Hypertension is a very common disorder and confers significant cardiovascular risk. Similarly panic disorder is a common condition. Panic disorder is unpleasant and disabling in its own right and may be accompanied by co-morbid disorders, most frequently agoraphobia, other anxiety disorders and major depressive disorder.

The reason for this editorial is to highlight that hypertension and panic disorder are associated and each complicates the other (Noyes et al., 1978; Katon, 1984, 1986; Bell, 1998; Weissman et al., 1990; Davies, 1999), and to explore possible neural mechanisms that could account for this association.

Why might an association between panic disorder and hypertension association exist? A simple explanation may be that patients with panic disorder appear artefactually to have higher blood pressures due to a greater ‘white coat’ (anxiety-induced hypertension) response compared with patients without panic disorder. However, in an earlier clinical study, we found no excess ‘white coat effect’ in patients with panic disorder and panic attacks making this explanation unlikely (Davies, 2003).

Secondly, the association might be due to a ‘labelling effect’ – in that a patient’s awareness of a diagnosis of hypertension may lead to vulnerability in the development of panic disorder. Indeed, in one study that examined this (Davies et al., 1999), the diagnosis of hypertension preceded panic attacks significantly more often than vice versa (P < 0.01).

Here, we suggest that an association between hypertension and panic disorder is due to some common aetiology that may affect blood pressure control and may also predispose to panic.

For many years, the majority of cases of hypertension were classified as ‘essential hypertension’, implying unknown aetiology. Recently however, there has been an acknowledgement that in many such cases, a dysfunction of the autonomic nervous system may be the underlying pathology (Mann, 2003). Evidence supporting this hypothesis includes studies demonstrating excess ‘spillover’ of catecholamines from both peripheral (Esler et al., 1988) and central (Ferrier et al., 1993) organs in patients with hypertension. In addition, heart rate variability, a proxy measure of sympathetic nervous system dysfunction is lower in hypertensives than controls. Both of these indices of autonomic function are similarly deranged in panic disorder. Wilkinson et al. (1998) reported excess adrenergic output from the heart and kidneys in panic disorder at rest and from many body organs during attacks. Heart rate variability is similarly reduced in panic disorder patients compared with controls. Note that despite their ability to diminish peripheral autonomic symptoms, beta-blockers are not effective in panic disorder, confirming that central autonomic symptoms are implicated.

Other evidence supporting autonomic dysfunction as a common aetiological factor in panic disorder and hypertension includes factor analysis of panic symptoms in a sample of 346 primary care and hospital patients, all of whom had experienced full or limited symptom panic attacks (Davies et al., 2006b). The dominant panic symptom cluster was made up entirely of autonomic symptoms – sweating, flushes, shaking and nausea. A regression analysis demonstrated that this factor, unlike all other major symptom clusters identified, was associated with hypertension.

If autonomic nervous system dysfunction, involving alterations in catecholaminergic activity, plays a role in both hypertension and panic disorder, what may drive this? One possibility is serotonin (5-HT). It is well known that serotonin-promoting antidepressants (SSRIs) are effective in the treatment of panic disorder and anxiety. Meanwhile, evidence has emerged that SSRIs may improve cardiovascular outcomes – notably of ischaemic heart disease in depressed patients (Glassman et al., 2002) and stroke victims (Rasmussen et al., 2003). In one study where hypertensives with panic disorder were studied, SSRI treatment achieved a lower 24-h ambulatory blood pressure than did treatment with a single antihypertensive drug in a cross-over design (Polyák, 2001). Finally, low
heart rate variability, a marker of autonomic dysfunction in panic disorder, is restored to normal by SSRIs (Yeragani et al., 1999).

If serotonergic systems indeed play a role in the association between hypertension and panic disorder, lowering 5-HT concentrations using the tryptophan depletion technique should alter both cardiovascular and psychological parameters relevant to these conditions. Indeed, studies showed that tryptophan depletion in patients with treated panic disorder (and social-anxiety disorder) led to significantly greater blood pressure and psychological responses to stress challenges than under non-depleted conditions, confirming the role of serotonin in buffering the blood pressure response to stress in this patient population (Davies et al., 2006a).

In the light of these studies, we sought to construct a model to illustrate possible neurochemical mechanisms and neuroanatomical pathways that may be involved in the association of panic and hypertension. Brainstem-mediated sympathetic activation may lead to hypertension, ischaemia, cardiac arrhythmias and sudden death (Grassi and Kiowski, 2002). Pathologically elevated levels of brainstem-mediated sympathetic activity could result from either excess excitatory drive, a deficit in inhibitory control, or a combination of the two. We have considered the preclinical work of Bago and Dean (2001), who demonstrated that stimulation of the midbrain ventrolateral periaqueductal gray (VLPAG) induces hypotension and sympathoinhibition that can be prevented by blockade of 5-HT1A receptors.

Thus, serotonin-dependent chemosensors to exert a negative feedback effect on R VLM activation.

Deficits in serotonergic systems underlying hypertension and behavioural and autonomic components of panic responses converge at the level of the brainstem and that these brainstem structures are under inhibitory control by serotonergic neurons in the VLPAG, which serve as an important sympathomotor control system.

Further research is indicated to explore this model in humans. Hypertensive patients, who are prone to panic disorder and other anxiety disorders, may have deficits in the inhibitory control mechanisms regulating autonomic nervous system function, deficits that may be ameliorated by enhancing serotonin function. As mentioned above, Polyák (2001) has provided preliminary data that increasing 5-HT may be useful in treating hypertension in this group, and it may also be cardioprotective in hypertensive patients with co-morbid anxiety disorders. The role of serotonin in this group should be elucidated further, using the methods of manipulation of serotonergic function and appropriate stress challenges. Building on the existing evidence from Polyák, there is scope for a larger randomized trial of serotonin-promoting drugs as adjunctive treatment in hypertensives with panic or related disorders. Additionally, there may be scope for translational research aimed at developing reproducible and reliable tests to aid identification of the subset of hypertensive patients, who may have co-morbid anxiety and autonomic dysfunction amenable to treatment with serotonin-promoting drugs.
Figure 1  Hypothetical model of neural systems underlying the association between hypertension and panic disorder. According to the model, deficiencies in inhibitory control, either local GABAergic inhibitory mechanisms within the DMH, or serotonergic inhibitory mechanisms, acting within the DPAG (5-HT1A/5-HT2 receptors) or RVLM (5-HT1A receptors), would result in vulnerability to both hypertension and panic disorder. Serotonergic neurons in both the ventrolateral part of the dorsal raphe nucleus (DRVL)/VLPAG region and the medullary RPa are directly excited by the panicogenic agent CO2 or decreases in extracellular pH. Normally, this mechanism would serve as a negative-feedback system, with increasing concentrations of CO2 or decreasing pH-activating serotonergic neuronal firing rates, preventing an over-activation of both the behavioural and autonomic symptoms of panic. If these serotonergic neurons are compromised, either by changes in their intrinsic properties or changes in the neural input regulating their activity (e.g., changes in executive function in the PFC), behavioural and autonomic responses would continue unchecked. Chronic, reduced activity of serotonergic neurons in the DRVL/VLPAG region would be expected to lead to vulnerability to both hypertension and the behavioural and autonomic symptoms of panic. Chronic, reduced activity of serotonergic neurons in the RPa region would be expected to lead to vulnerability to both hypertension and the autonomic, but not behavioural, symptoms of panic. Indeed, tryptophan depletion can exacerbate panic symptoms. In contrast, SSRIs, possibly by increasing serotonergic neurotransmission in these systems, can alleviate panic symptoms. Abbreviations: BP, blood pressure; DMH, dorsomedial hypothalamus; CO2, carbon dioxide; C1, C1-adrenergic cell group; DPAG, dorsal periaqueductal gray; PFC, prefrontal cortex; RPa, raphe pallidus; RVLM, rostral ventrolateral medulla; VLPAG, ventrolateral periaqueductal gray.

References

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