How can stress affect atherosclerosis?
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It is well known that acute stressful events affect the cardiovascular system and may cause cardiovascular disease. In acute stress, there is an immediate activation of neurohormonal systems in the body, resulting in increased heart rate and blood pressure and affecting excitability of the cardiac muscle, metabolism, clotting of blood and activity of the immune systems. All these factors can trigger acute cardiovascular events, especially in predisposed individuals.

It is also becoming increasingly clear that long-term exposure to stress accelerates development of both metabolic disturbances and cardiovascular disease. In chronic stress, long-term activation of neurohormonal stress systems may accelerate development of atherosclerosis both directly and via its long-term effects on blood pressure, metabolism, body composition and immune function.

In the recent large INTERHEART case-control study, psychosocial stress was shown to account for 33% of the population risk for myocardial infarction. Despite this threat to public health, not much is known about the mechanisms linking psychosocial health and cardiovascular disease.

Our research group focuses on identifying mechanisms by which exposure to a stressful lifestyle affects atherosclerosis and thereby cardiovascular disease. We hypothesise that repeated and/or exaggerated episodes of activation of stress-related neurohormonal systems promote atherosclerosis and thereby cardiovascular disease. In future work, we will address the hypothesis that a stress-induced inflammatory response is an important part of this reaction and that it acts to accelerate atherosclerotic disease.

Stress hormones accelerate atherosclerosis

During the past two years, we have studied the effects of individual stress-related neurohormones on atherosclerosis in atherosclerosis-prone mice (ApoE−/−). The stress hormone angiotensin II is released following activation of the sympathetic nervous system. We and others have shown that exogenous infusion of angiotensin II accelerates atherosclerosis and creates a more vulnerable plaque phenotype (1). We have developed a disease model in which we activate the endogenous angiotensin II system by placing a small silver clip on the mouse aorta. This physiological increase in angiotensin II also accelerates atherosclerosis but most likely via its effect on blood pressure (1). Angiotensin II acts on two
different receptors: the traditional type 1 receptor and the more enigmatic and less well-studied type 2 receptor. We have shown that the type 2 receptor is heavily expressed in the atherosclerotic plaques of both mice and humans (1, 2). However, we have not been able to identify a functional role for this receptor in the development of atherosclerosis. The basal activity of a number of stress hormones are affected by salt intake. Although we clearly show that a high salt intake in itself does not affect atherosclerosis, the combination of a high salt intake and increased angiotensin II markedly accelerates atherosclerosis.

Insulin, the hormone that regulates blood glucose levels, is thought to stimulate sympathetic nervous system activity and might thus facilitate sympathetically mediated stress-induced events. We studied the effects of insulin on stress reactions in rats but found no evidence that increased insulin levels stimulate sympathetic nervous system activity at rest or during stress exposure (3). However, we showed that insulin appears to interact with the angiotensin II system. Simultaneous treatment with an angiotensin II receptor antagonist and infusion of insulin dramatically reduces blood pressure, indicating that the angiotensin II antagonist unmasks a major blood pressure lowering effect of insulin (3). Furthermore, preliminary data show that the combination of insulin and angiotensin II appears to accelerate atherosclerosis.

**Exposing mice to stressful stimuli**

We have also directly exposed ApoE\(^{-/-}\) mice to different stressful situations. Surprisingly, repeated and prolonged exposure to physical and psychosocial stressful events did not accelerate atherosclerosis despite chronically increased cortisol levels. Mice exposed to stress combined with high salt were also resistant to atherosclerosis, in contrast to our findings with angiotensin II and high salt. However, atherosclerosis is accelerated when we induce chronic stress by housing mice in social isolation (4). This is an important finding as it is becoming increasingly clear that social isolation and lack of social support are among the most important stressors for humans. Therefore, our animal model may be suitable for important mechanistic studies in the future.

**Conclusion**

In summary we have studied the importance of individual stress hormones on the development of atherosclerosis. We have also shown that stress-induced disease in rodents follows similar patterns to those seen in humans. We aim to clarify mechanisms involved in the interaction between psychosocial load and cardiovascular disease. Increasing knowledge
within this area can help us understand the links between our minds, social environment and cardiovascular disease, and lead to the development of new coping strategies and/or new drugs to combat this disease.

References


