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Editorial

At the Core of Preeclampsia Genetics: Key Insights into the Neurohormonal Contribution to Hypertensive Diseases of Pregnancy and Their Complications

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See article by Baird et al., pages 68–76 of this issue.

The regulation of blood pressure and cardiac hypertrophy is detailed and complex, with multiple key neurohormonal regulators. Corin is a transmembrane serine peptidase that is expressed mainly in muscle tissues (especially heart muscle). Its function in regulating blood pressure was initially demonstrated in 2000.[1] In 2005, deletion of the corin gene in mice was shown to trigger hypertension.[2] The mode of action of corin is well established and is based on the post-translational conversion of the pro-atrial natriuretic peptide (ANP, encoded by the gene *NPPA*) into mature ANP, a polypetidic hormone promoting salt secretion, decreased blood volume, and relaxed vessel tension. Variants of corin have been associated with cardiac hypertrophy: the minor allele of corin T555I/Q568P (found at the heterozygous state in 12% of black people of African origin[3]) has been associated with an enhanced cardiac hypertrophic response to pressure overload, showing that this locus is involved in systemic hypertension.[4] Corin encompasses 2 frizzled-like domains, and the T555I/Q568P variant affects the second domain, which was shown to be crucial for efficient pro-ANP processing.[5]

Corin itself is synthesized as a propeptide that requires cleavage for activation. This cleavage is catalyzed by the protease proprotein convertase subtilisin/kexin-6. This protease is expressed in various tissues, especially the endometrium in epithelial gland cell cytoplasm, but also in the placenta at the level of the syncytiotrophoblast (source: protein atlas https://www.proteinatlas.org/ENSG00000140479-PCSK6/tissue/placenta#img).

Besides its action as an important modulator of blood pressure, a series of recent articles indicate that corin plays a significant role in the context of preeclampsia, a major hypertensive disease of pregnancy, affecting approximately 5% of pregnancies, with potentially lethal consequences for mother and child.[6] In mice, the knockout (KO) of corin leads to a moderate increase of blood pressure during gestation, especially in its last period (from E14.5 and ongoing), accompanied with proteinuria, reproducing the hallmarks of preeclampsia. In parallel, invasion of spiral arteries by trophoblasts, a prerequisite for efficient placental function in many mammalian species, is impaired in KO mice from E12.5.[7] In the same study, the authors identified human mutations that impede the capacity of corin to effectively cleave pro-ANP in vitro, thus providing a mechanistic rationale for the phenotype observed.

In this issue of the *Canadian Journal of Cardiology*, Baird et al.[8] pursue their exploration of the impacts of variants of human corin in transgenic mice. They focus on heart structure and function in mice with corin deficiency. Before pregnancy at 3 months of age, the wild-type (WT) and KO mice did not present differences in terms of cardiac hypertrophy, whereas at the end of pregnancy, an 11% ± 2% increase of heart weight/tibial length ratio was noted in corin KO mice (but not in WT), as well as a 7% ± 2% increase in cardiomyocyte diameter (Fig. 1A); this increase persisted 1 month postpartum. When the mice were mated later (at 6 months of age), the deleterious effects were higher, suggesting that age itself is an additional stress to the cardiovascular system in defective genetic backgrounds (Fig. 1A). This interesting observation concurs with the importance of considering maternal age as a risk factor for adverse outcomes during gestation,[9] but also for later consequences on maternal cardiovascular health. Together with cardiac hypertrophy, functional parameters were also altered as assessed by ultrasonography, with an increased stroke volume and cardiac output at 18.5 days postfertilization. A striking finding in the present study was the result of an elegant experiment to determine whether introducing a corin transgene in the mice, either encoding a WT protein or the T555I/Q568P variant described earlier, would correct the hypertrophic phenotype. Although the WT version of corin expressed in the heart was able to prevent cardiac hypertrophy, the expression of the variant gene was unable to reverse it (Fig. 1B).

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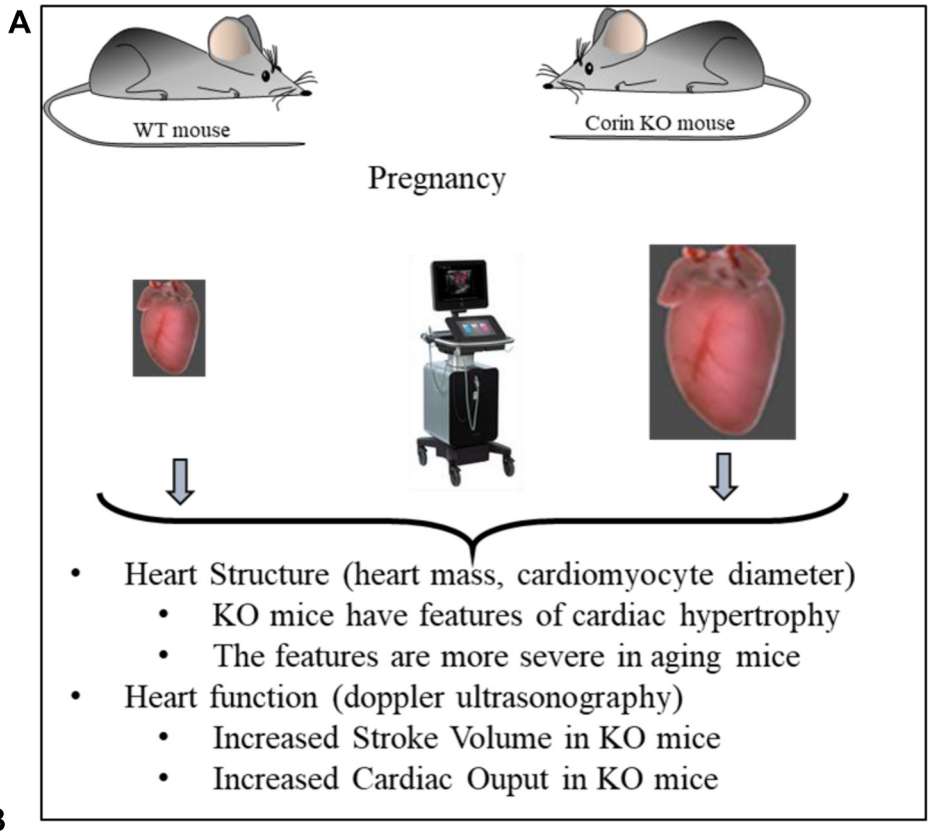
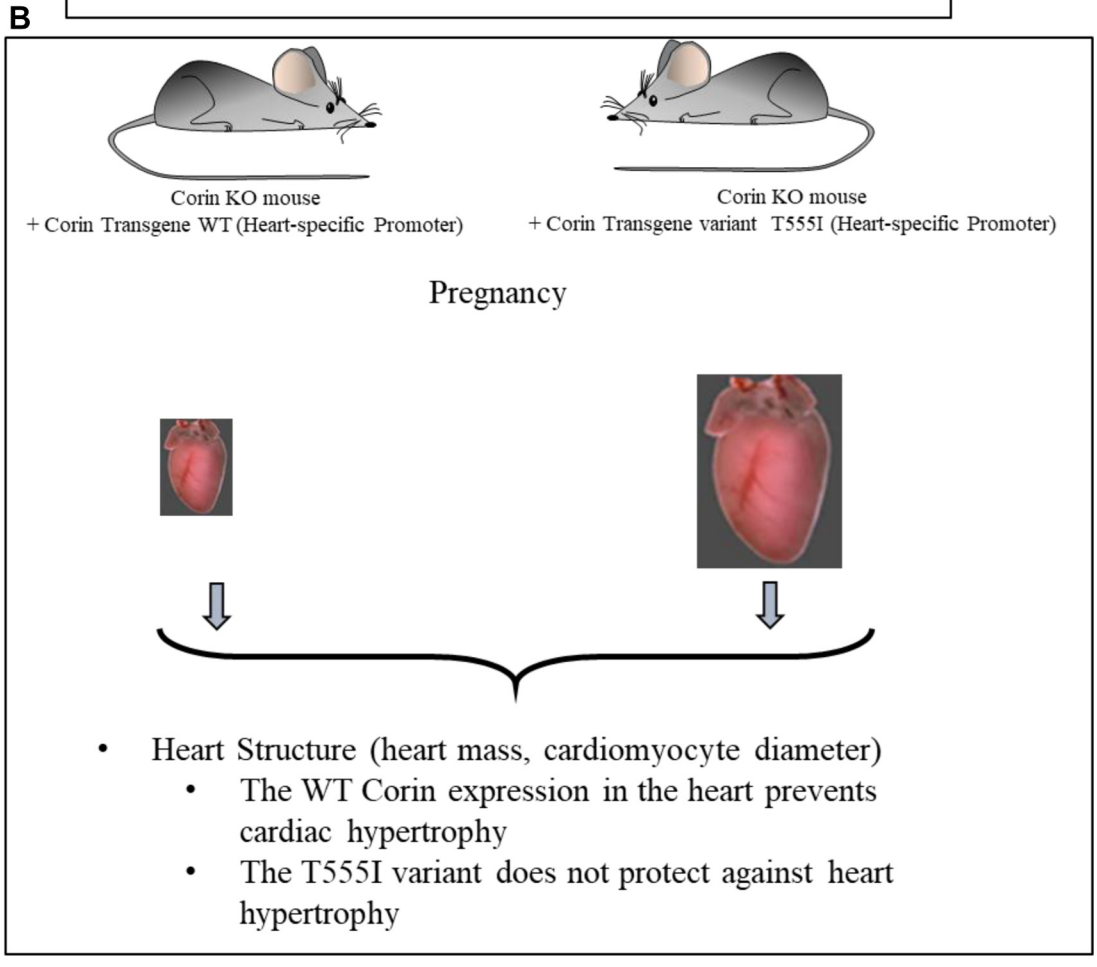

A
WT mouse
Corin KO mouse
Pregnancy
• Heart Structure (heart mass, cardiomyocyte diameter)
• KO mice have features of cardiac hypertrophy
• The features are more severe in aging mice
• Heart function (doppler ultrasonography)
• Increased Stroke Volume in KO mice
• Increased Cardiac Ouput in KO mice


B
Corin KO mouse
+ Corin Transgene WT (Heart-specific Promoter)
Corin KO mouse
+ Corin Transgene variant T555I (Heart-specific Promoter)
Pregnancy
• Heart Structure (heart mass, cardiomyocyte diameter)
• The WT Corin expression in the heart prevents cardiac hypertrophy
• The T555I variant does not protect against heart hypertrophy

The follow-up of preeclamptic pregnancies is improving in industrialized countries. The improvement is due partly to the development of new sets of early markers allowing for the prediction and early management of the most at-risk pregnancies through the analysis of circulating blood markers, especially PlGF or the sFLT1/PlGF ratio,[10] which has a good negative predictive value. The development of multiparameter algorithms also increases the ability to distinguish women who will develop preeclampsia.[11,12] These tools, combined with the use of low doses of aspirin before the 16th week of pregnancy[13] could eventually systematically improve the outcomes for the mother and child, as shown in the first large randomized control trial from the Kypros Nicolaides research group.[14] Recently, the potential economic benefits of combining early detection with aspirin treatment was evaluated on the basis of 1-year data from the Canadian Live Birth Registry. The simulation, based on 387,315 births, led to an estimated reduction from 1801 to 705 affected women after aspirin treatment, resulting in a $>$ $14,000,000 savings.

In the context of improving prevention and management of preeclampsia during gestation, there may be a future shift in research efforts toward the study of long-term cardiovascular effects of preeclampsia, which are now a major subject of investigation worldwide. Epidemiological studies have now clearly demonstrated that long-term cardiovascular risk is increased in women who had a preeclamptic pregnancy.[15] Other risks are increased as well, such as post-preeclampsia end-stage renal disease with a relative risk of 4.7 (95% confidence interval, 3.6-6.1) in women who experienced preeclampsia versus those who had a normotensive pregnancy.[16] A recent study showed that women with a history of preeclampsia have a 3.46-fold increased risk of vascular dementia (95% confidence interval, 1.97-6.10), but also more modest associations with Alzheimer's disease and unspecified dementia.[17] Overall, these results transform our understanding of preeclampsia from a disease for which the effects are restricted to gestation to a general injury of the complete endothelial compartment, programming both immediate and later diseases.

A general question about these long-term consequences is whether they are due to preeclampsia per se or to a previously nonoptimal cardiovascular state due to the genetic background. Although this question is difficult to address in women, in whom the genetic heterogeneity is huge, rodent models (especially laboratory mice that are congenic strains) are perfectly suited to address this issue. In the study presented, a genetic alteration (corin gene deletion or mutation, with or without the addition of a potentially compensating transgene) causes persistent cardiac hypertrophy. Other models also indicate that notwithstanding the genetic background, preeclampsia is sufficient to alter the vascular capacity to cope with future injury;[18] indeed, 2 months postpartum after a normal or a preeclamptic pregnancy (induced by overexpression of sFLT1), vascular remodelling is increased in previously preeclamptic mice, with increased vascular smooth muscle cell proliferation and vessel fibrosis compared with control mice. In another model of preeclampsia (♂C1qKO mice × ♀ WT female), Garrett et al.[19] recently showed that the maternal aorta is dysfunctional 2 months after pregnancy, with abnormal collagen I deposition. They also showed persistent hypertension and glomerular damage in the mothers. The consequences were reversed by pravastatin treatment, showing that controlling preeclampsia during pregnancy can improve health status in later life.[19] According to the results of the same study, successful preeclampsia management also could have significant positive effects on offspring health. In the 2 last models described, the long-term effects are independent of the genetic background of the mother. Combined with the observations of the present study, the mouse observations on long-term consequences of preeclampsia indicate that both a predisposition (e.g., genetic deficiency in corin) and the preeclampsia per se are able to induce long-term deleterious consequences. The same combinations of genetic and sporadic factors are almost certainly found in human patients.

One limitation of these recent studies on the links between corin and preeclampsia is that they do not reproduce the extreme heterogeneity of preeclampsia, for which the environmental contribution is estimated to be approximately 50%.[20] In addition, the genetic determinants are highly polygenic, with numerous gene variants each contributing to a small part of the clinical variability.

An important future objective will be to obtain a more detailed understanding of the regulation of corin expression. The limited information presently available is mainly based on comparative studies of the mouse and human promoter that were performed in 2002[21] and that revealed an important function of GATA-4 in the regulation of the corin promoter. Other investigations of conserved binding sites are warranted and would allow an improved characterization of the regulation of the corin gene in various tissues. In addition, an interrogation of the University of California Santa Cruz (https://genome.ucsc.edu/) database showed that near the first exon is located a CpG island (95 CpG in 1342 base pairs, chr4:47836588-47837929, in the hg38 version of the human genome), which could contribute to the regulation of the gene expression or to its deregulation in a pathological context. Together with an elucidation of the open chromatin structure near the corin gene, such epigenetic analyses could help to make a link between pathology and gene expression defects not directly related to genetic variants.

Baird et al.[8] have added important insights into the genetic control of preeclampsia and its consequences. The management of hypertension in pregnancy is an important challenge.[22] Further work of the type discussed promises to produce important new insights into the control of blood pressure and cardiac remodelling, and to allow for significant improvements in the health of women and their offspring.

Figure 1. An outline of the experiment by Baird et al.[8] In the first part of their study (**A**), the authors compared the heart structure and function of corin knockout (KO) mice after gestation. The authors showed that corin KO mice display the characteristic features of a preeclamptic gestation. This leads to a hypertrophic heart, with in addition alterations in functional parameters, and the pathology is aggravated when the mice have their gestation at a later age. The heart defects were not corrected 28 days postpartum (see text). In the second part of their study (**B**), a transgene encoding a wild-type (WT) corin gene or a defective corin variant found in humans, under the control of a heart-specific promoter, was expressed in the KO mice. This analysis showed that cardiac hypertrophy is corrected only with the WT variant.

Disclosures

The authors have no conflicts of interest to disclose.

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