The arteriolar injury in hypertension

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A B S T R A C T

In 1937, Drs. Moritz and Oldt described arteriolar injuries in the kidneys (and other viscera) in hypertension, across the age range, in both sexes, and, in different races. This hypothesis proposes that injuries to vasomotor nerves cause the arteriolar injury in the kidney in hypertension, (as well as that in the uterus in preeclampsia). Different patterns of perivascular hyalinisation in different viscera are clues to the varying causes and consequences of arteriolar injury. In the uterus there is a symmetrical, perivascular “halo of hyalinisation” that marks the lines of extension of regenerating, injured nerves to the placental bed, whereas in the kidney there is a disordered and asymmetrical “halo of hyalinisation” where persistent, and recurrent, increases in intravascular pressures interrupt development of regenerating nerves. Consequences of injuries to vasomotor nerves include releasing a “soup” of cytokines that cause regeneration of “new” nerves expressing primitive, pain and stretch receptors including TRPV-1 and P2X3 purinergic “stretch” receptors that may be significant in the afferent mechanism in preeclampsia. There is also concurrent, “background” hyperplasia of denervated tunica media and intima leading to narrowing of the arterioles and a further drive to hypertension through renal ischaemia (Goldblatt, 1942). These observations require support from animal studies and other investigations to establish causation. This hypothesis may provide a number of potential mechanisms that reinforce, or accelerate, the physiological processes that contribute to hypertension.

Renal arteriolar injury is the histopathological hallmark of hypertension [1]. Despite extensive studies between 1937 and the 1980’s its aetiology remains unknown [2]. However some of its antecedents became clear including the alternating constrictions and localised dilations of both small and large arterioles (“the sausage string appearance”) [3]. That, in turn, resulted in transudation of different proteins into, and through, the wall of the arteriole. The properties of the injured vessel were reproducible by infusion of angiotensin II or stimulation of perivascular nerves [4,5]. These observations, suggested the injured vessel were reproducible by infusion of angiotensin II or proteins into, and through, the wall of the arteriole. The properties of appearance pertension [1]. Despite extensive studies between 1937 and the 1980’s, causes of injuries to uterine vasomotor nerves

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Original descriptions of arteriolar injury

Drs. Alan Moritz and Mary Oldt (Cleveland, OH, 1937) described arteriolar injuries in kidney, spleen, pancreas and adrenals in hypertensive patients [1]. Histology of these arterioles showed hyperplasia of the tunica intima and media with accompanying “hyaline” and “fibrinoid” changes. In addition, there was an unrecognised and irregular layer of perivascular hyalinisation, that varied along the length of the vessel, and, over time (Fig. 1, 2). Dr. Arthur Hertig (Boston, MA; 1945) described similar findings in the uterus in pre-eclampsia [2]. Again, there was an unexplained perivascular “halo of hyalinisation” in the accompanying illustrations that did not attract comment (Fig. 1, 2–5). Those “halos” of hyalinisation have been present in almost every subsequent publication though rarely attract comment or investigation (Fig. 1, 2–5). More recently, injured, uterine arterioles surrounded by concentric layers of regenerating nerves were noted in painful, gynecologic syndromes associated with persistent, physical efforts during defecation, and, prolonged second stages of labor ([16], Fig. 2aii). These layers of hyalinisation differ between the uterus (Fig. 2ai) and the kidney (Fig. 2aii). In the uterus there is a complete, symmetrical, layer around the arteriole whereas in the renal arteriole there are incomplete, and asymmetrical, layers of hyalinisation where an intervening process appears to interrupt its development. Understanding the etiology of uterine “halos” of hyalinisation and regenerating, injured nerves offers a potential explanation for the renal arteriolar injury [7].

Causes of injuries to uterine vasomotor nerves

In the uterus, injuries to vasomotor nerves result from physical efforts during defecation, evacuation of the uterus, or, difficult first
Causes of injuries to renal vasomotor nerves

In the kidney (spleen, pancreas and adrenal) there are injured perivascular nerves around narrowed arterioles within the hilar anatomy (Fig. 2b–e, i–ii). Their “halo” has indistinct layers of hyaline cells that result, initially, from injuries to perivascular nerves complicated by recurrent, mechanical injury from pre-renal, or, renal sources of hypertension (Fig. 2bi). This hypothesis proposes that intermittently-raised intravascular pressures overdistend hilar and pre-hilar branches of the renal arteries, injuring accompanying vasomotor nerves. Injured vasomotor nerves release cytokines with perivascular and intramural regrowth of injured nerves that leads to proliferation of the tunica media and intima, and, development of irregular and indistinct, layers of perivascular hyalinisation. That process is complicated by recurring over-distension of the vessel, and, degeneration of the inner layers of the denervated arteriole caused by persistent, or recurrent hypertension (Fig. 2ei–iii). There may be other sources of injury to renal nerves e.g. persistent physical efforts during defecation that cause widespread injuries in the female lower genital tract [6].

Histological appearances of perivascular hyalinisation in the kidney are different from those in the uterus owing to the different mechanisms of injury (Fig. 2a–bi). In both viscera, the first phase of the arteriolar lesion results from release of neural cytokines by injured vasomotor nerves, leading to medial and intimal hyperplasia of denervated arterioles. Continuing hypertension, bearing on denervated arterioles, causes progressive hyaline and fibrinoid “degenerations”. Progressive narrowing of renal arterioles leads to renal ischemia and activation of the renin-angiotensin system in “classical” Goldblatt hypertension [9]. However the second phase of the arteriolar lesion is the “disappearance”, or “non-appearance”, of injured nerves from the histologic field in the visceral stroma. In the uterus this results from hyperplasia and hypertrophy of myometrial smooth muscle during pregnancy; in the kidney it results from recurrent injury associated with mechanical distension of pre-hilar and hilar vessels associated with persistent, hypertension, that is more pronounced in the proximal branches of the visceral arterial tree. The key question posed by Moritz and Oldt was “do the histological changes in the arteriole cause, or result from, hypertension”? [1] On this evidence, the renal appearances may be “both” cause and consequence.

Consequences of injuries to vasomotor nerves

Recognising neurological injuries to the cardiovascular system in both preeclampsia and hypertension with secondary mechanisms that reinforce the spiral of hypertension, carries clinical implications for both pregnant and non-pregnant, hypertensive patients ([10], Fig. 2a–bi). In pregnancy there is clear evidence for early onset of persistent hypertension in women following preeclampsia in their first pregnancy [11]. The mechanisms are unclear but may include some of...
those set out in this hypothesis. Obstetricians are largely unaware of the potential, permanent injuries to the maternal circulation resulting from preeclampsia that leaves the woman’s arterioles in a vulnerable situation that may express themselves as persistent and prolonged hypertension in the early postpartum years, or, lead to recurrent hypertension in some women. More aggressive management of maternal blood pressure during pregnancy may be necessary to avoid this serious, ensuing morbidity. Rapidly progressive (“fulminating”) preeclampsia may also result from some of these processes. Interrupting them with anti-hypertensive or anti-P2X3 agents may be helpful.

If there is a permanent injury to visceral vasomotor nerves in hypertension then there a number of consequences for the management of the condition. Lifelong medication is likely to be necessary. Preventing sustained hypertension or blood pressure “spikes” by avoiding exposure to known irritants of “primitive” regenerating, nerves e.g. caffeine, alcohol, nicotine, etc. will be important in preventing further neurological injury. Reducing the effects of risk factors for hypertension e.g. obesity, persistent hyperglycemia, smoking, preeclampsia, etc., may assist in preventing hypertension. Self-monitoring of blood pressure to detect, and prevent, exacerbations of blood pressure, and, define tailored, anti-hypertensive drugs and behaviours for an individual patient, is likely to be helpful. Developing anti-P2X3 agents may be useful, with, or without, established anti-hypertensive drugs.

**Conclusion**

It has been 80 years since Moritz & Oldt’s original description of the arteriolar injury in hypertension. Injuries to vasomotor nerves explain some of the original observations from 1945 to 1980 when this question was under active consideration. Finding aberrant nerves in the injured
arteriolar wall, aberrant reinnervation and novel P2X3 “stretch” receptors in perivascular and endothelial tissues may provide plausible mechanisms for some forms of hypertension and their response to treatment e.g. renal endovascular ablation in “resistant” hypertension. These observations do not amount to “causation” since we have not proven the mechanism of injury to the visceral arterioles in hypertension though there may be animal models that support this hypothesis. Neither do these observations establish which aspects of the arteriolar injuries are critical to the development of hypertension, nor, their natural history. Nevertheless they do provide new, potential mechanisms that may contribute to hypertension and some, potential avenues to improved understanding.

Injury to vasomotor nerves leading to a cascade of pathophysiologic consequences, is only one of the diverse and varying consequences of autonomic denervation [12]. Maintaining the integrity of autonomic nerves will prevent many clinical conditions, including some forms of hypertension [12].

Conflicts of interest

The author confirms no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.mehy.2017.12.025.

References