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Use of decongestants may disrupt cell signaling pathways that control Tbx gene expression, leading to hypoplastic left heart syndrome

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Use of Decongestants May Disrupt Cell Signaling Pathways That Control *Tbx* Gene Expression, Leading to Hypoplastic Left Heart Syndrome

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1. Background Information:

Hypoplastic left heart syndrome (HLHS) collectively refers to a range of congenital heart defects, all involving some degree of left ventricular hypoplasia, or underdevelopment of the left ventricle.[1,2] Additionally, HLHS often involves coarctation of the aorta,[1] and can also include hypoplasia of the ascending aorta, as well as mitral and/or aortic valve stenosis or atresia.[1,2] HLHS is extremely rare, as it has been reported to occur in only 1 in 5000 live births each year.[2] The cause of HLHS is currently unknown, however much research is being done to discover how and why these defects occur.

HLHS is known to be familially inherited in some instances and is also associated with many well-characterized genetic disorders, including Holt-Oram syndrome, Turner's syndrome, Noonan syndrome, Smith-Lemli-Opitz syndrome, as well as trisomies 13, 18, and 21.[1,2] Additionally, an autosomal recessive pattern of inheritance has been found amongst some siblings, however, no specific genes have been implicated.[2] Incidence of HLHS also varies significantly in certain geographical regions and some studies have found a seasonal correlation in HLHS, indicating a possible environmental cause.[2,3]

2. Hypothesis and Rationale:

A study done in 2011 by Eghtesady, et. al. found a moderate to strong correlation between seasonality and HLHS. Interestingly, among the four left-sided congenital heart defects studied at the time, HLHS was the only disease that showed such a correlation (*Figure 2.1*). HLHS was found to be more prevalent in babies born during the early summer months, particularly during the month of June.[3] If these were full-term pregnancies, infants born at this time of year would have been conceived during the fall, around September, right when the seasons are transitioning.

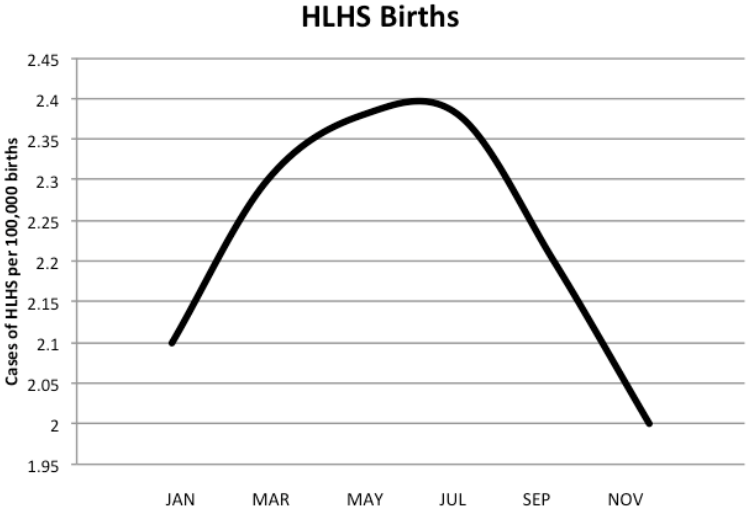

Figure 2.1. Seasonality of HLHS – incidence of HLHS was found to be increased in the summer months, and decreased in the winter months. This seasonal correlation was not found with any other left heart defects. *(Adapted from: Eghtesady, P., Brar, A., & Hall, M. Seasonality of hypoplastic left heart syndrome in the United States: A 10-year time--series analysis. Journal of Thoracic and CV Surgery. 2011; 432-438.)*

During the transition of seasons, symptoms of allergies, or even the common cold, may start to form. These symptoms could lead mothers to take medications, such as decongestants, to combat these seasonal illnesses. A common over-the-counter medication used is pseudoephedrine, also known as Sudafed, a decongestant. Studies have found that 25% of women are exposed to pseudoephedrine during their pregnancy.[4] In order to be effective, pseudoephedrine acts on the α_1 and the β_2 receptors found on the walls of the blood vessels. When pseudoephedrine binds to these receptors, it initiates the α_1 pathway in which the second messenger, DAG, activates Protein Kinase C (PKC). PKC then causes phosphorylation of a protein that promotes the constriction of the smooth muscle that makes up blood vessels. When this constriction occurs, blood flow is limited.[5]

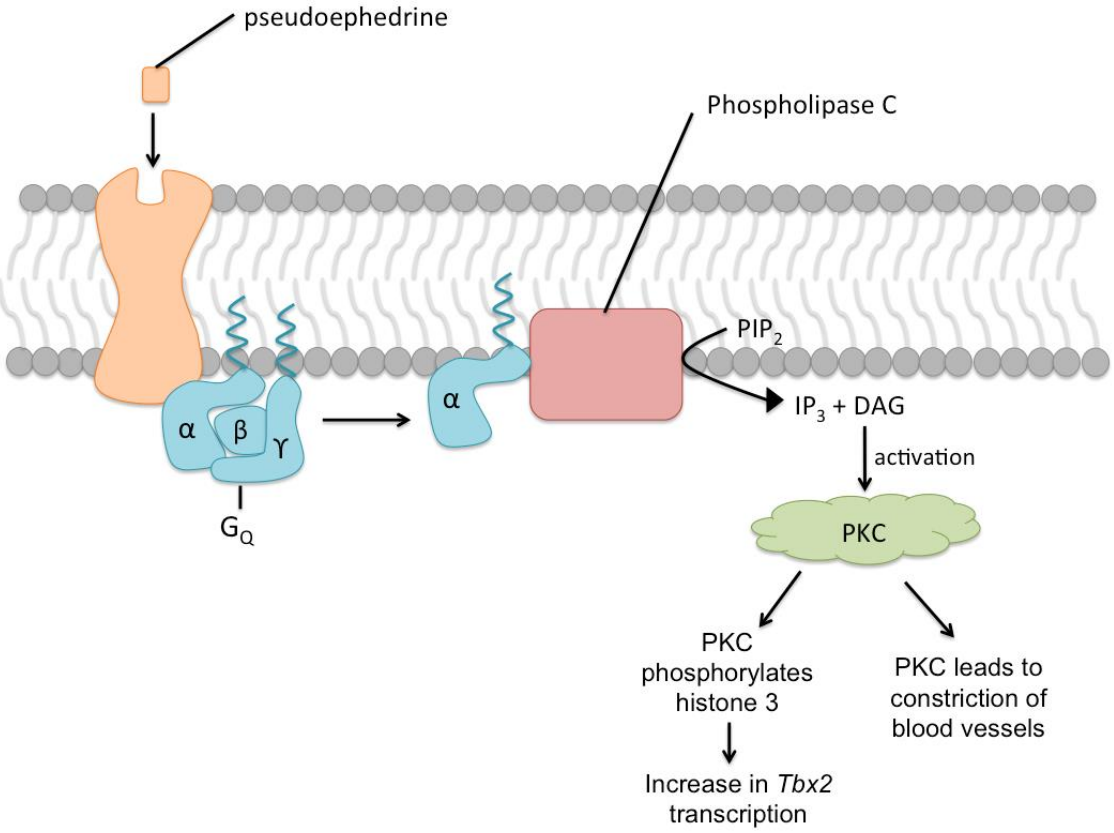

Figure 2.2. Mechanism of PKC activation by pseudoephedrine via the G_Q pathway.

PKC also plays a role in a number of cell signaling pathways including pathways that are responsible for controlling expression of some *Tbx* genes, particularly *Tbx2* (*Figure 2.2*).[6] *Tbx* genes code for a family of transcription factors, the T-box proteins, which are crucial for determination of cell differentiation in early embryogenesis, including cardiogenesis. Various T-box proteins play a role in initial specification of the cardiac mesoderm, regionalization of the primitive heart tube into chamber and non-chamber cardium, recruitment of second heart field cells, and formation of the valves and septa.[7]

Tbx mutations have already been identified as the cause for many other well-characterized genetic conditions involving congenital heart defects, including some of the diseases previously mentioned to be frequently associated with HLHS. For example, Holt-Oram syndrome is caused by a heterozygous mutation in the *Tbx5* gene.[7] Heterozygous mutation of

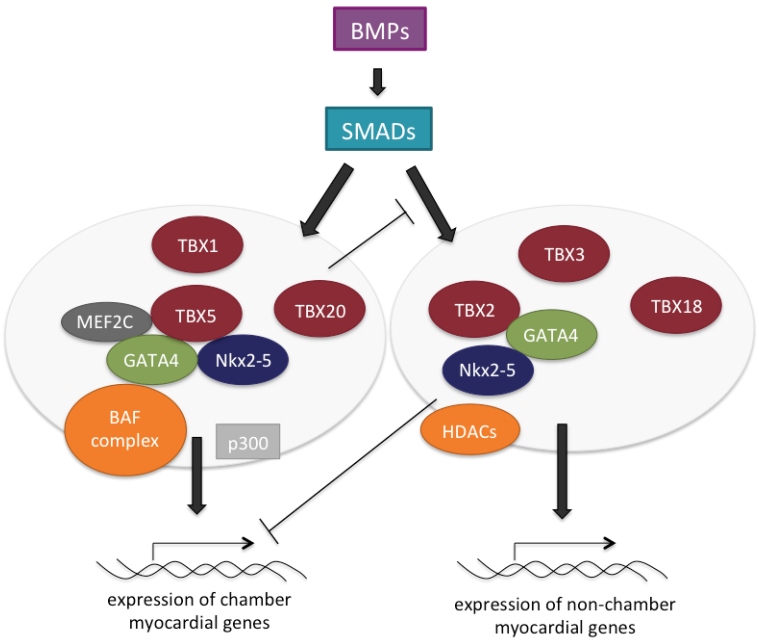

Figure 3.1. TBX2 represses the activity of TBX1, TBX5, and TBX20, leading to decreased expression of chamber myocardial genes.

another gene, *Tbx1* has been implicated as the cause of DiGeorge's syndrome, also called 22q11.2 deletion syndrome.[7,8] Interestingly, mosaic 22q11 deletion has also been reported in many HLHS cases.[2]

Evidence has also shown that a specific form of HLHS - aortic atresia with a hypoplastic but perforate mitral valve - is 55-70% more common in males.[2] This increased prevalence in males could indicate a sex-linked gene as the cause of that form. *Tbx22* is found on the X chromosome, and its mutation has been shown to cause birth defects.[7] Although no heart defects have been associated with *Tbx22* mutation, based on the complex roles T-box proteins play in embryogenesis, it is possible that TBX22 still affects cardiogenesis, and ultimately left heart development, in some manner. Additionally, there could be another sex-linked *Tbx* gene that is currently unidentified.

TBX2 is especially important, as this protein is known to have an effect on other T-box proteins. TBX2 is involved in a pathway that actually represses the activity of TBX1, TBX5, and TBX20, thus preventing expression of genes that lead to heart chamber formation (*Figure 3.1*).[8] It is therefore possible that overexpression of TBX2 can lead to an increase in this repressive mechanism. As mentioned previously, TBX5 and TBX20 are important in left heart development and it is therefore likely increased repression of TBX5 and TBX20 will specifically cause decreased formation of the left heart and HLHS.

3. Significance and Innovation:

In order to test this hypothesis, a large scale epidemiological study would need to be done that monitors the use of decongestants during pregnancy, and examines any correlations between their use and the occurrence of HLHS. If a correlation between pseudoephedrine usage during pregnancy and fetal HLHS was found, medications containing pseudoephedrine would need to be more clearly labeled as a possible cause for birth defects. Until definitive studies are done, we would strongly discourage pregnant women to take these medications during pregnancy. One reason the effects of decongestants on HLHS has not been researched heavily in the past, is because pregnant women are typically excluded from clinical trials.[6] Therefore, we suggest using an animal model to monitor the effects of decongestant use on PKC levels and cardiogenesis.

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