Sex, hormones and the cardiovascular system

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The meeting 'Sex Differences in Cardiovascular Health and Disease' was held in Madison, WI USA, on 24 July 2002.

Against the backdrop of the terminated Women's Health Initiative (WHI) trial to evaluate the benefits of estrogen plus progestin replacement therapy [1], 'Sex Differences in Cardiovascular Health and Disease' – a scientific advisory meeting organized by the Society for Women's Health Research – got underway. One of the meeting's goals was to address the molecular basis underlying hormonal effects on the cardiovascular system.

Ligands, receptors, genomes and physiology – an integrated approach

Virginia Miller (Mayo Clinic, Rochester, MN, USA) emphasized the need for an integrated approach to studying effects of sex hormones on physiology. This point was brought home only too well by the results of the WHI, which showed that a combination of estrogen and medroxyprogesterone, whilst decreasing the risk of colorectal cancer, increases the risk of breast cancer and thrombotic events. Miller stressed the need to understand fully the complex interactions between ligands, receptors and genomes before hormones or their analogs are used as potential therapeutics.

Crucial to this understanding is the fact that hormone receptors are distributed heterogeneously throughout the body. Endogenous estrogens, synthetic receptor modulators (e.g. raloxifene), and naturally occurring phytoestrogens obtained through the diet, for example, have varying effects on target cells and tissues. These variations might reflect differential expression of receptor isomers and/or different ligand-receptor affinities. In addition, single- and multi-nucleotide polymorphisms within the population add an extra level of complexity, and could explain, for example, why estrogen elevates plasma endothelin-1 in some recipients, but decreases it in others. 'It would be interesting,' said Miller, 'to go to the WHI and [ask] which women developed different types of cancer or cardiovascular events and what were the polymorphisms in their estrogen receptors.'

Elucidating the molecular mechanisms of hormonal action is essential to the integrated approach. Traditionally steroid effects have been viewed as genomic (i.e. mediated through transcriptional activation), but more recently evidence has grown in support of non-genomic actions.

Molecular effects on cardiovascular smooth muscle

In addition to the actions of estrogen on the endothelium, it has been known for some time that estrogen can relax denuded coronary arteries [2]. Richard White (Medical College of Georgia, Augusta, GA, USA) reported that 17β-estradiol, but not the biologically inert 17α-isofrom, relaxes the smooth muscle from porcine coronary arteries, confirming that this action is not caused by some non-specific steroidal action, as had been previously suggested. So, what is the molecular basis for this action?

To answer this question, White tested if estrogen activates K+ channels, because increasing K+ efflux is one of the most efficient means of hyperpolarizing (and therefore relaxing) smooth muscle cells. Patch clamp recordings show that 17 β-estradiol, even at concentrations as low as 1 nM, elicits a current through the cell membrane that can be inhibited by the K+ channel blocker, IBTX. The electrophysiological properties of this estrogen-activated channel were found to be consistent with only one known K+ channel – the Ca2+-activated large conductance channel, or big conductance channel (BKCa). Similar recordings made...
The effects of estrogen on the BK\textsubscript{Ca} channel, estrogen stimulates in smooth muscle. 

In the early 1990s it was discovered that women are almost twice as susceptible to drug-induced TdP than are men [3]. Two key observations indicate that the interaction between steroid hormones and cardiac ion channels could explain the sex difference in TdP susceptibility. First, it was noted that patients with long QT intervals – representing the duration of ventricular depolarization and repolarization on an ECG – are more susceptible to TdP and that these ‘long QT syndrome patients’ harbor genetic polymorphisms that compromise ion-channel function [4]. Second, it was shown that prepubertal boys and girls have statistically identical QT intervals, but as boys mature, their QT gets relatively shorter [5]. This is significant because a long QT interval can increase the chances that a second ventricular action potential is initiated before the previous one has finished, potentially leading to TdP arrhythmias.

To investigate this phenomenon experimentally, Steven Ebert (Georgetown University Medical Center, Washington, DC, USA) and his colleagues examined the QT intervals of isolated, perfused rabbit hearts that were electrically paced [6]. Female rabbit hearts were found to have longer QT intervals than did males, a difference that increases as the pace of the heart is slowed. Ovariectomy had little effect on QT intervals than did males, a difference that increases as the pace of the heart is slowed. Ovariectomy had little effect on QT intervals, whereas androgen treatment lengthened QT intervals, equaling the female one. This latter effect can be reversed by androgens might be beneficial, at least for males, is born out by future directions.

Molecular bases for sex differences in ventricular arrhythmias

Torsades de Pointes (TdP), literally a twisting of the points, is a potentially lethal heart condition described after its characteristic electrocardiogram – the ECG peaks are compressed together and twisted about the baseline. TdP can easily degenerate into ventricular fibrillation, leading to sudden death. Although it occurs naturally in a small number of individuals, more often than not, it is induced by drugs. For this reason TdP can be a major impediment to the development of new medicines of all types.

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Key conference outcomes

- Steroids act through both genomic and nongenomic pathways.
- The effects of estrogens on the vasculature is not confined to the endothelium or to activation of nitric oxide.
- Steroids can affect ion current densities, which could explain female–male differences in susceptibility to cardiac arrhythmias.

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References