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COMMENTARY

'Memory' and 'legacy' in hypertension and lifestyle-related diseases

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Hypertension and other lifestyle-related diseases are caused by the complex interaction of extrinsic (environmental) and intrinsic (genetic) factors. Previously, it was thought that the effects of extrinsic factors were transient and reversible. For example, if an antihypertensive medication or an antidiabetic medication was taken by a patient, its effects would continue during the treatment period, but if the medication was stopped, the beneficial effects would disappear. Similarly, if a patient started a high-salt diet, the effects on blood pressure would be reversed when the patient switched to a low-salt diet.

Recent studies have challenged this view that the effects of extrinsic (environmental) factors are transient, and suggested that several environmental changes may be 'remembered' by the body (the 'memory' phenomenon[1]), or leave a long-lasting effect after the initial stimulus has disappeared (the 'legacy' phenomenon[2]).

In the case of hypertension, previous studies by the groups of Harrap *et al.* and Berecek *et al.* showed that transient treatment of spontaneously hypertensive rats (SHR) during an early (prehypertensive) stage resulted in sustained suppression of hypertension. We reported similar results using an angiotensin receptor blocker (ARB) in several animal models, including the stroke-prone SHR, the Dahl salt-sensitive rat and the L-NAME-hypertensive nephropathy models, and found that the 'memory' of transient RAS blockade continued throughout the life of the animal.[3] In humans, Julius *et al.*[4] reported that transient treatment of subjects with high–normal blood pressure for 2 years with an ARB (candesartan) resulted in a reduced incidence of hypertension, which was maintained 2 years after discontinuation of the ARB treatment. Collectively, these results suggest that the effects of RAS inhibition may be 'memorised' even after the drug is discontinued.

In diabetes, it is known that the effects of good blood glucose control affect long-term cardiovascular outcomes several years after the conclusion of the trial. In the Diabetes Control and Complications Trial, patients with type 1 diabetes were randomized to either intensive glycemic control or conventional control, and these patients were followed up in the Epidemiology of Diabetes Interventions and Complications study.[1] Although the HbA1c levels in the two groups had converged, the group that originally received intensive therapy had a lower incidence of cardiovascular disease. The authors proposed the concept of 'metabolic memory' to explain these findings. Similarly, a follow-up study of patients enrolled in the UKPDS study demonstrated not only a persistent reduction in the incidence of microvascular complications, but also a lower incidence of myocardial infarction, and death from any cause in the intensive treatment group,[2] a phenomenon referred to as the 'legacy' effect. In the case of tight blood pressure control, a significant risk reduction was seen for peripheral vascular disease, but not for myocardial infarction or mortality.[5]

In the interesting study by Togashi *et al.*[6] this issue of *Hypertension Research*, the authors examined the effects of Ang II infusion for 4 weeks, and assessed 'legacy' effects after discontinuation of the infusion on blood pressure, insulin sensitivity, and parameters of skeletal muscle inflammation and oxidative stress. The authors showed that 4 weeks after discontinuation of Ang II infusion, blood pressure and insulin sensitivity remained increased. Moreover, MCP-1, TNF-alpha, TBARS, and total and activated Rac-1 were increased in the skeletal muscle. These effects were attenuated by coadministration of tempol. The authors suggested the hypothesis that the 'legacy' of transient Ang II infusion in youth could be explained by upregulation of inflammatory cytokines and increased oxidative stress in the skeletal muscle, which maintained the insulin resistance and hypertension.

It is possible to speculate about the potential link between oxidative stress and the memory/legacy effect seen in this study. Changes in oxidative stress have been shown to cause multiple downstream biochemical changes via covalent modification of proteins and nucleic acids. One potential mechanism is altered glycation and cross-linking of extracellular matrix proteins, resulting in enhanced remodeling and fibrosis. Another potential target is mitochondrial DNA, which exists in an open formation, making it particularly vulnerable to damage from oxidative stress.

In the report by Togashi *et al.*, the authors did not focus on the structural changes in the kidney and vasculature. Previous studies have shown that an important mechanism for the decreased blood pressure after transient RAS blockade may be suppression or reversal of the enhanced media/lumen ratios of the renal small arteries and arterioles, which is found in hypertensive animals before and during the onset of hypertension. As the arteriolar structural changes persist after the treatment is discontinued, they could contribute to the memory effect in hypertension. Other investigators have suggested that microvascular changes could also have an important role in the development of metabolic memory in diabetes.[7] It would be interesting to examine the skeletal muscle microvasculature in future studies.

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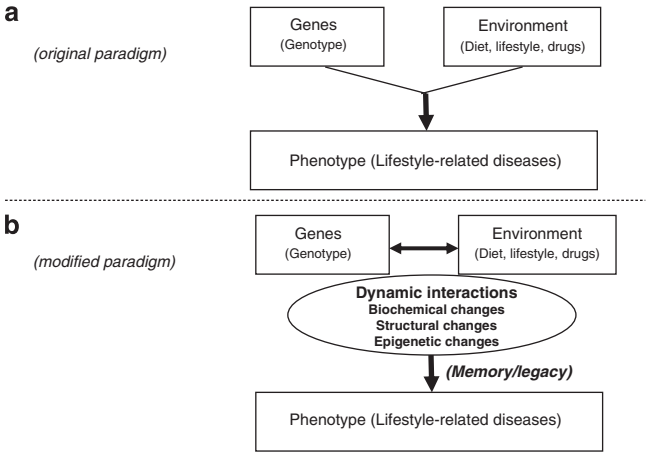

Figure 1 Original and modified paradigms for the interaction between genes and the environment in lifestyle-related diseases. (**a**) Original paradigm: independent role of genes and environment in producing the disease phenotype. (**b**) Modified paradigm: addition of dynamic interactions between genes and environment, resulting in the new concept of memory/legacy.

Another important area for further research is the potential role of DNA methylation and histone modifications in the mechanism of the memory/legacy effect.[8] For example, an important recent study has shown that beta(2)-adrenergic stimulation causes inhibition of histone deacetylase-8 activity and suppression of WNK4, a regulator of sodium reabsorption.[9] Another study has suggested that statins may also cause epigenetic modification of multiple genes.[10] Taken together, these results suggest that multiple dynamic interactions between the genes and the environment, including biochemical, structural and epigenetic changes, may be involved in the mechanisms of the memory/legacy effect (Figure 1).

In conclusion, the study by Togashi *et al.* has highlighted an important potential role of skeletal muscle inflammation and oxidative stress in the memory/legacy effect of angiotensin infusion. The molecular mechanism of the interaction between genes and the environment is a new and complex field, which requires further study.

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