A new theory of essential hypertension based on analysis of the association between a polymorphism of the $\alpha_2$-adrenoceptor at the 10q24–q26 locus and hypertension in African-Americans

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ABSTRACT

Some key historical observations about essential hypertension (HTN) are reviewed, analyzed logically, and used to construct a new theory of hypertension. The historical observations are as follows: Lockette reported a statistical association between HTN in African-Americans and the 6.3-kb allele of a restriction fragment-length polymorphism of the gene for the $\alpha_2$-adrenoceptor, which is found on platelets. Individuals carrying at least one copy of the 6.3-kb allele had increased in vitro epinephrine-induced platelet aggregation. Systemic or blood-wide platelet activation (SPA) induced by epinephrine has been shown to be an in vivo feature of HTN, and serotonin and thromboxane $A_2$, two vasoconstrictors released by activated platelets, synergize in vitro with angiotensin II. Esler showed that there is increased noradrenergic drive in the heart and kidney in HTN, although renin levels are usually normal. Mulvany's group showed that small arteries controlling vascular resistance undergo remodeling in HTN. Putting together these observations leads to the following theory.

Essential HTN is a disease in which the brainstem set point for blood pressure (BP) is reset, which causes the autonomic nervous system to release increased norepinephrine in the heart and kidney and increased epinephrine from the adrenal medulla. Epinephrine release causes SPA. In the first stage of the disease, when renin is high, serotonin and thromboxane $A_2$ released by activated platelets synergize with high angiotensin II to raise BP. Rising BP causes vascular remodeling, a structural attempt at autoregulation of blood flow which maintains normal flow artery-by-artery but has the side-effect of increasing total peripheral resistance (TPR), even beyond that caused by high renin. The presence of ever rising TPR and, therefore, ever rising BP, gradually overcomes the effect of noradrenergic drive in the kidney and leads to suppression of renin release by the juxtaglomerular apparatus. Renin levels fall pari passu with rising TPR caused by vascular remodeling. In the second stage of the disease, when renin has fallen back to normal (or low), increased TPR caused by vascular remodeling persists as a factor raising BP.

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Introduction

Lockette et al. reported a statistical association between essential hypertension (HTN) and the 6.3-kb allele of a restriction fragment-length polymorphism of the gene for the $\alpha_2$-adrenoceptor in African-Americans in Detroit, Michigan [1]. The prevalence of 6.3-kb homozygotes was markedly increased in hypertensive African-Americans compared to normotensive African-Americans ($p = 0.02$). The statistical association between 6.3-kb homozygosity and hypertensive African-Americans vs. normotensive African-Americans plus normotensive whites was even stronger ($p = 0.002$). The purpose of this paper is to explain why $\alpha_2$-adrenoceptors, specifically the $\alpha_2$-adrenoceptors on platelets, are relevant to an understanding of HTN. The prevalence of this allele in one population group does not “explain” HTN in general; however, it points to an aspect of the pathophysiology of HTN which is of general importance.

The format of this paper will be to construct a new theory of HTN using Lockette's polymorphism as the starting point. $\alpha_2$-Adrenoceptors have a number of different functions; the place to start is the $\alpha_2$-adrenoceptor on platelets.
Systemic platelet activation

Lockette's group reported that individuals carrying at least one copy of 6.3-kb allele had increased epinephrine-induced platelet aggregation, measured by optical density changes, p < .05, adenosine diphosphate being used as a negative control [2]. They speculated that this might relate to a high rate of thrombotic stroke in African-Americans but did not relate it to hypertension. At first it might seem that focal thrombosis initiated by local tissue injury might not be relevant to HTN, but there is another aspect to platelet activation.

Systemic platelet activation (SPA) was first described by Sicureti in 1961 in the context of migraine [3]. He found that many migraineurs, during headaches, had up to a 3- to 5-fold increase in urinary excretion of 5-hydroxyindoleacetic acid, which is the chief end product of serotonin metabolism. The serotonin was eventually understood to come from activated platelets undergoing degranulation and appeared to be a systemic or blood-wide phenomenon. Curran et al. hospitalized 18 migraineurs for metabolic studies [4]. Using measurements of urinary serotonin metabolites, they reported that platelet degranulation and release of serotonin occurred during 68% of migraine headaches. They had data for total plasma serotonin shortly before and during headaches in six patients and found that it fell by average of 66% (p < 0.01), i.e. 66% of platelets were activated and degranulated, which makes this a major physiological phenomenon. D’Andea et al. showed that plasma β-thromboglobulin, a cytokine released by activated platelets, was equally elevated during and between attacks in patients with classic migraine, p < 0.001 migraineurs vs. healthy controls [5]. Hamilton, using the optical density of lightly spun plasma as an index of platelet aggregation, also found evidence of SPA in migraineurs during afebrile attacks, p < 0.01 migraineurs vs. age-matched controls [6]. Researchers at that time were looking for confirmation of Harold Wolff's theory that migraine aura was caused by vasoconstriction, which led to interest in vasoconstrictors such as serotonin. Inability to correlate levels of serotonin metabolites with headache symptomatology ultimately led to abandonment of this research and loss of interest in SPA. In the present context, the important points are that the phenomenon exists and that it does not have to be associated with a headache. Interestingly enough, there do not appear to be any reports of low platelet counts; this may be due to the broad range of the “normal” platelet count and to the fact that platelets can be released quickly from the bone marrow.

The mechanism of SPA is probably platelet stimulation by epinephrine released by the adrenal medulla, as reviewed by von Kanel et al. [7]. A study which combined epinephrine infusion with measurement of plasma epinephrine levels was that by Wallen et al., who showed that intravenous infusion of epinephrine into human subjects from a baseline value of 0.14 nmol/L up to 3.34 nmol/L was associated with a significant increase in platelet aggregation (p < 0.01) [8].

There are several articles in the literature documenting platelet activation in essential HTN. Brunner et al. studied 17 adult hypertensive men (average BP 212.67 ± 23.27/110.5 ± 8.52) who had taken no medications for 2 weeks and compared them to 25 age-matched controls [9]. The mean serotonin level of platelet-poor plasma was higher in hypertensives than controls, (1.06 ± 0.050 vs. 0.70 ± 0.05 nmol/L, p < 0.001), which supports the idea that HTN is associated with platelet activation and degranulation. Kjeldsen et al. studied twenty-three 50-year-old men with untreated sustained HTN and compared them to 14 age-matched controls [10]. They found that the hypertensive men had a 74% elevation of plasma β-thromboglobulin (p < 0.01) and 53% elevation of arterial epinephrine (p < 0.05). Arterial epinephrine levels correlated statistically with β-thromboglobulin levels in both the normotensive (p < 0.01) and hypertensive (p < 0.05) men. Epinephrine levels ranged between approximately 0.20 and 1.00 nmol/L in the combined group. It is not clear to what extent platelet activation in hypertension is episodic as opposed to a continuous process.

At this point, the theory has progressed to the idea that SPA is a feature of essential HTN; this is important because, as noted above, activated platelets release vasoconstrictors and vasoconstrictors can raise BP.

Synergy of vasoconstrictors

The three most relevant vasoconstrictors in the context of this paper are serotonin, thromboxane A2 (TxA2, a second vasoconstric-tor released by activated platelets), and angiotensin II (the question of renin/angiotensin II levels in HTN will be discussed below). Van Neuten et al. reported that 30 nmol/L serotonin increased the contractile strength of rabbit femoral arteries to 0.15 nmol/L angiotensin by 1077 ± 159% [11]. MacLennan et al. studied synergy between serotonin and U46619, a stable TxA2 mimetic, in causing contraction of vascular rings of rabbit femoral artery [12]. The inflection points of the curves of contraction strength vs. concentration of serotonin added to different constant nanomolar concentrations of U46619 were in the low nanomolar range, which is within the physiological range of action of sero-tonin. The inference to be drawn is that these two synergies, and a hypothetical synergy of all three vasoconstrictors, for which there appears to be no data, are a normal physiological mechanism for supporting blood pressure in situations of stress in which the autonomic nervous system is activated and epinephrine is released from the adrenal medulla, for example, in response to trauma or sepsis. All the data involve clinically-relevant nanomolar concentrations. MacLennan et al. point out that all three vasoconstrictors have second messenger pathways involving hydrolysis of inositol phospholipids, which could be the mechanism of synergy.

The theory linking the 6.3-kb allele to HTN has now been brought to the following point: the 6.3-kb allele enhances epinephrine binding to α2-adrenoceptors on platelets, thereby increasing platelet activation, degranulation, and release of serotonin and TxA2, which synergize with angiotensin II to raise BP. There is, however, a problem with the theory, which is that epinephrine infusion in normal human subjects does not raise blood pressure. Fellows et al. infused epinephrine into seven young male volunteers, achieving venous concentrations as high as 2.19 nmol/L, yet BP did not rise: systolic BP rose slightly, diastolic BP fell slightly and mean BP fell from 80 to 75 mmHg [13]. In order for epinephrine infusion to raise BP, it appears that angiotensin II must also be high so that the serotonin and TxA2 released from epinephrine-activated platelets can synergize with elevated angio-tensin II. Unfortunately, the renin/angiotensin II system is not, in general, elevated in HTN. Brunner et al. reported a study of 219 patients with essential HTN (diastolic BP > 95 on three occasions) who had been taken off all-hypertensive medications and maintained on a normosodium diet for 3 weeks [14]. 16% of the patients had high renin, 57% normal renin, and 27% low renin. In order to make sense out of the theory that is being developed, renin should be high in HTN, but, in general, it is not. A clue about how to find a way out of this potential dead-end can be found by looking at NE levels in HTN.

Esler's theory of HTN

Esler et al. performed a classic study of the release or “spillover” of norepinephrine (NE) into the venous circulation of normal
subjects compared to patients with a variety of other diseases [15].
Patients were given a radiolabeled precursor of NE (tyrosine or
dopamine) and then spillover of endogenously-synthesized NE
was measured by venous catheterization of various organs. Fifty
untreated hypertensives had significantly-increased NE spillover
from the heart (p < 0.05, compared to 28 healthy controls) and kid-
nneys (p < 0.01). The authors commented that this provided a “plau-
sible mechanism” for understanding HTN. NE release in the heart
relates to the force of cardiac contraction and NE release in the kid-
ney relates to renin release from the juxtaglomerular apparatus
(JGA) and vascular tone. It is tempting to try to explain essential
HTN as a disease of the autonomic nervous system involving nor-
adrenergic overdrive in the heart and kidneys. However, there is an
immediate problem with this line of thinking, which is, again, that
renin is not elevated in the majority of patients with essential HTN.
The fact that NE release in the kidney is high in most or all patients
but renin release by the JGA is often normal or low suggests that
HTN is often driven or maintained by something other than renin
and the JGA’s attempt to release excess renin is suppressed, i.e.
lowered from high to normal or low.

The theory has arrived at the idea that autonomic overdrive in
the adrenal medulla and kidney can explain HTN in high-renin
patients but, in low- and normal-renin patients another factor
must be at play which also raises BP and suppresses renin release
by the JGA. What this factor might be can be found by looking at
the vascular pathology of HTN.

Vascular remodeling and the stages of hypertension

Mulvany entitled a review of vascular remodeling in HTN as fol-
lows: “Are vascular abnormalities a primary cause or secondary
consequence of hypertension?” [16]. “Resistance arteries”, which
are the small arteries or arterioles which determine vascular tone
and peripheral resistance, are usually defined as small arterial
blood vessels with diameters less than 500 μm. Korsgaard et al.
studied the histology of subcutaneous resistance arteries in sixteen
untreated hypertensives and compared them to sixteen age- and
sex-matched normotensive controls [17]. The arteries from the
hypertensives had significantly smaller lumen diameters (p < 0.05),
smaller outer diameters (p < 0.05), and higher media-lumen ratios (p < 0.05), but no difference in number of smooth muscle cells per vessel segment length (p NS). This was interpreted to indicate a “rearrangement of smooth muscle cells
within the medial layers of the arterial wall”. Mulvany points out
that these “alterations in the structure of small arteries...enable
them to maintain an increased resistance with a normal degree
of activation”, there being no evidence of increased activation or
increased sensitivity to vasoconstrictors. The increased arterial
resistance can be interpreted as a structural attempt at autoregula-
tion of blood flow in response to gradually rising BP; however,
remodeling all small arteries simultaneously, while it solves the
flow problem artery by artery, ends up worsening the HTN by
increasing total peripheral resistance (TPR).

The concept of vascular remodeling is the final piece of the puzzle
needed to construct a complete theory, which is the hypothesis
of this paper:

Hypothesis. Essential HTN is a disease in which the brainstem set
point for BP is reset, which causes the autonomic nervous system
to release increased norepinephrine in the heart and kidney and
increased epinephrine from the adrenal medulla. Epinephrine
release causes SPA. In the first stage of the disease, when renin is
high, serotonin and thromboxane A2 released by activated platelets
synergize with high angiotensin II to raise BP. Rising BP causes
vascular remodeling, a structural attempt at autoregulation
of blood flow which maintains normal flow artery-by-artery but has
the side-effect of increasing total peripheral resistance (TPR), even
beyond that caused by high renin. The presence of ever rising TPR
and, therefore, ever rising BP, gradually overcomes the effect of
noradrenergic drive in the kidney and leads to suppression of renin
release by the JGA. Renin levels fall pari passu with rising TPR
caused by vascular remodeling. In the second stage of the disease,
when renin has fallen back to normal (or low), increased TPR
caused by vascular remodeling persists as a factor raising BP.

A number of comments can be made about the theory, as follows:

(1) There is no evidence that renin levels are high at the onset of
the disease, assuming essential HTN is one disease. Relevant
data is not available in the literature and is probably unob-
tainable because HTN is very often asymptomatic and, at
the time of diagnosis, there is no way to know how long
the condition has been present. A clue is to be found in a
paper by Drayer et al. [18]. The authors studied 956 patients
with a diagnosis of essential HTN (diastolic BP > 90 on two
occasions), 40% of whom were already being treated.
Treatment was either delayed or patients were taken off
anti-hypertensive medications and all were maintained on
a normosodium diet for 2 weeks. The high renin subgroup
(11% of the total) had an average age of onset at
32 ± 12.9 years, the normal renin subgroup (62%) at
40 ± 13.9 years, and the low renin subgroup (27%) at
45.7 ± 13.1 years, (p < 0.001 between successive subgroups);
this suggests but does not prove that renin levels fall over
time.

(2) The reason for elevation of the brainstem set point for BP is
unknown. It is possible that it relates to stress, at least in
some individuals [19].

(3) The theory explains why the 6.3-kb allele is associated with
HTN: enhancing SPA facilitates onset of the disease,
although it does not per se cause it, because change of the
set point and increased NE drive in the kidney are also
required.

(4) The theory extends and completes Esler’s theory by explain-
ing why high NE drive in the kidney can be associated with
normal or low renin.

(5) The answer to Mulvany’s question is that vascular abnor-
malities start as a secondary consequence of hypertension
and then become a primary cause.

(6) This theory supplies an additional mechanism of action for
thiazides and calcium-channel blockers in treating HTN. In
addition to their recognized diuretic and vasodilatory
effects, drugs from both categories have also been found to
block platelet activation. Gleerup et al. reported a study in
which thirteen patients with “mild” hypertension (diastolic
BP 95–114) were treated with either placebo,
hydrochlorothiazide, or spirapril (an angiotensin converting
enzyme-blocker) [20]. Platelets from patients treated with
hydrochlorothiazide, but not with spirapril or placebo, had
a ten-fold elevation in the threshold for in vitro platelet
aggregation induced by epinephrine, comparing pre-
to-post-treatment values (p < 0.05). There was no effect on ade-
nosine diphosphate-induced platelet aggregation. Ikeda
et al. reported decreased in vitro platelet aggregation
induced by either epinephrine or adenosine diphosphate in
platelets from normal (non-hypertensive) volunteers treated
with conventional anti-hypertensive doses of verapamil,
a calcium-channel blocker [21]. Cremer et al. reported a

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similar study with conventional doses of diltiazem, another calcium-channel blocker, administered to normal volunteers [22]. Inhibition of platelet activation would be relevant only in high-renin patients.

Conflict of interest statement

There are no conflicts of interest.

References