The heart, the brain, and the Kounis syndrome

In the elegant editorial concerning the recent paper published in EHJ, the authors have asked why the two seemingly unrelated conditions, namely depression and left ventricular depression, should be related and what mediators or common pathways could link the two. They have concluded that as far as the brain and the heart are concerned 'the twain have met'. Although, they have done so, they did not elaborate enough in the mechanisms connecting the two conditions.

Depression and the heart seem to be the two main elements of a magnificent biological pathway. Major depression has often been regarded as a prototype of repeated, chronic, or exaggerated stress, the depressogenic stress, which is not responsive to counter-regulatory forces. Depressogenic stress commences with impulses arising from high cortical centres of the brain that are relayed through the limbic system to hypothalamus. Chemical mediators, such as norepinephrine, serotonin, and acetylcholine, are released and activate cells of the paraventricular nucleus of the hypothalamus to produce corticotropin-releasing hormone (CRH), the main coordinator of the depressogenic response. CRH enters the portal venous system of the hypothalamus and activates the corticotrophs of the anterior pituitary gland to produce proopiomelanocortin, which is cleaved to form adrenocorticotropic hormone (ACTH). It also stimulates the lobe coeruleus, a dense collection of autonomic cells in the brainstem, to secrete norepinephrine at the sympathetic nerve endings. Activation of the sympathetic system centrally is also transmitted to the adrenal medulla to produce large amounts of epinephrine. ACTH stimulates the adrenal cortex to produce corticosteroids. Depressogenic stress also induces the release of glucagon, growth hormone, and homocysteine. The renin-angiotensin system also participates in the depressogenic stress through the sympathetic innervation of the kidney. All this cascade induces a heightened cardiovascular activity, endothelial injury, myocardial damage, induction of adhesion molecules on the endothelial cells to which recruited inflammatory cells adhere and translocate to the arterial wall.

An acute phase response, similar to that associated with inflammation, is also engendered, and is characterized by macrophage activation, production of cytokines such as IL-1, IL-6, TNF-α, acute phase proteins, and mast cell activation.

In contrast, the same cytokines such as IL-1, IL-6, TNF-α are released in congestive cardiac failure and play a mediating role in the genesis of depression.

Kounis syndrome is the concurrence of acute coronary syndromes with conditions associated with mast degranulation and is caused via inflammatory mediators released through the mast cell activation. Increasing evidence suggests that emotional or other stress may contribute to myocardial ischaemia and sudden cardiac arrest.

Mast cell degranulation was induced by immobilization stress in rat cardiac mast cells. This effect was inhibited by pre-treatment with the mast cell stabilizer sodium cromoglycate and was also blocked locally by pre-incubation with antiserum against CRH and was partially inhibited by a CRH type-1 receptor selective antagonist. It has been found that the neuuropeptide neuropeptins is present in the heart and triggers mast cell degranulation. These findings suggest that acute stress could result in local CRH and neuropeptins release, which could contribute to myocardial pathophysiology through direct or indirect cardiac mast cell degranulation.

It has been suggested that Kounis syndrome might be a nature’s own experiment, because mast cell membrane stabilization could abrogate late cardiovascular events. This has already been achieved experimentally.

References

2. van Melle JP, de Jonge P, Ormel J, Crijns HJGM, Patras Highest Institute of Education and Technology 7 Aratou Street Queen Olga’s Square Patras 26221 Greece E-mail address: ngkounis@otenet.gr

Nicholas G. Kounis
Medical Sciences, School of Health Patras Highest Institute of Education and Technology 7 Aratou Street Queen Olga’s Square Patras 26221 Greece

George N. Kounis
Patras Highest Institute of Education and Technology Patras Greece

Sophia N. Kounis
Patras Highest Institute of Education and Technology Patras Greece

George D. Soufras
Department of Cardiology Patras State General Hospital Patras Greece

Letters to the Editor 7 February 2006

The heart, the brain, and the Kounis syndrome: reply

Kounis et al. are correct that in our editorial, we noted with respect to the brain and the heart, 'the twain have met,' but we did not elaborate very much on the mechanisms connecting the two. This was deliberate. There are many more potential mechanisms that might connect the brain and the heart than could reasonably fit in an editorial. Kounis et al. describe some of these in their letter. While their discussion is superb, it is really only scratching the surface. For example, platelet activation is not mentioned at all, and the behavioural link between depression and cardiovascular disease (i.e. one mediated by an increased prevalence of cigarette smoking among depressed individuals or by the poor adherence to medications and risk-reducing behaviours, which is common in patients with depression) is not even noted. It must also be pointed out that even after these are mentioned, we still have only focused on...