Are Sildenafil Derivatives Useful Even in Unborn Males?

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As noted by Romo et al, the past decade has witnessed an increased incidence, in the general population, of intrauterine growth retardation (IUGR), currently averaged at 5.13% of all newborns. An elegant survey by Hutter et al subsequently highlighted the major causes of intrauterine hypoxia often associated with IUGR. Those authors additionally argued in favor of an important role for intrauterine hypoxia-induced alteration of gene expression in the increased incidence of risk factors in premature cardiovascular diseases at later life stages.

In the present study, Bourque et al provide experimental evidence toward a role for the precursor of endothelin-1 (ET-1), big-ET-1, as a new stressor in aged male rats that experienced prenatal hypoxia-induced IUGR. Interestingly, the authors demonstrated a vascular hyper-responsiveness to big-ET-1 and a 2-fold reduction in nitric oxide (NO)–dependent physiological antagonism of the precursor’s contractile properties in vessels derived from aged male but not female rats. Furthermore, an orally available mixed ET$_A$/ET$_B$ antagonist, tezosentan, attenuated the hypertensive state of aged IUGR male rats.

Additional questions are prompted on analysis of this study: (1) what are the triggering events involved in the sex-specific hyperreactivity to big-ET-1 in vessels derived from aged IUGR male rats? (2) are there enzymatic pathways involved in the sex-specific hyper-responsiveness to big-ET-1 in vivo? (3) what is the main cellular source for big-ET-1 in the investigated model? (4) is the increased sensitivity to big-ET-1 a direct result of fetomaternal impairment of NO production? and finally, (5) why are the vasoconstrictor responses to big-ET-1 less physiologically repressed by endogenous NO than those afforded by ET-1 in vessels of aging IUGR male rats?

From the pharmacological point of view, the latter question perhaps deserves the most attention. Current wisdom suggests that big-ET-1 must be converted to ET-1, which subsequently activates endothelial and vascular smooth muscle cell ET$_A$, as well as vascular ET$_B$ receptors. Thus, in conditions in which endogenous NO production is altered, such as in IUGR male rats, one would expect similarly enhanced vascular responsiveness to ET-1 and big-ET-1; this is not the case in the current article by Bourque et al. To further clarify this aspect, performing the same type of experiments in endothelium-denuded arteries (with or without L-$N^\text{G}$-nitroarginine methyl ester [L-NAME]) may be warranted.

From the pathophysiological point of view, however, Bourque et al teach that impairment of fetomaternal normoxic conditions is associated, in the long-term, with cardiovascular disorders in a sex-specific fashion, at least in the rat model. Albeit the mechanisms involved in this sex-specific vascular hypersensitivity remain unknown, Bourque et al put forward the attractive hypothesis of a sex hormone–dependent modulation of ET-1 release from Weibel-Palade vesicles in endothelial cells.

The maternal administration of ET antagonists during pregnancy, even in conditions of uterine hypoxia, is clearly contraindicated because of the well-documented teratogenicity of these molecules, thus limiting their use perhaps at the first clinical signs of hypertension in adult male patients. NO, in contrast, in conjunction with other vasodilator factors is responsible for the maintenance of optimal uterine blood flow. Prenatal and perinatal administration of NO donors may, therefore, constitute a more viable alternative if the results shown in the study by Bourque et al in the rat model can be ultimately translated to the human condition. This particular paradigm may of course

Figure. Putative effects of sildenafil in male intrauterine growth retardation (IUGR) fetal resistance arteries. Sildenafil, an inhibitor of PDE5 (cGMP-dependent phosphodiesterase type 5), causes an increase in cGMP in fetal vascular smooth muscle cells (VSMC) and hence favors vasodilation. In addition, it is suggested that sildenafil increases nitric oxide (NO) in endothelial cells (EC), as recently shown in human umbilical vein ECs by Mammi et al by potentiating insulin-dependent activation of phosphatidylinositol-3 (PI3)-kinase and subsequently endothelial NO synthase (eNOS), as well as by inhibiting EC-located PDE-5. EC-derived NO can also inhibit the synthesis of big-ET-1 (big-endothelin-1), and potentially its conversion to ET-1, in ECs. ET$_A$, indicates endothelin A receptor; ET$_B$, endothelin B receptor; and GC, guanylyl cyclase.

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be extended to the use of phosphodiesterase inhibitors, such as sildenafil during pregnancy, to reduce IUGR-triggered hypertension in the aging male population (Figure). It is indeed of interest that sildenafil citrate has recently been reported to alleviate complications associated with early-onset IUGR in female patients and reduced fetal growth retardation. Considering also that sildenafil has been recommended for combined administration with Actelion’s mixed ET antagonist Tracleer (bosentan), in primary pulmonary hypertensive patients, the same biphasic pharmacotherapy may be indicated eventually for hypertensive male patients subjected to prenatal IUGR.

Conclusions
The present study by Bourque et al provides a new paradigm related to the opposing roles of big-ET-1 and NO in postnatal hypertension triggered by IUGR in aging male but not female offsprings. If the mechanistic bases presented in this study are eventually reproducible in human subjects, the clinical usefulness of sildenafil in the future may not be limited anymore to the fully grown male population.

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Disclosures
None.

References