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Is the brain the essential in hypertension?

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Abstract

The brain is typically considered a target for late stage hypertensive disease due to the high prevalence of stroke among hypertensive patients. Research is reviewed, however, that suggests that the brain is implicated in the initiation of high blood pressure and is itself altered by early disease processes. A substantial literature establishes neural control of the vasculature and kidney as candidate etiological factors in essential hypertension. This research, largely done in animals, is now supplemented by behavioral and brain imaging studies in humans. This review suggests that the brain and vasculature may be independently and concurrently targeted by the factors inducing essential hypertension. Early stage hypertension is associated with cognitive deficits, altered cerebral blood flow support for cognitive processing, and decreased grey matter in specific cortical regions. Pharmacological reversal of hypertension is less successful in patients with premature brain aging and fails to reverse either the progression of functional or structural changes within the cerebral cortex. Furthermore, magnetic resonance imaging Blood Oxygen Level-Dependent (BOLD) responses during psychological challenge differ between normotensive individuals at risk and those not at risk for hypertension because of their exaggerated blood pressure responses to psychological challenge. Further examination of mechanisms of action and early influences of the disease on the brain are required to understand the pathophysiological mechanisms having concurrent influences on the brain and the peripheral vasculature.

Keywords

hypertension; regional cerebral blood flow; neuropsychology; brain morphology; cognitive processing; positron emission tomography; magnetic resonance imaging

Essential hypertension is a disease of pandemic proportions in North American and Europe. In the United States fully half of the persons aged 55 to 56 have hypertension (NHANES:1999–2004). Essential hypertension is defined by chronically elevated blood pressure for which there is no known, single underlying cause (Chobanian et al., 2003; Delgado & Weder, 2005). Hypertension, when untreated, typically progresses to levels of blood pressure that threaten the integrity of cerebral vessels, potentially inducing stroke (Shapiro, 1997). This sequel of hypertension, which occurs late in the course of the disease, is typically discussed as the primary link between the brain and essential hypertension in medical textbooks (Fotherby, Eveson, & Robinson, 2007). The current review suggests, however, that the brain is an essential aspect of hypertension-- potentially initiating the disease, influenced at early stages of the disease, and functionally impaired during the maintenance of the disease, i.e., both failing to regulate

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blood pressure and exhibiting functional deficits in information processing. Neurophysiological work is briefly noted that has established the potential importance of neural regulatory circuitry in the initiation and maintenance of hypertension. We then review in more detail how imaging studies in humans have similarly suggested that essential hypertension is a disease of both the brain and the vasculature.

Essential Hypertension—Etiology and Natural History

The vasculature may be subject to mo re forms of regulation than any other system of the body. We can, for example, behaviorally regulate the vasculature by moving from a cold to a warm environment; while at a more molecular level, local changes in adenosine can elicit vasodilation within a single vessel (Buxton, 2002). Thus, it is not surprising that dysregulation in a large number of systems has been related to the initiation and/or maintenance of hypertension. In their review of the pathogenesis of hypertension, Oparil and colleagues (Oparil, Zaman, & Calhoun, 2003) provide a rather exhaustive listing of these potential etiological factors, "..increased sympathetic nervous system activity, perhaps, related to heightened exposure or response to psychosocial stress; overproduction of sodium-retaining hormones and vasoconstrictors; long-term high sodium intake; inadequate dietary intake of potassium and calcium; increased or inappropriate renin secretion with resultant increased production of angiotensin II and aldosterone; deficiencies of vasodilators, such as prostacyclin, nitric oxide, and the naturiuretic peptides; alterations in expression of the kallikrein-kinin system that affect vascular tone and renal salt handling; abnormalities of resistance vessels, including selective lesions in the renal microvasculature; diabetes mellitus; insulin resistance; obesity; increased activity of vascular growth factors; alterations in adrenergic receptors that influence heart rate, inotropic properties of the heart, and vascular tone; and altered cellular ion transport.' (p. 761). This list clearly illustrates the complexity that has been revealed in attempts to understand hypertension. The list also is generally suggestive of a failure of an overall control system, the central nervous system, in that multiple physiological systems typically regulated by the brain are dysregulated. After briefly defining hypertension, we will summarize work done primarily in animal models that solidly implicates the brain in the etiology of hypertension. We cannot do justice to the plethora of factors involved, however, and refer the reader to three excellent reviews for further detail (Guyenet, 2006; Oparil et al., 2003; Sved, Ito, & Sved, 2003). Our focus will be on the cluster of potential etiological factors related to the renin angiotensin system (keyed on kidney function) and on the sympathetic nervous system.

The natural history of essential hypertension as a disease is difficult to describe in humans because the onset of high blood pressure (that is, greater than 140 mmHg systolic blood pressure and/or greater than 90 diastolic blood pressure) is typically not precisely known. Elevated blood pressure is not associated with overt symptoms, and can only be detected via blood pressure measurement. Research in animal models, reviewed by Folkow (Folkow, 1978; Folkow et al., 1984), suggests a natural history of vascular change in which an increase in cardiac output induces an overperfusion of tissue which is then followed by vasoconstrictive influences and a remodeling of the vasculature increasing the area of the vascular wall. Vascular resistance is increased due to changes in the structure of the vessel wall (vascular remodeling). These structural changes in the blood vessel walls both lead to a decrease in the diameter of the blood vessels as well as to an increase in reactivity to vasoconstrictors (Boegehold, 2007). Arterial wall thickening is thought to occur in response to increased blood pressure and increased blood flow (Touyz, 2005). Furthermore, hypertension has been shown to be associated with a loss of arterioles and capillaries (rarefaction). As rarefaction results in a decrease in the number of available pathways for blood flow conduction, it leads to further increases in vascular resistance, adding to the effects of vascular remodeling (Touyz, 2005). Both vascular remodeling and rarefaction may contribute to end organ damage (Boegehold, 2007), with the brain typically considered an end-organ within this perspective.

A number of etiologic factors underlying this natural history are related to kidney function with particular importance placed on angiotensin, a peptide with clear influence both in the brain and in the periphery. The kidney has a central role in the salt and water balance regulating blood volume and through this blood pressure (Folkow, 1992; Guyton, 1990). Guyton has led work examining the complexity of blood pressure regulation and emphasizing the importance of kidney regulation in the onset and course of hypertension (Guyton, 1991; Guyton, Hall, & Montani, 1988). Much of kidney regulation is effected through the renin-angiotensin (RAS) system. The RAS system is a neuroendocrine regulatory system whose most active component, angiotensin II, is a powerful vasoconstrictor. Activation of the RAS system has also been shown to contribute to vascular remodeling and vascular lesions (Rossi, Rossi, Sacchetto, Pavan, & Pessina, 1995). Specifically, angiotensin II acts through various pathways, promoting pro-inflammatory factors leading to a cascade of processes that result in vascular injury, and ultimately, vascular remodeling (Touyz, 2005). Central nervous system involvement in these renal-related factors derives both from the influence of the hypothalamus and sympathetic innervation on kidney function and the effects of angiotensin in the brain (Guyenet, 2006). Although further definition of circuitry and transmitter function is required, the hypothalamus receives information on blood volume and osmolality. Hypothalamic action (largely via the paraventricular nucleus) in response to this information then influences the kidney via sympathetic efferents. This action may enhance or parallel the response of the angiotensin system to sodium concentration (Guyenet, 2006). In short, appropriate hypothalamic regulation of osmality/blood volume seems necessary if normal blood pressure is to be maintained. More recently, angiotensin has been recognized as a centrally active peptide. Angiotensin has been shown to be produced in the brain in addition to other sites (de Wardener, 2001; Paul, Poyan Mehr, & Kreutz, 2006). It appears to directly excite the primary brainstem area known to project to sympathetic efferent, the rostral venterolateral medulla. An antagonist to the angiotensin I receptor directly injected into this area has been shown to have an antihypertensive action in a number of animal models of hypertension (Sved et al., 2003). Interestingly, Diz (Diz, 2008) suggests that angiotensin is also cause or concomitant of brain aging, just as research on the peripheral vasculature has suggested that hypertension hastens aging of the circulatory system (Lakatta, 1989, 1990). Diz (Diz, 2008) first relates angiotensin to aging of the kidney and vasculature, and then reviews work in a transgenic rat model showing that specific antagonism of brain angiotensin counters autonomic changes associated with aging, for example, improving kidney function and energy metabolism. Interpretation of both causes of hypertension as well as brain aging is complicated, however, by the host of other factors that influence both the vasculature and brain function, e.g. other vasoconstrictors, such as endothelin (Schirger, Boerrigter, & Burnett, 2005)or metabolic markers, such as homocysteine, (Raz & Rodrigue, 2006).

In parallel to research on the kidney and the renin angiotensin system, convincing evidence also implicates the central adrenergic and noradrenergic systems in essential hypertension (Esler et al., 2008; Esler, Lambert, Brunner-La Rocca, Vaddadi, & Kaye, 2003; Esler et al., 2001; Esler et al., 2006; Guyenet, 2006; Sved et al., 2003) A starting point of such work is the observation of heightened sympathetic activation among hypertensive individuals and the efficacy of sympathetic blocking medications in reducing blood pressure. Blood pressure is modulated by functional circuitry linking the hypothalamus, nucleus tractus solitarius, and the rostral ventrolateral medulla. Guyenet (Guyenet, 2006) and Sved and colleagues (Sved et al., 2003) ably review studies, primarily in animal models, that document the responsiveness of these areas to acute blood pressure changes (via activation of the baroreceptors) as well as the long term alteration of blood pressure when lesions and neurochemical manipulations alter function within this circuitry. Although adrenergic effects are now clearly associated with hypertension, the precise factors initiating these effects and their role in initiating hypertension is not clear. Current work has re-emphasized central regulatory factors: central control of baroreceptor function (e.g. (Lohmeier et al., 2005; Lohmeier, Dwyer, Irwin, Rossing, & Kieval,

2007; McMullan, Goodchild, & Pilowsky, 2007; Sleight, 2004; Thrasher, 2005; Yamamoto et al., 1988)) and dysregulation within midbrain areas that influence brainstem vascular regulatory areas, e.g., (Dampney et al., 2003; Dampney, Tan, Sheriff, Fontes, & Horiuchi, 2007; Madden & Sved, 2003; Osborn, Fink, Sved, Toney, & Raizada, 2007; Saha, 2005; Schreihofer, Ito, & Sved, 2005). Sympathetic and kidney mechanisms are clearly not independent, but controversy continues on which is primary, see also (Grassi & Esler, 2002).

In conclusion, mechanistic studies primarily in animal models of hypertension clearly implicate the kidney and sympathetic nervous system function as causes or participatory factors in essential hypertension. Hypertension appears to initially be characterized by an over perfusion of tissue that is then followed by an increase in vascular resistance that is maintained both by vessel remodeling and reduction in the number of vessels. Both sympathetic and renal systems appear to contribute to these changes and both are regulated by the central nervous system. Manipulations of these regulatory systems alter the onset and course of hypertension in animal models. The exact initiating cause(s) of hypertension remain elusive and a multifactorial origin remains the leading hypothesis. Thus, we cannot say that the brain initiates hypertension, but it is clear that hypertension is incompatible with a normally functioning brain. Central vascular control is dysregulated in essential hypertension. In short, existing literature on mechanisms of essential hypertension are consistent with the view that the brain is either an early target of the disease and/or that the disease originates in the brain.

Human Hypertension is associated with cognitive deficits, altered cerebral blood flow and accelerated brain aging

Cognitive deficits

In a review of early studies examining the relationship between hypertension and cognitive functioning, Waldstein and colleagues (1991) concluded that possible confounding factors were not sufficient to explain the cognitive performance deficit in hypertensives. They concluded that " *Our review of the literature examining the neuropsychological correlates of hypertension has revealed that most consistently, hypertensives perform more poorly than normotensives on tests of memory, attention, and abstract reasoning*"(Waldstein, Manuck, Ryan, & Muldoon, 1991). Subsequent work has only further verified this summary, although the deficits seem more readily detected in middle-aged hypertensive patients. Indeed in elderly samples, both hypotension and hypertension appears to be related to cognitive deficits (Elias et al., 2007; Robbins, Elias, Elias, & Budge, 2005; J.M. Starr & Whalley, 2005; J. M. Starr, Whalley, Starr, & Whalley, 2005; Waldstein, Giggey, Thayer, & Zonderman, 2005; Waldstein et al., 1996). These observations suggest that hypertension has a functional effect on the brain, at least by the time of early stage hypertension--when hypertension is detected in middle age.

Brain aging

Hypertensive individuals have been found to show structural abnormalities in the brain, suggesting that hypertension is associated with accelerated aging of the brain. Studies have shown that pathological changes associated with hypertension include white matter hyperintensities, reductions in brain grey matter as well as increased sulcal and ventricle size due to brain atrophy (DeCarli et al., 1995; Korf, White, Scheltens, & Launer, 2004; Raz, 2005; Raz & Rodrigue, 2006; Raz, Rodrigue, & Acker, 2003; Sierra et al., 2004; Soderlund, Nyberg, Adolfsson, Nilsson, & Launer, 2003; Strassburger et al., 1997). Raz & Rodrigue (2006), for example, published a review examining age-related structural changes in the brain. The authors conclude that hypertension exacerbates brain aging. Furthermore, they conclude that successful treatment reduces, but does not eliminate effects of aging on the brain; compared to normotensives, treated hypertensives have more white matter hyperintensities, prefrontal

volume shrinkage and reduced hippocampal volume. Their conclusions were drawn both from clinical and epidemiological studies.

Research in our laboratory has added to this work suggesting that hypertensive individuals have less grey matter volume in specific regions as well as other indicants of brain aging. Using voxel based morphometry techniques, Gianaros et al. (Gianaros, Greer, Ryan, & Jennings, 2006) found in male hypertensives reductions in prefrontal, medial frontal, inferior temporal and cerebellar areas. Furthermore, these reductions in grey matter were related to neuropsychological test performance. The same sample showed increases in white matter hyperintensities, as well as marginal increases in sulcal size, and ventricular size relative to normotensive controls (Jennings et al., 2005).

Taken together, the literature reviewed above suggests that hypertension alters the anatomical integrity of the brain prior to late stage hypertension. These findings also align well with the speculation of Diz (Diz, 2008) that actions of angiotensin may trigger both brain aging and peripheral blood pressure increases. Empirical evidence for this link is, however, lacking—particularly in humans.

Hypertension is associated with altered cerebral blood flow support for cognitive processing

In addition to structural changes in the brain, hypertension has also been shown to be associated with different overall and regional cerebral blood flow (rCBF);(Beason-Held, Moghekar, Zonderman, Kraut, & Resnick, 2007; Dai et al., 2008; Efimova, Efimova, Triss, & Lishmanov, 2008; Fuji et al., 1990; Fujishima, Ibayashi, Fuji, & Mori, 1995; Jennings, Muldoon, Ryan, Price, Greer, & Sutton-Tyrrell, 2005) (Jennings, Muldoon, Ryan, Price, Greer, Sutton-Tyrrell et al., 2005; Jennings et al., 1998; Mentis et al., 1994; Nobili et al., 1993; Rodriguez et al., 1987). This evidence has been garnered from xenon, single photon emission computed tomography (SPECT), functional MRI, and positron emission tomography (PET) studies. Most studies have only examined resting flow values and studies varied in age of participants and whether or not hypertensive participants were never medicated, currently medicated, or medication free at time of testing.

Despite this variability among studies, on balance, findings appear to suggest that hypertension is associated with a small decrease in resting CBF relative to normal, age-matched controls. Early studies (Fuji et al., 1990) focused on total cerebral blood flow using PET and failed to observe any difference in CBF between hypertensive and normotensive participants. Later studies using xenon clearance, single photo emission computed tomography (SPECT), and ^{15}O positron emission tomography (PET) suggest that CBF at rest is decreased among hypertensive relative to normotensive participants (Efimova et al., 2008; Fujishima et al., 1995; Nobili et al., 1993; Rodriguez et al., 1987). Dai et al. (2008), using the asynchronous spin labeling MRI technique, reported less resting rCBF among hypertensives relative to controls in subcortical, medial cortical, and limited frontal and temporal areas. In contrast, cerebral glucose and oxygen utilization does not appear to differ between groups (Fuji et al., 1990; Mentis et al., 1994). The measurements of Fuji et al. (1990) showed that this discrepancy was possibly due to a greater oxygen extraction fraction among hypertensives relative to controls.

Our laboratory has examined differences between never medicated hypertensive individuals and controls in regional cerebral blood flow (rCBF) activation during cognitive tasks (as opposed to resting rCBF). Cerebral blood flow responses to cognitive processing appear to be damped in amplitude but spread over greater cerebral area among hypertensive compared to normotensive individuals (Jennings, Muldoon, Ryan, Price, Greer, Sutton-Tyrrell et al., 2005; Jennings et al., 1998). In the initial study, participants were nine unmedicated hypertensives and five controls (normotensive participants) in the age range of 59–68 years

who performed working memory tasks during rapid infusion of the radiotracer [^{15}O] water. Memory tasks were presented at two levels of difficulty. In comparison to normotensives, hypertensive participants showed a decreased rCBF response in dorsolateral prefrontal and posterior parietal areas as a function of task difficulty (Jennings et al., 1998). The damped rCBF responses were, however, only significant in right hemisphere areas and compensatory activity was evident in homologous left hemisphere areas as well as in greater hippocampal activation in hypertensive individuals. This initial study suggested that the cerebral blood flow support for cognitive processing differed between hypertensives and normotensives. This association does not, of course, clarify whether hypertension induced a change in blood flow with possible consequences for neuropsychological function or whether altered neuropsychological function preceding the reorganization of the cerebral blood flow support.

A larger follow-up study confirmed the general conclusions from our initial study, but the pattern of compensatory rCBF activation was somewhat different (Gamalo, Ombao, & Jennings, 2005; Jennings, Muldoon, Ryan, Price, Greer, Sutton-Tyrrell et al., 2005). Quantitative PET blood flow techniques were applied to 37 never treated hypertensive and 59 normotensive individuals (mean age=60 years). Again two difficulty levels of working memory tasks were compared to a sensorimotor control task. The finding of reduced rCBF activation in the posterior parietal area during memory performance was replicated, but prefrontal findings were marginal. Damped thalamic rCBF activation during memory was also observed in this study, but not in the prior study. As in the prior study, a compensatory spread of activation was observed, but only in the prefrontal area (Gamalo et al., 2005). The apparent hemispheric compensation that was previously observed was not replicated (Jennings et al., 1998). Interestingly, hippocampal increases during memory performance only occurred among hypertensives performing relatively well on the memory tasks. Overall, our two studies supported a quite selective damping of rCBF activation in some brain areas among hypertensives as well as a compensatory spread of rCBF activation. Both parietal activation and compensatory hippocampal activation appeared to be related to level of memory performance.

In sum, hypertension appears to induce a mild reduction in CBF that may be more marked in frontal and subcortical regions. Activation during cognitive tasks appears to be reduced in some of the areas active during cognitive processing, but activated rCBF is found over a greater area in hypertensive relative to normotensive individuals.

Hypertension is associated with altered organization of the functional response to cognitive processing

In addition to the anatomical and functional findings in hypertensive individuals, brain areas that are activated during cognitive task performance show correlated levels of response in hypertensives that are minimally present in normotensive individuals (Jennings, Muldoon, Ryan, Price, Greer, Sutton-Tyrrell et al., 2005). Areas of activation appear to show yoked/coordinated responses sharing high or low levels of rCBF response during memory performance. Correlations of rCBF between regions of interest for the amygdala/hippocampus, prefrontal, and parietal areas were examined. Correlations of the amygdala/hippocampus and both prefrontal and parietal areas were significantly higher in hypertensive relative to normotensive individuals. Interestingly, an early study examined resting cerebral glucose utilization with PET comparing controls and hypertensive participants at similar ages as those in our work (Mentis et al., 1994). They observed a decrease in correlation in glucose utilization among brain regions at rest in hypertensive relative to normotensive participants. These changes in the functional organization of the brain appear to be an additional form of compensation potentially maintaining cognitive function hypertensive individuals.

To this point, we have reviewed evidence first from animal model studies that implicates the renin-angiotensin system and sympathetic nervous system in the etiology of hypertension in animal model forms of hypertension. The same literature was interpreted as leading jointly to premature brain aging as well as high blood pressure. In human imaging studies, we have further found in early to mid stage hypertension that cognitive function is mildly impaired, that signs of premature brain aging are evident in morphological and anatomic indices, that activation of brain blood flow is selectively muted during memory performance, that areas of compensatory brain blood flow during memory performance are evident, and finally that changes in the organization of the function brain blood flow support for cognitive function are present.

We initially presented a hypothesis that the autoregulatory adjustment of cerebral blood flow to peripheral high blood pressure resulted in a reduced capability for selective vasodilation in active brain regions during cognitive performance, a deficit that then induced compensatory blood flow adjustments (Jennings, 2003). This hypothesis guided our first two studies and essentially mirrored the medical view that essential hypertension was primarily (in time as well as importance) a vascular disease. The hypothesis assumed that vascular factors such as remodeling and rarefaction due to the disease had a subsequent effect on the capability of blood vessels to support cognitive performance. Vascular dysfunction was assumed to be disrupting the brain's normal function, but the brain itself was not seen as a direct target of the disease.

According to our early view, hypertensive levels of blood pressure change would precede changes in cognitive function; peripheral blood pressure was viewed as inducing changes in brain structure and function. From this perspective, reducing blood pressure and reversing its effects on the vasculature would likely have beneficial effects on cognitive function as well as cerebral blood flow. In contrast, in the 'brain as essential' hypothesis, essential hypertension may initially induce effects on the brain prior to or concurrently with effects on blood pressure. Thus, the 'brain as essential' view would expect cognitive and cerebral blood flow anomalies prior to the establishment of hypertensive levels of blood pressure. If the latter view is correct, then blood pressure reduction in itself may not improve cognitive function. Indeed, further research as well as the studies reviewed below do suggest that the cognitive and cortical associates of hypertension are not due to hypertensive levels of peripheral high blood pressure.

Human Pre-Hypertension relates to neural activation patterns during psychological challenge and to cognitive deficits

Neuropsychological performance in young adults that are genetically at risk for hypertension already shows subtle differences with those who are not at risk (Muldoon, Waldstein, & Jennings, 1995). Although this literature is not large or completely consistent with regard to the nature of the neuropsychological deficit, it does suggest that some aspect of essential hypertension is influencing the brain prior to frank hypertension.

Support for this contention is found in an fMRI study of family history of hypertension. Recently, Haley and colleagues (Haley et al., 2008) compared BOLD response to cognitive challenge in young individuals genetically at risk for hypertension to individuals who are not at risk. Haley et al. found that those with a parental history of hypertension showed different brain activation patterns from those not at risk, during performance of a working memory task (Haley et al., 2008). Haley et al. (2008) found that family history positive relative to family history negative individuals, showed less task-related activations in the posterior cingulate cortex, the right inferior parietal lobule and the right inferior temporal gyrus during task performance. While this pattern of results does not correspond directly to that found in older and hypertensive individuals, the results do support the possibility of early effects of essential hypertension on the brain.

Another type of evidence comes from a second risk factor for hypertension: individuals who show heightened cardiovascular reactivity to stressors may be at greater risk for developing hypertension later in life (Treiber et al., 2003); (Matthews et al., 2004); (Krantz & Manuck, 1984). Thus, exaggerated blood pressure responding to psychological stress may be regarded as a risk factor for the development of hypertension. Gianaros and colleagues (Gianaros, Jennings, Sheu, Derbyshire, & Matthews, 2007; Gianaros, May, Siegle, & Jennings, 2005; Gianaros et al., 2008) demonstrated that participants who show greater blood pressure reactivity to a Stroop color-word stressor also show enhanced BOLD fMRI responses in brain areas that play a role in both blood pressure regulation and in cognitive processes related to stress. This evidence is reviewed in detail in another paper within this issue (Gianaros & Sheu, in press) in this issue. Interestingly, this pattern of enhanced responsivity relating to greater pressure differs from the reduced responsivity found later in those with hypertension (Jennings, Muldoon, Ryan, Price, Greer, Sutton-Tyrrell et al., 2005). For present purposes, this again indicates that brain changes may occur in the absence of high blood pressure among those that have a reasonable likelihood of developing hypertension later in life.

In summary, initial evidence suggests that individuals at risk for hypertension show altered neural responses to cognitive tasks, altered neuropsychological performance, and altered brain networks in response to psychological challenge. As high blood pressure has not developed in these individuals, the possibility is raised that essential hypertension is acting directly on the brain prior to the occurrence of high peripheral blood pressure.

Pharmacological treatment of hypertension—Influence on brain indices

Another form of evidence examines the manipulation of blood pressure in hypertensive individuals. If peripheral blood pressure is inducing functional and morphological changes in the brain, then reducing blood pressure might be expected to reverse or halt the effects on the brain. A number of observations suggest, however, that reducing blood pressure does not alter the progression of brain effects—or, at least, has reasonably minimal effects on this progression.

Cognition

First, successful treatment of hypertension typically does not reverse specific cognitive deficits associated with hypertension, see reviews (Muldoon et al., 1995; Muldoon et al., 2002). Typically, the pattern of mild cognitive deficits differs in treated and untreated hypertensive individuals, both when examined cross-sectionally and longitudinally. Interpretation is clouded, however, by the inability to precisely separate deficits that may be drug-related from those related to hypertension or its remediation. In addition, a few studies report striking recovery of neuropsychological function after relatively brief treatments e.g., (Efimova et al., 2008).

Morphology

Second, although anti-hypertensive treatment has been shown to reduce the risk for white matter hyperintensities, pathological changes in the brain have been found in both treated and untreated hypertensives relative to normotensives (Kraut, Beason-Held, Elkins, & Resnick, 2008; Raz & Rodrigue, 2006; van Dijk et al., 2004). These studies as well as others, such as Nobili et al. (1993) have clearly supported the beneficial effects of treating hypertension on brain morphology, but they also suggest that morphological changes are not fully reversible with successful treatment. A specific exception to this generalization is a study of hippocampal volume in a community sample of older (mean age=80) individuals. In this study, Korf et al. (Korf et al., 2004) found that treatment of hypertension reduced the risk of hippocampal atrophy

below that of normotensive individuals. Untreated hypertensive individuals showed a greater risk of hippocampal atrophy.

We examined the issue of change in brain morphology with reduction of blood pressure in a recent treatment study(Jennings, Muldoon, Price, Christie, & Meltzer, 2008; Jennings, Muldoon, Whyte et al., 2008). Previously unmedicated hypertensive participants were treated for a year with either an ACE inhibitor (lisinopril) or a beta-blocker (atenolol). Quantitative measures of cerebral blood flow (using the same PET techniques as prior work (Jennings, Muldoon, Ryan, Price, Greer, Sutton-Tyrrell et al., 2005) neuropsychological performance and brain aging were taken during an initial assessment and after a year of antihypertensive treatment. Blood pressure was successfully decreased by approximately 18 mmHg in both treatment groups. Post-treatment groups did not differ in their rCBF responses (contrary to our initial hypothesis) (Jennings, Muldoon, Whyte et al., 2008). The reduction of blood pressure was appropriately coupled with an improvement of indices of peripheral vasodilation following an ischemic challenge. Prior work (von zur Muhlen, Kahan, Hagg, Millgard, & Lind, 2001; von zur Muhlen, Millgard, & Lind, 2000) had shown that treatment of hypertension improved the nitric oxide mediated dilation of a peripheral vessel that follows a period of occluded blood flow. This suggests that our treatment reversed, at least to some extent, the vascular sequelae of hypertension as well as reducing blood pressure during the year of treatment.

Our results showed a progressive decrease in gray matter volume despite successful treatment of peripheral blood pressure, although we did not see significant changes in white matter hyperintensities or ventricular/sulcal volumes over the year of treatment. We examined the grey matter areas that showed structural differences between hypertensive and normotensive individuals in our cross-sectional study (Gianaros et al., 2006). Prefrontal and temporal lobe grey matter volumes were observed to decline between the initial evaluation and the evaluation after one year of treatment (Mendelson et al, in preparation). Medial frontal (also differing in our cross-sectional study) did not show pre/post differences. Conclusions from our study must be tempered though by the absence of a wholly appropriate control group, i.e., current results cannot separate possible changes due to 1 year of aging from changes due specifically to essential hypertension. A sample of somewhat older (and thinner) normotensive individuals was, however, examined from the control volunteers from the Alzheimer's Disease Neuroimaging Initiative dataset (http://www.loni.ucla.edu/ADNI/, an openly available dataset originating from the Laboratory of Neuro Imaging, UCLA). MRI scans separated by one year failed to show the prefrontal or temporal lobe decreases that we observed in our treated hypertensive individuals. These results suggest that reductions in grey matter volume in prefrontal and inferior temporal areas are progressive among hypertensives independent of the status of peripheral blood pressure.

Brain aging indices also appear to progress despite treatment. We did not observe significant changes in ventricle size, sulcal size or white matter volume over one year of treatment. Other studies with a greater follow-up duration have however generally observed continued changes in white matter hyperintensities despite the successful treatment of hypertension (see review, (van Dijk et al., 2004)).

CBF and rCBF

Studies examining the effects of antihypertensive treatment onlongitudinal changes in CBF have yielde d inconsistent results. Beason-Held and colleagues (Beason-Held et al., 2007) found that decrements in rCBF among treated hypertensives were progressive. They followed treated hypertensive patients over a seven-year period, measuring relative rCBF among brain regions. Results suggested a decrease in prefrontal, anterior cingulate, and occipital regions. Interestingly, over time relative rCBF appeared to increase in motor, superior temporal, and hippocampal areas and this increase was larger in normotensive individuals than in

hypertensive individuals. Efimova (Efimova et al., 2008) report striking increases in CBF measured with SPECT after 24 weeks of antihypertensive treatment in a reasonably small sample. We (Jennings, Muldoon, Price et al., 2008) failed to see any significant change in CBF during control conditions after one year of treatment. We also examined rCBF responses during working memory performance before and after treatment; no significant change was observed. Results from an examination treating the spontaneously hypertensive rat for 12 weeks with a variety of calcium channel blockers and hydralazine may be relevant in explaining these conflicting results. Sabbatini et al. (Sabbatini, Tomassoni, & Amenta, 2001) demonstrated loss of frontal, occipital, and hippocampal nerve cells in association with progression of hypertension in the spontaneously hypertensive rat. Treatment with calcium channel blockers prevented nerve cell loss to varying degrees but calcium channel blockers were generally more effective than hydralazine, which failed to differ from control values. Importantly, hydralazine was as effective as the successful calcium channel blockers in decreasing blood pressure. Thus, some, but not all anti-hypertensives may have beneficial effects on the brain and these effects may be independent of their pressor effects. A further consideration is time course of treatment. Meyer et al. (Meyer, Rogers, & Mortel, 1985) in a Xenon study found increases in CBF after up to 24 months of treatment but a return to control values by 36 months. In short, changes in resting rCBF over time in treated hypertension are complex—varying over brain regions and in direction of change. The variation may be due to the specific treatment applied, course of the disease, or the interaction of course and patient characteristics such as age.

Brain aging indices predict success of blood pressure treatment

In other results from our treatment study, indices of brain aging and cerebral blood flow responses to information processing were predictive of antihypertensive treatment success (Jennings, Muldoon, Whyte et al., 2008). Brain aging was operationalized using a combination of ratings for white matter hyperintensities, ventricle size and sulcal size that were obtained using structural MRI. Together, structural indices of brain aging and rCBF response in the thalamus during working memory predicted 20% of the variance of the change in BP, after controlling for age, gender, medication type (lisinopril, atenolol) and initial (pretreatment) BP. Posterior parietal rCBF responses (which separated normotensive and hypertensive groups in our cross-sectional study (Jennings, Muldoon, Ryan, Price, Greer, Sutton-Tyrrell et al., 2005), however, failed to contribute to the prediction of success of hypertensive treatment. Overall, however, the results suggested that processes impacting the brains of hypertensives were indicating the severity of hypertensive disease. This would be consistent with the speculation that essential hypertension induces both brain aging and heightened peripheral blood pressure.

Altered organization of rCBF support independent of treatment

Jennings, Muldoon, Price, Christie, Meltzer (Jennings, Muldoon, Price et al., 2008) reported that the enhanced correlation among rCBF responses in different brain areas during working memory among hypertensives failed to decrease with treatment, but rather increased. Correlations among areas previously shown to be enhanced among hypertensives; prefrontal, parietal, and amygdala/hippocampus (Jennings, et al. 2005), were examined before and after one year of treatment in the study just reviewed (Jennings, Muldoon, Price et al., 2008). All correlations increased from approximately .5 prior to treatment to approximately .8 after one year of treatment. The altered organization of blood flow to active tissue that appeared characteristic of hypertension appeared to progress despite a reversal of peripheral hypertension in these participants—again suggesting that brain changes may be primary rather than secondary to heightened peripheral pressure.

Conclusion

Essential hypertension remains a complex disease with elusive causes. Research reviewed here, however, suggests that the brain is an essential component of essential hypertension. Changes in brain function, structure, and organization correlate with the presence of the disease early in its course. Reducing peripheral blood pressure typically fails to reverse the changes in brain function, structure, and organization that are associated with the disease. The latter findings suggest that influences on the brain are not secondary to peripheral blood pressure elevation.

Virtually all of the research on human hypertension that we have reviewed has been done with the assumption that the brain will exhibit changes that are secondary to the increase in peripheral blood pressure characterizing hypertension. Based on this assumption, most studies were keyed to finding deficits in overall cerebral blood flow, general failures of activation, or similar changes that would be expected based on an overall hemodynamic adjustment within the brain. Our own work made the same assumption and began as an examination of how the hemodynamic adjustment of the brain altered its ability to show the vascular recruitment that occurs during cognitive performance. Because neural influences were not thought to be primary, virtually no human work (with the possible exception of that reviewed by Gianaros and Sheu in this volume) has been done in humans to identify specific neural structures that might be directly impacted by essential hypertension. Central circuitry implicated in the control of autonomic, endocrine, and through this renal function clearly requires closer examination if the brain is to be viewed as an early target or source of essential hypertension. It remains possible though that early elevations in blood pressure alter the brain. Co-occurring metabolic disease or white matter pathology may also provide complementary explanations for apparent influences of essential hypertension, e.g. (Kraut et al., 2008; Mancia et al., 2007). An important caution is that most of our measures of brain function are based on vascular perfusion and hypertension could alter this in such a way as to confound our measurements. Overall, however, recognition of the co-occurrence of vascular and brain effects calls out for a substantial research effort. Further studies in humans with mildly elevated blood pressure and risk for hypertension may be helpful in this regard. Animal model studies, complementing imaging studies, may be more directly helpful in establishing whether essential hypertension originates primarily as a brain disease or as a disease of the peripheral vasculature. Despite the complexity of the genetics of hypertension, research on the central nervous system characteristics of those with genetic risk for hypertension would be of great value. The major implication for future research though is simply the recognition that the brain is essential to essential hypertension and should be examined concurrently with peripheral vascular measures.

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