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Is the Hypertensive State an Integral Etiopathogenesis Centrally Involving Vascular Myofiber Ischemia?

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Abstract: One might strictly recognize the essential hypertensive state as a form of evolving influence, itself both a cause and an effect of integral pathways of etiopathogenesis in vascular myofiber hypercontractility and vascular myofiber ischemia. Indeed, perhaps it is in terms of a circulatory hemodynamic disturbance that evolves both in terms primarily of myocardial hypertrophy and of vascular smooth myofiber hypercontractility that one would best understand the sustained series of both phasic and tonic responses to various systems of influence in inducing progression of the hypertensive state. Even in terms that would go beyond simple threshold considerations of such myofiber responsiveness or of myofiber contractility, the essential hypertensive state might primarily arise and evolve simply as one pathway of ischemic events that somehow progresses as positive feedback systems. Indeed, ischemia in hypertension would beget even more ischemia that evolves in terms of parameters that are themselves inherently not related to the hypertensive state. Indeed, ischemic organ events in arterial hypertension might evolve via systems ranging from hypercontractility of the vascular myofiber to fibrinoid necrosis of vessels, to specific vascular bed organ systems in renal failure and as systems also of intracranial hemorrhage, myocardial hypertrophy and of accelerated atherosclerosis and aneurysm formation.

Key words: Typertensine, vasular myofiber, schemia, etiopathogenesis

INTRODUCATION

A GIVEN ANGIOTENSIN II ACTION OF ONE OR OTHER ANGIOTENSIN RECEPTOR OPPOSING TYPE AS A BASIC MODEL OF HOMEOSTATIC CONTROL OF THE MICRO-ENVIRONMENT

In general terms, the nature of interacting homeostatic control mechanisms would appear to necessarily implicate opposing pathway mechanisms that compensate for each other towards strict range variability in maintenance of micro-environmental parameters. A working paradigm might particularly concern the activation of clustered turnkey genes towards the development of coronary heart disease in particular-effects might range from angiogenesis to proliferation, metabolism, ion transport and adrenergic receptors [1]. In particular, the final common pathway for regulation of blood pressure level would appear via alterations in renal sodium handling. Common genetic variations encoding components of the renin-angiotensin-aldosterone systems, the epithelial sodium channel, adrenoceptors, G-protein subunits appear implicated in inducing ischemia target organ complications due to both arteriosclerosis and atherosclerosis[2].

Hence, the particularly powerful vasoconstrictor action of angiotensin II involving anti-natriuretic and anti-diuretic effect would appear admirably balanced at the level of the angiotensin receptor type level. In such a scenario, the AT1 receptor, which is the predominantly physiologically active angiotensin receptor type, would mediate the vasoconstrictor, anti-natriuretic and anti-diuretic effects in a manner counterbalanced by the AT2 receptor in implicating a single agonist pathway of pressor and renal effects in stimulation and counteraction.

This concept of a single agonist, such as the angiotensin II, binding to either AT1 or AT2 receptors, which would stimulate or counteract stimulatory effects, might implicate fundamental mechanisms in homeostatic control of body mechanisms.

In simple conceptual terms, such an inbuilt control mechanism that self-regulates the actions of a given agonist at the level of 2 or more receptor types of involving opposing or conflicting actions might ultimately prove a valid basis for further elucidation of a whole series of homeostatic endocrinologic and other receptor mediated events in health and disease.

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ARE ATI AND AT2 RECEPTORS BOTH COMPONENTS OF A CLOSED LOOP OF REGISTERED OPERABILITY OF CIRCULATING ANGIOTENSIN ACTION

The angiotensin 2 (AT2) receptor would appear to constitute an inbuilt regulatory system of control of the physiological actions following stimulation of the AT1 receptor involving binding of angiotensin either to the AT1 or the AT2 receptor. Endothelial and inducible nitric oxide synthase expression would appear normalized in brain microvasculature of spontaneous hypertensive rats by inhibiting angiotensin II ATI receptivity; this would operate via a mechanism of decreased reduction in cerebral blood flow in the periphery of the ischemic lesion[3,4].

This situation might operatively implicate elevated angiotensin circulating levels in patients treated with antagonists to the AT1 receptor. Beyond any attempt of the AT2 receptor as a clearance means of circulating angiotensin, perhaps intrinsic regulation of the AT1 receptivity itself would be mediated essentially by AT2 receptors. In other words, angiotensin itself might be modulated by dually operative systems involving combined sets of AT1 and AT2 receptors in organs such as the heart, brain and kidney. Possible modes of operation would involve not only clearance of circulating angiotensin, but also a modification of the ligand-binding properties of angiotensin as a subsequent event to interactions with the AT2 receptor.

Another aspect of AT2 receptivity might actually concern binding to the angiotensin molecule both prior to and subsequent to its binding to the AT1 receptor in a manner suggestive of a high rate of repeated turnover of circulatory angiotensin through binding to the AT1 and AT2 receptors. In broader terms, multiple types of genotype-phenotype interaction, and also polymorphisms, would appear involved in the angiotensin 1I type 2 receptor's role in neointima formation after vascular injury, cardiac hypertrophy and myocardial infarction[5].

Basic physiologic dynamics of angiotensin as a potent vasoactive agent, might in fact implicate a highly dynamic series of repeated binding events of this ligand to various successive sets of AT receptors. Such repetitive angiotensin binding would incorporate both AT1 and AT2 receptor binding in a closed loop of regulated operability. Hence, in simple terms, the AT2 receptor as a "mirror image" form of the AT1 receptor might functionally constitute an effective mode of modulation and modification of physiologic effects of powerful agents such as angiotensin.

THE TISSUE LEVEL CONVERSION OF ANGIOTENSIN I TO ANGIOTENSIN II BY CAGE IN THE VESSEL WALL WOULD REPRESENT AN EFFECTIVE MEANS OF TARGETING ANGIOTENSIN II MOLECULAR ACTION

The endpoint as recognizable states of renal vasodilatation arising from blockade of the renin angiotensin system would appear particularly significant in deciphering the variability patterns controlling such systems in different species. In this regard, also, hypertensive individuals with microalbuminuria and/or salt sensitivity appear to manifest an increased prevalence of silent ischemia[6]. Indeed, lower serum albumin levels appear associated with an increased risk for coronary heart disease in both sexes[7].

Certainly, the angiotensin converting enzyme (ACE) step in plasma would constitute the fundamental event around which variability in control of ancillary mechanisms might operatively modulate the angiotensin-renin system as a whole.

Indeed, the development of non-ACE-dependent pathways, such as chymase or CAGE in the conversion of angiotensin I to angiotensin II, would appear to constitute a fundamental byproduct of species-differentiation among animal species in in terms of a basic binary pathway in the production of angiotensin II.

In simple terms, non-ACE-dependent pathways in angiotensin II production would constitute secondary components in an overall operative system of plasma versus tissue control in eliciting modes of action of renin-angiotensin systems.

Indeed, the ACE versus non-ACE dependent pathways would generate angiotensin II via classically recognized hormonal mechanistic pathways fundamentally susceptible to second order operative factors at the tissue level, in some but not all animal species.

In this sense, perhaps, animal species differentiation would constitute in large measure the development or suppression of collateral pathways bypassing alternative pathways whereby generated control of the renin-angiotensin system could be operatively exerted.

The location of CAGE in human, monkey, or dog arterial adventitia towards angiotensin II generation would constitute not simply amplifying mechanisms in angiotensin II production but also a specifically targeting system in the delivery of angiotensin II action to the vascular tunica media.

Indeed, perhaps, vascular wall localization of CAGE itself constitutes particularly efficacious systems of

operative localization that induce specialized angiotensin II action to specific vascular sites, particularly involving both direct and indirect modes of generation of specific vascular action as variability systems in targeting of action of angiotenin II, as a strictly molecular characterization chemically or biophysically.

In a sense, localization of the effect of the angiotensin II molecules to a particular vessel would appear achievable precisely by ensuring that the angiotensin II receptor is actually generated in that specific vessel concerned would act as a target for the generated angiotensin II molecule.

DOES HEART FAILURE OR RENAL FAILURE ASSOCIATED WITH SYSTOLIC HYPERTENSION IN THE OLDER PATIENT ARISE FROM COMPLEX VASCULAR NARROWING AND RESPONSIVE HYPERTENSIVE EVENTS TOWARDS FURTHER PROGRESSIVE PATHOLOGY

Systolic hypertension associated with a relatively low diastolic blood pressure would be significant in promoting the development of myocardial infarction, renal failure, heart failure and stroke, in older patients[8].

Such a combined scenario might induce the possible mediation of both systolic hypertension and of diastolic hypotension via various pathways involving specific pathology integral to the circulatory system rather than with reference to the vessels themselves. In addition, hypertension appears to enhance thrombogenic activity[9].

Indeed, combined systolic hypertension and relative diastolic hypotension might function as integral cardiovascular disturbances rather than as simply in terms of arterial vessel stiffness. On the other hand, cardiac fibrosis would appear an important cause of diastolic dysfunction arising in patients suffering form ischemic heart disease with previous infarction and in hypertensive heart disease[10].

In this regard, also, it would appear that diastolic dysfunction very often accompanies hypertensive heart disease, even before left ventricular hypertrophy develops; myocardial ischemia and fibrosis would appear particularly important in inducing such diastolic dysfunction in hypertension[11].

Systolic blood pressure in the face of a near normal diastolic blood pressure might actually comprise a resultant series of responses to dynamic pathophysiologic disturbances evolving as altered cardiovascular hemodynamics that are not resolvable in terms of essential structural/anatomic lesions of the vessel wall itself.

In other words, the considerable significance of systolic hypertension as an index of risk susceptibility for cardiac, cerebral and renal ischemia might operatively call into action various responsive mechanisms affecting the cardiovascular system, primarily as an integral system beyond simple anatomic[12] or morphologic component systems of vessels or heart as an individual ages.

Indeed, systolic hypertension as a pathophysiologic pathway aimed at compensating for progressive narrowing of cerebral, myocardial and renal vessels, might directly induce ischemia to these organs as a primary pathway of combined etiopathogenesis series of factors. In this regard, also, the prevalence of silent ischemia would be markedly increased amongst hypertensive patients with left ventricular hypertrophy when compared with those with normal left ventricular dimensions[13]. In addition, the real risk of heart and renal failure resulting from systolic hypertension might involve complex sets of lesions ranging from vascular narrowing to responsive hypertensive levels of hemodynamic disturtance to the subsequent evolution of a series of changes leading directly to cardiac failure or renal failure beyond even significance attributable to ischemic events or to organ infarction. In this regard, especially, damaged coronary microvasculature would appear a main set of factors inducing decreased coronary flow reserve and myocardial ischemia in cases with essential hypertension with left ventricular hypertrophy[14].

STRICT ANALOGY BETWEEN NEURONAL AND VASCULAR SMOOTH MUSCLE MYOFIBER DEPOLARIZATION AND THRESHOLD FIRING IN INDUCED HYPERTENSIVE STATE AND ISCHEMIA—MYOFIBER HYPERCONTRACTION PREDISPOSING TO MALIGNANT HYPERTENSION

An essential feature of predisposition to evolving hypertension in terms of an acute reactivity of arteriolar smooth myofibers would center on vascular contractility responses. Indeed, a lowered threshold value analogous to threshold action potential firing in neurons might operatively involve smooth myofiber hypercontractility. A basic phenomenon of ion channel gating might implicate smooth myofibers as a series of contractile responses in arterioles that would strictly define certain characteristics of development of hypertensive states that are paradoxically both evolving and established pathways of pathologic involvement.

How might such ion channel transport produce an essential phenomenon of tonic and phasic hyper-responsiveness based on lowered threshold values and response involving stretch reflex action and myofiber cytoarchitecture components.

It would appear that intracellular signal transduction, as indicated by Platelet-activating-growth factor-induced rises in intracellular (Ca2+) and Na+(Li+) CT (sodium-lithium countertransport) is not associated with increased risk of coronary heart disease in nondiabetic patients with essential hypertension[15].

An essential aspect of gated depolarization of the cell membrane, based either on ligand induced voltage-induced or on stretch-induced mechanisms, might implicate the incorporation of two essential phases—one of progressive depolarization to a certain determinate threshold at which firing produces a subsequent second phase of more rapid depolarization of the cell membrane.

Hypertension would indeed involve applied disturbances as a paroxysmal system that somehow would also sustain raised blood pressure. Such events might be based on essential phasic and tonic contractile responses of the arteriolar myofibers in integrally determining the magnitude of evolving pathology as characterized by increased peripheral vascular resistance.

In simple terms, perhaps, the various types of ion transporters such as the Na+/H+ exchanger and Na+-K+-2Cl- cotransporter might induce progressive depolarization of the smooth muscle myofiber in leading to various modifications arising from disturbed firing threshold and consequently to more prolonged phases of hypercontractility of the vascular smooth muscle myofiber.

Within such frameworks in the creation of significant hypertensive states would operate factors resulting in the development of a malignant hypertensive hemodynamics characterized especially by fibrinoid necrosis of the vessel wall.

Such vascular fibrinoid necrosis would relate especially to sustained forms of hypercontraction of the vascular smooth muscle fiber comparable in some ways to the hypercontraction bands seen in ischemia of cardiomyocytes. In this sense, perhaps, ischemia of the vascular smooth muscle fibers of the arteriolar wall might operatively evolve as sustained hypercontraction of such fibers. Within such conceptual frameworks, actual positive feedback pathways might initially induce both phasic and tonic systems of progression and of variable firing threshold depolarization events of the smooth muscle membrane. Subsequent to the development of important ischemic events, further hyper-contractile responsiveness on the part of the vascular smooth muscle fiber would tend to be activated and result in integral systems of hypercontraction and of hypercontractility in terms of degree and of sustained duration. Various mechanisms implicated in defective vascular relaxation might induce increased diffusional barrier/or nitric oxide, L-arginine depletion, altered levels of reactive oxygen, inactivation of nitric oxide by superoxide anions[16].

Particularly in view of possible or probable analogy between neurons and myofibers, myofiber contractility might implicate depolarization as a final mechanism of integrative pathologic progressiveness promoting sustained hypercontraction and hypercontractility. Indeed, ischemic injury to vascular smooth myofibers might constitute the one single system of integrative progression accounting for a whole series of circulatory hemodynamic disturbances in hypertension. Indeed, a more holistic approach to management of the hypertensive patient beyond simple lowering of the blood pressure would appear essential[17].

The malignant phase of hypertension in particular might characterize essential progressiveness that, once initiated, would strongly predispose to ischemia-induced hypercontraction and hypercontractility as a basic mechanism of progression. Fibrinoid necrosis itself would constitute fundamental manifestations of the malignant phase of hypertension in terms of essential characteristics of an ischemic hypercontractility evolving via pathways of sustained hypercontraction seen microscopically and as observed also in cases of cardiomyocyte ischemia immediately surrounding fresh foci of acute infarction.

BIOPHYSICAL PHENOMENA ACTING THROUGH MEMBRANE DEPOLARIZATION AND Ca2+ FLUX AND Ca2+ MOBILIZATION IN DETERMINING BIOPHYSICAL CONTRACTILITY AND CONTRACTION OF THE VASCULAR MYOFIBER

An apparent end-pathway of operation in terms of both membrane depolarization and of control of calcium flux might involve dynamic disturbances of vascular tone and contractility in responsiveness. In a sense, perhaps, levels of intracellular calcium, that result from both mobilization of intracellular Ca2+ stores and also from influx of Ca2+ through the plasmalemma might be directly implicated in integral hypercontractility and in sustained hypercontraction characterizing hypertenive vascular states. Ca2+ channels would both influence membrane depolarization and also be influenced by membrane depolarization.

In a wider sense, membrane stretch, membrane depolarization and perhaps also other biophysical alterations of the cell membrane might influence Ca2+ influx into the vascular muscle fibers. The intracellular stores of Ca2+ in both the endoplasmic reticulum and in the sub-sarcolemmal regions would in addition constitute an effective means of control and of responsiveness in terms of mobilization of Ca2+ intracellularly.

Indeed, cell membrane biophysical events in communicability t hat intracellularly evolve as systems of influence exerted by the endoplasmic reticulum/sarcoplasmic reticulum might constitute key

control pathways determining intracellular Ca2+ homeostasis and flux dynamics. Ca2+ might itself constitute a significant component system in terms of key end-stage mediation, determining cell membrane depolarization and also contractility thresholds of the vascular myofibers.

Biophysical modes of control and of manipulation of Ca2+ mobilization and influx would ultimately determine characterized dynamics of hypercontractility and of sustained contraction of vascular myofibers in influencing vascular wall tone and luminal dimensions via systems ultimately determining blood pressure maintenance in hypertensive individuals.

Reduced nitric oxide bioavailability in arterial hypertension would appear to result from dysfunctional endothelium[18], resulting subsequently in disturbances of resting vascular tone, maladaptation of blood flow to metabolic tissue demand, and also disturbed flow and mediated vasodilation[19]. In an apparently closely analogous fashion, in diabetics, there is also endothelial dysfunction and altered platelet activity leading to an increased risk for coronary heart disease[20].

MYOFIBER HYPERCONTRACTILITY AS A SELF-PROPAGATION IN SEVERITY OF BOTH MYOCARDIAL HYPERTROPHY AND OF HYPERTENSIVE ARTERIOLAR SPASM

A specifically characterizing property of myofibers in general would concern their reactivity to stretch, in terms particularly that would implicate often hypertrophy of these myofibers. Indeed, perhaps, myofiber hypertrophy would evolve as an extension of contractility responses of myofibers arising as a series of stretch reflexes.

The left ventricle might actually operate as systems of activated susceptibility in the development of hypertrophy of myofibers. Indeed, a stretch stimulus that transcends even concepts of physiologic parametry might implicate pathologic over-response in terms of myofiber hypercontractility that would perhaps help account for an essentially integral circulatory hemodynamic disturbance in the hypertensive patient.

And it is perhaps in this particular sense that ventricular hypertrophy would involve a phenomenon of counteraction as arteriolar myofiber hypertrophy that evolves as the etiopathogenesis of the hypertensive state. Indeed, in a true sense, myocardial hypertrophy would simply induce a pathologic state that would apparently evolve from simple compensation to preload or afterload disturbances of progression in creating the hypertensive state.

It is the recognition of such a role for myocardial hypertrophy as an intrinsically abnormal phenomenon of progression in hypertension in its own right that would help explain for example the occurrence of apparently primary forms of myocardial hypertrophy as characterized by the idiopathic hypertrophic cardiomyopathies. This, however, would have to be interpreted in a context of DNA breaks in cardiomyocytes, as detected by TUNEL and insitu ligation assays with characteristics suggestive of an epiphenomenon to cardiac hypertrophy rather than as a manifestation of myocyte death[21].

Of course, recognition of an increased ventricular muscle mass might actually promote the precipitation of a whole series of decompensatory disturbances evolving as essential ischemia and even as infarction of myofibers. Hence, perhaps, myocardial hypertrophy would constitute particularly progressive forms of pathology strongly conducive to potential pathologic effects arising from induced myocardial ischemia. Also, the considerable concentric ventricular hypertrophy developing in patients with long-standing aortic stenosis or sustained hypertension might actually activate aberrant forms of ventricular filling during diastole or even disturbances in systemic hemodynamic flow patterns.

With arterial hypertension, of course, primary modes of increased reactivity of arteriolar smooth muscle would help account for increased susceptibility traits in terms of a marked and sustained increase in arteriolar tone and of peripheral vascular resistance.

Indeed, strong familial incidence of hypertension might both arise and evolve simply as effective pathways of integrative response whereby pathogenesis is itself an etiologic factor in subsequent evolution of circulatory hemodynamic disturbances in hypertensive states.

It is perhaps in terms of such progressive involvement as a vicious circle of increasing reactivity of myofiber contractility that one might consider arterial hypertension simply as different modes of self-propagating upset in hemodynamic responsiveness primarily dependent on myofiber contractility threshold settings as induced by states of vascular myofiber ischemia..

A ROLE OF DIRECTLY INDUCED VASCULAR REACTIVITY IN SUSTAINED VASOSPASM AND RENAL ISCHEMIA IN ARTERIAL HYPERTENSION EVEN WHEN BLOOD RENIN LEVELS ARE NOT RAISED

It is conceivable that the important roles played by severe renal vasoconstriction in several different forms of ischemia-induced states of renal insufficiency would help account for renal and tubular pathology primarily in terms of nephron susceptibility.

It is in terms particularly of degrees of susceptibility of specific segments of the individual nephron to ischemia, in a context of specific hemodynamic patterns of blood flow, that one might recognize responsiveness of

vascular myofibers that would induce alterations in renal blood flow systems. In addition, loss of autoregulation occurring on a focal basis with subsequent focal segmental glomerulosclerosis and affecting also arterioles, would appear characteristic of the aging kidney and also of essential hypertension[22]. In addition, preglomerular vascular disease together with tubulointerstitial inflammation would appear instrumental in mediating salt sensitivity in patients with essential hypertension[23].

Particularly significant would appear to be acute drops in the amount of blood delivered to the renal vascular bed. Such a phenomenon would be integral to a whole series of "compensatory mechanisms" characterizing in particular hypovolemic shock clinically and pathophysiologically.

Indeed, it is conceivable that a whole series of partly overlapping patterns of injury would preferentially involve specific segments of the nephron as ischemic events of acute tubular necrosis[24]. In fact, acute tubular necrosis as evolving ischemia might constitute specific subgroup patterns of evolving response and effect arising from specific forms of hemodynamic disturbance. It is in terms particularly of bilateral renal cortical necrosis classically associated with severe uterine bleeding in pregnant women or abortion that one might better recognize a full participation of responses and of evolving influence directly arising from characteristics of renal or organ specific disturbances beyond even strict circulatory considerations only. Decreased endothelium-dependent mechanisms of vascular relaxation and enhanced vascular smooth muscle contraction would appear involved in inducing increased vascular resistance and hypertension in pre-eclamptic patients[25].

One particular mechanism, for example, might relate to increased peripheral resistance in the renal vascular bed.

It would appear in fact that renal blood vessels possess a particularly well-developed capability in increasing peripheral vascular resistance both intrarenally and also systemically that would evolve as pathophysiologic states of primary organ specificity.

As such, the initial oliguric phase of acute renal failure would constitute essentially a response to an abnormal blood flow that in turn would influence the oliguric phase itself. This mutual interrelationship between decreased blood flow and increased intrarenal vascular resistance would in fact appear to operate in terms of a renal ischemia evolving subsequently as acute renal failure. In fact, acute tubular necrosis due to hypovolemia might actually represent a self-propagating series of events whereby decreased blood flow in the renal vascular bed would induce subsequent renal vascular spasm and further renal ischemia.

In such terms, ischemia-induced sustained renal vasospasm would appear central to the whole phenomenon of renal ischemia in a way that is related for example with renal causes of systemic arterial hypertension.

One particular aspect of such cases of renally induced vasospasm and of subsequent increased vascular resistance would concern especially the sustained progressiveness characterizing the nature of the renal damage that progresses to renal failure and thus characterizing complicating malignant hypertensive states in particular.

Certainly, beyond any considerations of hypersecretion of renin or of states of hyper-aldosteronism, reactivity of the vascular wall might operate in decreasing intravascular blood volume and blood flow. Increased intrauterine pressure as seen in cases of abruptio placentae would involve mechanisms of induced renal vasospasm and ischemia via mechanisms of vascular wall reactivity.

Perhaps, it is especially in terms of such a directly induced vasospasm that is self-progressive that one might better understand not only the pathogenesis of acute renal failure due to ischemia or hypovolemia but especially the prominent role played by impaired renal blood flow in inducing and in perpetuating sustained arterial hypertension even when plasma renin levels are not raised.

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