Cardiovascular Pharmacology of Thyrotropin Releasing Hormone

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SIRÉN, A.-L. *Cardiovascular pharmacology of thyrotropin releasing hormone*. PEPTIDES 9: Suppl. 1, 69–73, 1988.—Thyrotropin releasing hormone (TRH) and its receptors are present in the cardiovascular nuclei of the brain as well as in the intermediolateral cell column of spinal cord. Anatomical, neurophysiological, functional and pharmacological studies suggest that TRH is a neurotransmitter/neuromodulator in the central nervous system. Administration of TRH to experimental animals or human subjects induces pressor and tachycardic responses and increases plasma levels of catecholamines. These effects are likely to be mediated by a central nervous system activation of the sympathoadrenomedullary system with no involvement of vasopressin or renin-angiotensin system. In the conscious rat, the TRH-induced pressor response is accompanied by an increment in cardiac output and a distinct change in organ blood flow, a hindquarter skeletal muscle vasodilation accompanied by renal and mesenteric vasoconstriction. The role of TRH in hypertension has not been studied. However, the extremely potent pressor and vasoconstrictor properties of TRH makes this tripeptide a candidate for neurotransmitters/modulators involved in the development and/or maintenance of hypertension. The role of TRH in the therapy of shock is at present controversial. Though preliminary experimental work raised hopes and expectations for therapeutic usage of TRH in shock and trauma, the more recent studies have shown no effect or a detrimental effect for TRH in some experimental shock states.

TRH   Blood pressure   Organ blood flow   Sympathetic nerve activity

THYROTROPIN releasing hormone (TRH, l-pyroglutamyl-l-histidyl-l-prolinamide) was the first hypothalamic releasing factor to be isolated, chemically characterized and synthesized [43]. In addition to its neuroendocrine effects (TSH, prolactin, growth hormone release), this tripeptide has central nervous actions which are totally unrelated to its effect on the hypothalamopituitary axis (for review see [29,38]). The presence of TRH immunoreactivity and TRH receptors in brain areas related to the cardiorespiratory control, together with the extremely potent pressor and tachycardic actions of exogenously administered TRH suggest that this peptide might have a role in modulating the brain regulation of blood pressure and respiration. This review aims to summarize the studies on TRH in the central nervous system with special emphasis on the cardiovascular pharmacology of this peptide.

TRH SYSTEM IN THE BRAIN

TRH immunoreactivity is unevenly distributed throughout the central nervous system (see [42,43]). Although the highest local concentrations are found in the hypothalamus (especially in the median eminence, periventricular arcuate, dorsomedial and ventromedial nuclei), more than 70% of the total CNS TRH is located in extrahypothalamic areas. Outside the hypothalamus high local levels of TRH are found in the lateral nucleus of the septum in the limbic area and in the nucleus of the solitary tract (NTS) in the medulla oblongata; moderate to low levels in preoptic nuclei, midbrain and cor-

tex and in the spinal cord [42]. Specific binding sites for TRH in the rat brain were first characterized by Burt and Snyder [6]. Since then, TRH receptors have been found in the brain and spinal cord of many vertebrates including man [35, 36, 45, 49, 54]. Autoradiographic mapping of the receptor sites has revealed a somewhat different distribution of the TRH receptors from that of the peptide TRH. However, the extensive distribution of TRH receptors in the CNS provides an explanation for a variety of central nervous actions observed when TRH is administered into the brain [48].

In the rat brain, TRH arises from the post-translational cleavage of a large precursor protein [31,46]. Brain synaptosomes are rich in immunoreactive TRH and immunocytochemically TRH has been shown to be present in nerve endings [42]. Moreover, TRH is released *in vitro* by various stimuli to be retaken up by the rat brain slices *in vitro* [43].

The findings that TRH is co-localized with substance P and serotonin in some brain nuclei and TRH is able to increase the number of serotonin receptors [20,48] further suggest a neuromodulator role for TRH in the CNS. For more detailed review on the neurochemistry of TRH see the recent reviews of Prasad [43] and Sharif [48].

CARDIOVASCULAR PHARMACOLOGY OF TRH

TRH induces a strong pressor response in both experimental animals [3, 10, 14, 27, 32, 52] and in man [1, 4, 39, 55]. In animals the TRH-induced hypertensive effect is accom-

panied with a moderate to strong tachycardia, while in humans it does not seem to affect heart rate. In both anesthetized [32] and conscious [50] rats intracerebroventricularly (ICV) administered TRH is one of the most potent pressor agents known, producing significant increments of mean arterial pressure at subnanomolar doses. A prolonged pressor effect can also be induced by using TRH-analogs such as the CG3703 compound [51] which are highly resistant to TRH metabolizing enzymes [19,38]. Furthermore, the apparent lack of tachyphylaxis to the cardiovascular effects of TRH [32,50] further suggests that this tripeptide might be involved in the pathophysiology of hypertension. However, the potential role of TRH in various experimental hypertensive models must still be elucidated.

Site of Action

The cardiovascular effects of TRH are likely to be due to an action of the agent on the central nervous system, since the doses needed to elicit rises of mean arterial pressure and heart rate after systemic injections are a thousandfold higher than the doses used ICV or for injections into discrete brain nuclei [12, 14, 32, 50]. Moreover, in anesthetized rabbits, transections in the cervical spinal cord abolished the pressor response to ICV administered TRH while spinal transections below T_1 had no effect on the TRH response [27]. The reversal of leukotriene D_4 induced hypotension is also totally abolished in the pithed rat in which the entire CNS and cardiac reflexes are eliminated [15].

A few studies to date have so far tried to localize the pressor and tachycardic effects of TRH in the brain. Feuerstein and coworkers [14] injected nanomolar doses of TRH or its histidyl analogs [16] into the nucleus preopticus medialis (POM) of conscious rats. The magnitude of the increments in mean arterial pressure and heart rate after the POM injections were, however, at the same range as the effect produced by ICV injections of the same doses of TRH [32,50]. However, the increase in heart rate was somewhat higher. Microinjections of picomolar doses of TRH into various hypothalamic nuclei in halothane anesthetized rats also elicited slight increases of blood pressure and heart rate without any changes in respiration or body temperature [9]. Immunohistochemical visualization of TRH containing nerve cells and fibers as well as a high density of TRH receptors in the hypothalamus [36, 42, 45] further suggest that these brain areas might be important for the cardiovascular actions of TRH. Moreover, endogenous TRH might have a role in the hypothalamic regulation of the cardiovascular system. In contrast to these findings, it was recently reported that the pressor response to TRH can be elicited also with injections into the fourth ventricle [41]. Moreover, occlusion of the cerebral aqueduct attenuated the increment of blood pressure produced by ICV administered TRH, while the tachycardia induced by TRH was unaffected by this procedure [41]. These findings suggest that the pressor response to TRH can, at least in part, be due to an activation of brain areas within the reach of the fourth ventricle. The nucleus of the solitary tract has been shown to have a high content of TRH immunoreactivity [42] and also TRH receptors [36]. However, microinjections of nanomolar doses of TRH into the NTS of the pentobarbitone anesthetized rat elicited, instead of a pressor effect, a moderate depressor response on blood pressure which was accompanied by a slight tachycardia [14]. The NTS has been indicated to be a sensitive brain site for the respiratory stimulant action (tachypnea, increase in ventilatory volume) in the rat [8,22].

Hemodynamic Mechanism Involved in the Cardiovascular Actions of TRH

Although the pressor and tachycardic effects of TRH have been repeatedly documented (see above), little is known for the hemodynamic and regional blood flow changes after TRH administration. By using the thermodilution technique we found that the pressor and tachycardic effects of both ICV and systemically administered TRH were accompanied by a simultaneous increase in cardiac output, while TRH had no effect on total peripheral resistance (Sirén *et al.*, manuscript in preparation). The same pattern of hemodynamic changes was observed also after systemic injection of a potent TRH analog, CG3703 [19], in conscious rats [51]. In man, TRH injected intravenously seems to produce opposite changes in gross hemodynamic variables and the pressor response in humans is more likely to be due to an increase in resistance than to an increment of cardiac output [55]. By using the ultrasound directional pulsed Doppler method we have also shown [50] that ICV administration of low doses (0.8–80 nmol/kg) of TRH produced a distinct pattern of regional blood flow changes in the conscious rat: the blood flow to skeletal muscles significantly increased and vascular resistance decreased after TRH injections, with opposite changes in the renal (and to a lesser degree in the mesenteric) blood flow and vascular resistance. The differential pattern of blood flow changes in these vascular beds might explain the lack of effect of TRH on total peripheral resistance. These findings also underline the importance in studying the effect of TRH (and other peptides) on regional blood flow and vascular resistance; the potent vasoconstrictor effect of TRH on the renal vasculature might not only play a role in the regulation of renal hemodynamics but also indirectly in the control of systemic blood pressure.

The Role of the Autonomic Nervous System

The cardiovascular effects of TRH have been related to an activation of sympathetic outflow, since these changes are accompanied by increases in plasma catecholamines in both animals [5,14] and man [39]. Although measuring plasma catecholamines might not be a good index for the sympathetic nerve activity, these suggestions are further supported by the findings that the pressor effect of ICV administered TRH in rat endotoxic shock is abolished by adrenal demedullation [26]. In conscious adrenal demedullated rats, the tachycardia elicited by TRH injections into the POM was also inhibited and the pressor response partly attenuated by bretylium treatment [14]. Studies in progress in our laboratory have revealed that the increments in blood pressure, heart rate and cardiac index induced by TRH are partly attenuated in adrenal demedullated rats, and are not significantly effected by further treatment with bretylium. The renal vasoconstrictor response to TRH, on the other hand, is reduced to 50% in adrenal demedullated animals and the vasodilation in skeletal muscle almost totally inhibited by bretylium in these rats. As compared to the other known vasoactive substances such as epinephrine, norepinephrine, angiotensin, vasopressin or platelet activating factor ([11, 13, 51], unpublished findings of our laboratory), the pattern of the changes in blood flow in skeletal muscle, mesenteric and renal vascular beds by TRH mostly resembled that induced by norepinephrine while all the other above mentioned agents induced totally different changes in blood flow as that produced by TRH. Furthermore, direct resolving of renal sympathetic nerve activity in anesthetized rats revealed a
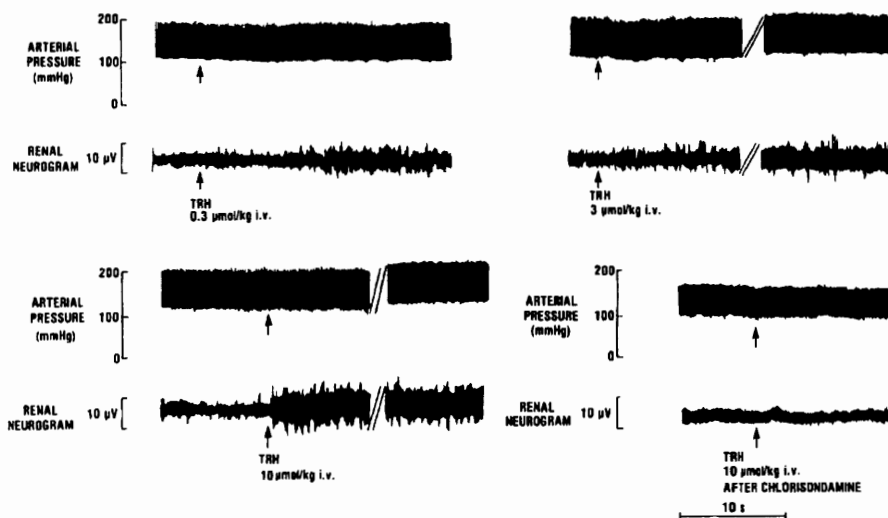
FIG. 1. A representable chart recording of arterial pressure (AP) and renal sympathetic nerve activity (RSNA) in the anesthetized rat after intravenous injections of THR (0.3–10 μmol/kg). Chlorisondamine (5 mg/kg) was administered intravenously 20 min before injection of TRH at the highest dose (10 μmol/kg) was repeated.

profound activation of nerve firing by TRH even at doses which did not affect the arterial pressure (Fig. 1). Both the hemodynamic and neural effects of TRH were abolished by the ganglion blocker chlorisondamine (Fig. 1). These data taken together suggest that the cardiovascular effects of TRH, at least in part, involve an activation of the sympathoadrenomedullary axis. However, any pharmacological intervention to block the sympathetic or parasympathetic pathways (hexamethonium, reserpine, phentolamine, propranolol, atropine) were not effective in inhibiting the increases in blood pressure and heart rate produced by TRH ICV in the anesthetized rabbit [27,28]. Thus, the involvement of sympathetic nerves and adrenal medulla in the cardiovascular actions of TRH is at present clearly controversial. Although an incomplete blockade of adrenergic nerves and/or receptors by sympathetic blocking agents might explain the lack of inhibition of TRH effects in the studies cited above, a nonadrenergic component of action may also be proposed. This view is further supported by the recent clinical findings by Zaloga and coworkers [55] that the pressor response to TRH in humans was not accompanied by any increments of plasma catecholamines. The importance of vasopressin and renin-angiotensin system in the TRH-induced cardiovascular changes is discussed in the next chapter. Briefly, neither of these systems seem to be involved. It is therefore possible that neurotransmitters other than norepinephrine which are released by sympathetic activation contribute to the cardiovascular responses to TRH. Possible candidates for such neurotransmitters might include neuropeptide Y (NPY) or opioid peptides which are colocalized and coreleased from sympathetic nerve endings and adrenal medulla with norepinephrine [18,40]. Systemic administration of NPY to rats results in vasoconstrictor and pressor responses similar to TRH [40], while the effects of various opioid peptides are more complex [18]. However, the importance of these mediators in the cardiovascular action of TRH must still be elucidated. Furthermore, direct recording of sympathetic nerve traffic to various organs following TRH administration would further clarify the role of the sympathoadrenomedullary system in the vasoconstrictor/vasodilator actions of TRH.

Other Possible Mediators of the TRH Effect

Plasma vasopressin levels have been reported to increase after systemic or central administration of TRH in rabbits [28,53], while in dogs TRH does not have any effect on plasma vasopressin [30]. However, the increment in plasma vasopressin seems to be unrelated to its cardiovascular actions, since hexamethonium blocked the effect of TRH on vasopressin but had no influence to its concomitant pressor response [28]. Moreover, repeated administrations of vasopressin to anesthetized rabbits (to induce tachyphylaxis) had no effect on the TRH-induced hypertensive response [28]. Studies in progress in our laboratory have shown that in the conscious rat systemic administration of a high dose of TRH (2 mg/kg) induced a statistically significant rise in plasma vasopressin, but the magnitude of this increase was below the levels at which vasopressin can induce changes in blood pressure [7]. Pretreatment of urethane-anesthetized rats with a vasopressin antagonist failed to block the cardiovascular actions of ICV administered TRH [37]. The involvement of the other pressor system, the renin-angiotensin system, in the hypertensive effect of TRH seems also likely, since TRH has no effect on plasma renin activity in either the conscious rat (own unpublished observations) or in man [39].

TRH in Shock

Holaday and coworkers [24,25] were the first to suggest that TRH might have a beneficial effect in cardiovascular shock. They found that a systemic injection of a high dose of TRH (2 mg/kg) reversed the hypotension in rat hemorrhagic [24] and endotoxic shock [25]. Studies in our laboratory have shown that TRH, administered both systemically and di-

rectly into the brain ventricles, reversed also the hypotension induced by leukotriene D$_4$, platelet activating factor, soybean lipoxygenase or antigen induced anaphylaxis in the conscious guinea pig [17, 33, 34]. In contrast to its well documented pressor response in cardiovascular shock, the beneficial effect of TRH in various shock states seems to be controversial. Holaday *et al.* [25] reported increased short-term survival (2 hours after the shock) by TRH in endotoxic shock but had no data on the survival in rat hemorrhagic shock. Some preliminary studies on cynomulgus monkeys [21,44], on the other hand, suggest a beneficial effect of TRH on survival in hemorrhagic shock but not in the endotoxic shock. In mice anaphylactic shock TRH significantly reduced mortality which was probably mediated by a central nervous stimulation of the sympathetic outflow [2]. Our recent results [51] clearly showed that TRH or its long-acting analogue CG3703 (see above) increased mortality in conscious rats exposed to hemorrhage. In addition to the reduced survival, we also found that the pressor effect induced by CG3703 in rat hypovolemic hypotension was due to a sharp increase in the total peripheral resistance, while the cardiac output tended to be reduced by the treatment. Moreover, the regional blood flow in skeletal muscle, mesenteric and renal vascular beds was significantly impaired by the treatment. These results may thus provide explanation for the lack of beneficial effect of TRH; reduced blood flow to vital organs together with the reduction of cardiac output. The lack of any beneficial effect of TRH on either cardiovascular parameters or survival in cat or rabbit hemorrhagic shock or in rat traumatic shock was recently confirmed by others [23,47].

Thus, the beneficial effect of TRH in shock seems to be dependent on the shock model as well as the species studied. TRH and its stable analogs may prove to be beneficial in anaphylactic shock whereas in hypovolemic shock, TRH exacerbates the shock and causes a sustained reduction of blood flow in vital organs.

SUMMARY

TRH immunoreactivity and highly specific binding sites for TRH are found in neuronal cell bodies and fibers throughout the vertebrate central nervous system. The neuromodulator role for TRH is further suggested by the facts that in the brain this tripeptide arises from a large precursor protein and has its own releasing, uptake and degradation mechanisms. Administration of TRH to animals or man induces a potent pressor response and increases plasma catecholamine levels probably mainly by a central nervous activation of sympathoadrenomedullary axis. In the rat, the TRH-induced pressor response is accompanied by increases in heart rate and cardiac output and skeletal muscle blood flow, while in renal and mesenteric vasculature it produces vasoconstriction. The cardiovascular actions of TRH seem not to involve other known pressor systems such as the renin-angiotensin system or vasopressin release. The role of TRH in different hypertension models has not been studied. However, the extremely potent pressor effect of this peptide makes TRH a candidate for neurotransmitters or modulators involved in the development and/or maintenance of hypertension.

The role of TRH in the therapy of a variety of shock states and trauma is at present controversial. Although preliminary experimental work raised hopes and expectations for therapeutic usage of TRH in shock and trauma, the more recent studies have shown no effect or a detrimental effect for TRH in some experimental shock states.

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