ang IV produces its effect by inhibiting activity of IRAP/AT4. This might be one of the mechanism by which Ang IV binds to AT4/IRAP and reduce the cleavage of important peptides and prolong their actions (61). IRAP/AT4 receptor has a role in maintaining homeostasis during pregnancy by cleaving and inactivating Ang III, oxytocin and vasopressin. The expression of IRAP/AT4 receptor is seen in heart, muscles, liver, spleen, colon and kidney. In kidney these receptors are restricted to proximal tubules, glomerulus, thick ascending loop and collecting ducts (41). The physiological function of IRAP/AT4 receptor is believed to be similar to that of AT_2 receptor in the sense that they can antagonize the function of AT_1 receptor by regulating blood flow and promoting Na-excretion (15, 40).

AT_1 receptor

AT_1 receptor belongs to the family of G-protein coupled receptors. Human AT_1 receptor is made up of 359 amino acids and has almost 95% homology with bovine and rodent AT_1 receptors (14). It has an extracellular N-terminus followed by a seven transmembrane domain which is connected by three extracellular and intracellular loops linked to the C-terminus. Ang II binds to the extracellular loop and to the

transmembrane domain. Receptor internalization, desensitization and phosphorylation of AT_1 receptors are linked to the C-terminus of AT_1 receptor (28, 29, 72). Majority of the action of Ang II such as Na-retention, increase in blood pressure, sympathetic activation and aldosterone release are known to be mediated via AT_1 receptor because they are more in numbers as compared to AT_2 receptors or other angiotensin receptors. The AT_1 receptors are expressed in most of the tissue including lung, heart, liver, vascular smooth muscles and kidney. Within the kidney they are found abundantly in the glomerulus, renal tubules and efferent arterioles (8, 45, 49, 71). In kidney, stimulation of AT_1 receptors recruits various Na transporters like Na_+/H_+ exchanger (NHE) to the brush bordered membrane, NKA and Na_+/HCO_3- (NBC) on the basolateral membrane of the proximal tubules and leads to Na and water absorption (7, 27). Studies suggest that effect of Ang II on the sodium transporters are biphasic. That means that at low concentration, Ang II stimulates the Na-transporters whereas at higher concentration the Na-transporters are inhibited (4, 6, 44). The activation of AT_1 receptors initiates a cascade of signaling events which are mediated via G-protein dependent and G-protein independent intracellular second messengers. Ang II on activation of G-protein coupled AT_1 receptors affects several downstream molecules like adenylyl cyclase, phospholipase A2, phospholipase C (64, 66) and produces its cellular effects.

AT_2 receptor

General characteristics

AT_2 receptor belongs to the family of G-protein coupled receptor with a molecular mass of 41,000 kDa (15, 69). The gene which codes for AT_2 receptor is present on the X chromosome and has 34% resemblance with the protein sequence of AT_1 receptor (48, 51). There are five potential N-glycosylation sites on the extracellular surface of AT_2 receptor (15).

Signal transduction

Although, AT_2 receptor belongs to the family of G-protein coupled receptor (GPCR), but the entire signaling cascade through G-protein coupling is not known (43). It is suggested that the third loop of this 7-TM receptor is involved in the downstream signaling cascade. Some evidence of AT_2 signaling comes from studies in COS-7 cell line and neuronal cell line where it has been shown that agonist occupied AT_2 receptor stimulates $Gi\alpha$ (42, 76). This receptor is different as compared to other GPCR as these agonist occupied receptor does not undergo desensitization. The reason is still not known but it is speculated that the third intracellular loop is short and does not provide enough binding sites for phosphorylation. Stimulation of AT_2 receptor leads to an increase in phosphotyrosine phosphatase activity and inhibition of MAP kinase (p42/p44) or ERK1/2 (9, 74). AT_2 receptor stimulation also leads to increase in bradykinin production which via NO/cGMP pathway causes vasodilation (67). In our laboratory, we have demonstrated that in proximal tubules of obese Zucker rats, acute activation of AT_2 receptor inhibits NKA via NO/cGMP pathway and promotes Na excretion (33).

Expression

The expression of the AT_2 receptor is observed in several organs like heart, brain, vasculature, testes and kidney. Within the kidneys, proximal tubules, distal tubules, afferent and efferent arterioles express AT_2 receptor (12, 59). The AT_2 receptor is widely expressed during embryonic stage and gradually decreases after birth (15, 26). AT_2 receptor has drawn limited attention mainly due to its low expression (77). However, AT_2 receptors are overexpressed in various pathophysiological and experimental conditions like obesity/diabetes, nephrectomy, atherosclerosis, cardiac overload and myocardial infarction. We believe that these overexpressed receptors in these pathophysiological conditions might have a protective role in disease conditions.

Physiological Function

AT_2 receptor opposes AT_1 receptor function

AT_2 receptors have been shown to produce cellular and physiological responses that are opposite to that produced by AT_1 receptor. For example AT_2 receptor mediates cellular differentiation and apoptosis in various cells/tissues like vascular smooth muscle cells, endothelilal cells whereas AT_1 receptor causes cellular hypertrophy and growth (50). While Ang II via AT_2 receptor causes vasodilation via NO/cGMP pathway whereas AT_1 receptor causes vasoconstriction (9). The mechanism by which AT_2 receptor opposes the action of AT_1 receptor is not clear. However, there are some studies which suggest that AT_2 receptor binds directly to the AT_1 receptor and antagonizes its function and this antagonism was linked to the heterodimerization of these receptors in transfected foetal fibroblast and myometrium of pregnanat women (1). Ang II via activation of AT_1 receptor is known to stimulate NKA causing anti-natriuresis while activation of AT_2 receptors inhibits NKA and causes sodium excretion (32, 34, 56). Further, AT_1 receptor stimulates NKA activity by reducing cellular cAMP contents (45) whereas AT_2 receptor increases cGMP generation which via a cGMP-dependent pathway inhibits NKA activity in the proximal tubules of obese rats (33). Since cGMP is a known inhibitor of phosphodiesterase-3 (PDE-3), an enzyme that degrades cAMP, AT_2 receptor, by increasing cGMP could be inhibiting PDE-3, preventing cAMP reduction and thereby reversing AT_1-mediated NKA stimulation (18).

AT_2 receptor and Na-excretion

Studies on the role of AT_2 receptors on renal sodium transport are limited. In-vitro studies suggest that AT_2 receptor mediates inhibition of sodium transport in the proximal tubules of rabbit (31). AT_2 receptor knock-out mice show antinatriuretic hypersensitivity to Ang II and a shift in pressure natriuresis curve. Pressure natriuresis is the mechanism by which renal function is linked to long-term blood pressure regulation. However it is difficult to predict whether the effects on sodium excretion are due to absence of AT_2 receptor activation or due to enhanced AT_1 receptor activity (70). AT_2 receptors are over expressed in the proximal tubules of obese Zucker rats. Activation of AT_2 receptors inhibit NKA activity in the proximal tubules and promote natriuresis (3, 33). Infusion of this AT_2 receptor agonist does not affect the glomerular filtration rate (GFR) or mean arterial pressure, suggesting that the changes in natriuresis may be linked to the changes in tubular sodium transport (33). It is known that acute activation of renal AT_2 receptors promote natriuresis/diuresis but whether the long-term AT_2 receptor activation modulates the tubular sodium transport, leading to a decrease in sodium balance is not known.

AT_2 receptor and blood pressure

The long-term regulation of blood pressure is linked to the ability of kidneys to excrete sufficient sodium to maintain normal sodium balance and blood volume (53). The AT_2 receptor is involved in the production of cGMP, NO and prostaglandin F2α thereby playing an important role in renal function, vasodilatation and blood pressure regulation (52, 65). Data from our laboratory and elsewhere suggest that AT_2 receptor plays a protective role against increase in blood pressure by promoting sodium excretion. The argument that increase in sodium excretion due to AT_2 receptor activation may shift the blood pressure can be supported by selective inhibition/disrupting AT_2 receptor gene in the kidney. AT_2 receptor disrupted mice have increased blood pressure compared to the wild type control and there is sustained hypersensitivity of blood pressure and sodium excretion to Ang II (69). In conscious rats, direct stimulation of AT_2 receptor with its agonist CGP42112A in the presence of AT_1 blocker lowers the arterial pressure. The studies so far have been focused on the acute stimulation of AT_2 receptor by CGP42112A in spontaneously hypertensive rat (SHR), normotensive or Sprague Dawley (SD) rats (74). There is no study done to look at chronic activation of AT_2 receptor and its role in long-term blood pressure regulation in obese rats.

Current therapeutic target

Obesity associated hypertension and other renal-cardiovascular diseases are the leading causes of death in the United States. It leads to cardiovascular diseases including renal ischemia and its dysfunction. In obesity associated hypertension the regulatory function of kidney is severely disrupted resulting in irregular sodium excretion and retention. While the known therapeutic target such as ACE, renin inhibitors and AT_1 receptor blockers have been effective in treating various forms of hypertension, these targets are often not sufficient to achieve blood pressure goals in obesity/diabetes related hypertension. Recently, discovery of AT_2 receptors in adult renal tissues has offered the potential for a novel approach in improving renal function and decreasing high blood pressure. An increase in AT_2 receptor expression has recently been reported in animal models (34). The selective activation of AT_2 receptor leads to a greater increase in renal sodium excretion in hyperglycemic animals compared to the normal animals (35). Since excessive retention of sodium is a factor for developing hypertension in obesity and diabetes, AT_2 receptor may therefore be a potential candidate for treating hypertension in obese individuals. Understanding the role of AT_2 receptor in renal function and blood pressure control will provide a new potential target to treat obesity/diabetes related hypertension.

Acknowledgment

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