Brain receptor identified as link between obese mothers and children's high blood pressure

12 October 2016

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Exposure of babies to high levels of the 'fullness' hormone, leptin, in the womb irreversibly activates receptors in the brain that regulate blood pressure, according to a new study by researchers from King's College London, part-funded by the British Heart Foundation. This activation may lead to a lifelong increased risk of high blood pressure and kidney disease.

Previously, observations in humans have shown a link between obesity in pregnant mothers and high blood pressure and chronic kidney disease in their children, leading to a greater risk of cardiovascular disease, such as heart attacks, later in life. However, when observing families it is difficult to exclude the effect of other factors such as poor household diet.

The new research, published in the journal *Proceedings of the National Academy of Sciences*, used a mouse model to investigate the role of the hormone leptin, as children of obese mothers are exposed to high levels of leptin during development in the womb. Leptin is a signal produced by cells in the body, especially fat cells, after eating to indicate satiety - fullness - and is important in suppressing appetite, but it is also thought to play an important role in the control of blood pressure.

Exposure of newborn immature mice to high levels of leptin activated neurons with a melanocortin-4 receptor (Mc4r) in the brains of infant mice. The Mc4r is found on neurons in a region of the hypothalamus in the brain, which controls hunger and blood pressure.

Mice that experienced activation of Mc4r neurons by elevated leptin had high blood pressure and kidney damage later in life. The exposure to leptin reset the brain's response to leptin, so that in adulthood their brains produced a bigger increase in blood pressure in response to leptin.

Professor Lucilla Poston, senior author on the paper, Head of the Division of Women's Health at King's College London and co-leader of the Women's Health Clinical Academic Group at King's Health Partners said: 'We are increasingly aware of the important role played by maternal metabolic and nutritional status in the risk of adulthood disease in the offspring. Maternal obesity has been linked to later obesity, diabetes and hypertension in the child, but the mechanisms have proved elusive. This study identifies an exquisite vulnerability of certain cells in the developing brain to metabolic disturbance associated with maternal obesity, and shows how this may contribute to development of high blood pressure in later life.'

Dr Anne-Maj Samuelsson, lead author on the paper from the Division of Women's Health at King's College London, said: 'Several recent mother-child cohorts demonstrate higher blood pressure in

children born to obese mothers. High blood pressure in children is an important risk factor for cardiovascular disorders in adulthood. This study identified a mechanistic link between maternal obesity and childhood hypertension. The absence of one specific gene, called Mc4r, in the brain, protected the offspring of obese mice from hypertension. By adding the Mc4r back to the mouse brain, we were able to reinstate the hypertension in offspring born to obese mice. Our findings need to be verified in human studies to determine if Mc4r is a therapeutic target for hypertension.'

More information: Anne-Maj S. Samuelsson et al, Central role for melanocortin-4 receptors in offspring hypertension arising from maternal obesity, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1607464113

Provided by King's College London