The sigma-1 receptor: a molecular chaperone for the heart and the soul?

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This editorial refers to ‘Decreased brain sigma-1 receptor contributes to the relationship between heart failure and depression’ by K. Ito et al., pp. 33–40, this issue.

Heart failure patients suffer much more often from clinically relevant depression than the general population. The prevalence of depression among heart failure patients steeply increases with the severity of heart failure, reaching a rate of >40% in patients with New York Heart Association functional class IV, and the risk of death and secondary events is more than two-fold higher in heart failure patients with depression than in non-depressed patients.1 However, while these epidemiological data clearly suggest a significant role of depression in the clinical course of heart failure, the biological mechanisms contributing to this association are still incompletely understood. Ito et al.2 provide experimental evidence that sigma-1 receptors expressed in the central nervous system may play a crucial role in the link between heart failure and depression.

The sigma-1 receptor is widely expressed in many tissues, including the brain, lung, liver, adrenal glands, and the heart. It was originally postulated as an opioid receptor to explain the drug-induced psychotom effects of N-allylnormetazocine (SKF-10047) in dogs,3 but subsequent studies disproved this concept by demonstrating that the sigma-1 receptor fails to bind the specific opioid receptor antagonist naltrexone. At the cellular level, the sigma-1 receptor localizes to the membrane of the endoplasmic reticulum (ER) at the interface to the mitochondria. There it forms a Ca\(^{2+}\) -sensitive und ligand-operated chaperone complex with binding immunoglobulin protein.4 ER stress causes disintegration of this complex, allowing the sigma-1 receptor to bind to inositol 1,4,5-trisphosphate receptors, thereby enhancing Ca\(^{2+}\) signalling from the ER to the mitochondrial.5 Accordingly, a major function of the sigma-1 receptor appears to be to safeguard mitochondrial Ca\(^{2+}\) levels required for normal energy production under conditions of cellular stress.

A broad range of synthetic compounds have been identified that can bind to the sigma-1 receptor and exert agonist or antagonist actions. In preclinical studies, several of these compounds exhibited antidepressant effects in animal models of depression,6 including the tail suspension test used by Ito et al.2 In rodent Alzheimer’s disease-related depression models, sigma-1 receptor agonists were even more effective than tricyclic antidepressants.5 Supporting a role of reduced sigma-1 receptor activation in the pathogenesis of depression, two recent studies reported that sigma-1 receptor knock-out mice exhibit increased immobility in the forced swimming test, indicating a depression-like phenotype.6,7 Ito et al.2 now show that mice with impaired cardiac function induced by aortic banding and high salt intake5 also exhibit reduced expression levels of sigma-1 receptor protein in the brain and depression-like behaviour. All pathophysiological alterations were reversed completely or at least in part by a 4-week intracerebroventricular infusion of the sigma-1 receptor agonist PRE084. Since heart failure and depression are both associated with sympathetic overactivity, the authors also determined urinary catecholamine excretion and calculated power spectra from blood pressure and pulse interval recordings as measures of sympathetic activity. Chronic infusion of PRE084 significantly reduced sympathetic activation after aortic banding. Conversely, intracerebroventricular infusion of the specific sigma-1 receptor antagonist BD1063 enhanced sympathetic activity and slightly impaired cardiac function in sham-operated mice. These observations suggest a key role of an impaired activation of brain sigma-1 receptors in the pathogenesis of sympathetic overactivity associated with heart disease.

An important aspect of this study is the fact that stimulation of sigma-1 receptors selectively in the brain was sufficient to rescue cardiac function. The sigma-1 protein is expressed in the left and right ventricle at even eight- to 10-fold higher levels than in the cerebral cortex, striatum, or hippocampus, and direct exposure of isolated cardiac myocytes to sigma-1 receptor agonists inhibits K\(^{+}\) and Na\(^{+}\) channels and alters contractility.6 In mice, aortic banding caused a time-dependent decrease in sigma-1 protein expression in the left ventricle to <30% of its control value, which was associated with the development of left ventricular hypertrophy and a decreased fractional shortening.10 All of these changes were reversed by systemic treatment with fluvoxamine, a selective serotonin reuptake inhibitor and potent sigma-1 receptor agonist. Notably, fluvoxamine also prevented angiotensin II-induced cardiomyocyte hypertrophy in vitro by up-regulation of eNOS and AKT signalling.10 On the contrary, the present results rather indicate that most of the anti hypertrophic effects of fluvoxamine in vivo are mediated secondary to activation...
of sigma-1 receptors in the brain. Further studies to clarify this issue would be certainly of great interest.

The finding in the present study that blocking brain sigma-1 receptors increased sympathetic activity and caused an impairment, albeit modest, of cardiac function in sham-operated mice raises an interesting question concerning the endogenous ligand(s) which maintain an appropriate physiological activation. Steroids are well known for their property to bind to sigma-1 receptors to induce either inhibition or activation.\(^{11}\) Dehydroepiandrosterone (DHEA) and its sulfate ester DHEAS, which are potent sigma-1 receptor agonists, appear to be of particular importance within the context of cardiovascular disease. DHEAS plasma concentrations gradually decrease with age and are inversely related to death from cardiovascular disease in men over age 50.\(^{12}\) Consistent with a possible role of DHEAS as an endogenous ligand of sigma-1, Ito et al.\(^{2}\) observed a significant reduction in DHEAS concentration in brain circumventricular and hypothalamic tissue after aortic banding. However, other ligands may be more important. For example, a recent study demonstrated that \(\text{N,N-dimethyltryptamine}, \) a hallucinogenic trace amine produced in the mammalian brain and lung, is an endogenous sigma-1 receptor agonist.\(^{13}\) The identification of the endogenous ligand responsible for the influence of brain sigma-1 receptors on cardiac function and sympathetic activity would be an important step forward to better understand the pathogenesis of heart failure.

Finally, the present results may encourage clinical research to re-evaluate the potential benefit of sigma-1 receptors for the treatment of depression in heart failure. A secondary analysis of the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial showed that antidepressant treatment with the selective serotonin reuptake inhibitor sertraline, which also has sigma-1 receptor agonist activity in the nanomolar range, was associated with >40% reduction in the relative adjusted risk of death and reinfarction.\(^{14}\)

On the other hand, in a prospective cohort study in 136,293 community-dwelling post-menopausal women, the use of various selective serotonin reuptake inhibitors was associated with an increased risk of all-cause mortality and stroke, in particular incident haemorrhagic stroke.\(^{15}\) A prospective clinical trial comparing selective serotonin reuptake inhibitors with low or high sigma-1 agonist activity would be most interesting to shed more light on the clinical relevance of sigma-1 receptor activation in patients with broken hearts.

**Conflict of interest:** none declared.

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