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Dipeptidyl Peptidase IV inhibition protects against developmental programming of metabolic diseases in maternal obesity

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Keywords

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Abstract

The obesity pandemic produces immense health and economic burdens globally. More than 65% of women entering pregnancy in the US are overweight or obese and maternal obesity leads to the developmental programming of obesity and metabolic diseases in the offspring. Although maternal obesity is recognized as a major driving force behind the obesity pandemic, there are currently no effective therapies to address the detrimental effects of maternal obesity. Dipeptidyl peptidase IV (DPPIV) is a ubiquitous aminopeptidase that regulates development, metabolism, and inflammation. Emerging evidence indicates that increased plasma DPPIV activity is an early marker of obesity. Furtthermore, DPPIV inhibitors such as Sitagliptin improve systemic metabolism and promote weight loss in diabetics . We found that at term, maternal obesity in human mothers and offspring is associated with a fetal-sex dependent dysregulation in plasma DPPIV activity. We also found that baboons and mice born to obese VS lean mothers had increased plasma DPPIV activity regardless of fetal sex and that this effect persists into adulthood. These findings prompted us to determine the effects of DPPIV inhibition using Sitagliptin on developmental programming in maternal obesity. In a pre-clinical study using female FVB/N mice fed either a regular (RD) or high fat diet (HFD), we administered oral Sitagliptin (3 mg/kg/day) to RD and HFD-fed mothers prior to pregnancy and until weaning (Mat-Sita), or to offspring (Off) after weaning (Off-Sita). We found that compared to controls, Mat-Sita and Off-Sita prevented obesity and metabolic dysfunction in Off of HFD (Off-HFD) and had no effect in Off of RD (Off-RD) -fed mothers. Furthermore, Off-HFD VS Off-RD had increased inflammation in vital organs such as the heart, kidney and liver, and Off-Sita decreased these effects. Therefore, these findings suggest that DPPIV inhibition is a viable therapeutic strategy to address the detrimental effects of developmental programming in maternal obesity.