

# Cognitive function in offspring of mothers with gestational diabetes—the role of insulin receptor

## Abstract

There is increasing evidence that the offspring of women with gestational diabetes during pregnancy are at increased risk for the neurocognitive abnormalities. Moreover, the exact molecular mechanism by which gestational diabetes affects the developing central nervous system (CNS) remains to be defined. In the recent decades, it found that the Insulin has a crucial role in the development and function of the brain in both fetuses and adults. The researchers found that the alteration in expression/localization of insulin receptor (InsR) in the brain may be part of the cascade of events through which gestational diabetes affects the newborn's CNS structures. Dissecting out the mechanisms responsible for gestational diabetes-related changes in the development of CNS is helping to prevent from impaired neurocognitive functions in offspring.

**Keywords:** Gestational Diabetes, Cognition, Insulin, Offspring, Neurocognitive, Teratogenic

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**Abbreviations:** InsR, insulin receptor; CNS, central nervous system; IQ, intelligence quotient; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase

## Introduction

Gestational Diabetes is one of the most common metabolic complications that is associated with brain development abnormalities in offspring.<sup>1-5</sup> Several lines of studies have reported the wide spectrum of effects of gestational diabetes on the central nervous system (CNS) development and function including neurocognitive and neurodevelopmental defects.<sup>1-4,6-9</sup> Overall, it appears that these offspring have an increased risk for lower general IQ, inattention and hyperactivity and a poorer cognitive function.<sup>1-4,10-13</sup> Earlier investigations demonstrated a significant correlation between diabetes during pregnancy and lower IQ in offspring.<sup>10-13</sup> There are also reports demonstrating a close relationship between maternal diabetes and a higher incidence of psychological disorders such as schizophrenia in offspring.<sup>14,15</sup> Taken together, these studies not only suggest the teratogenic effect of gestational diabetes on the development of fetal CNS but also provide the perhaps earliest indicator of postnatal CNS problems reflected in intellectual and behavioral problems exhibited by children born to diabetic mothers. However, no report can fully explore the molecular mechanisms of gestational diabetes-induced neurocognitive defects because the CNS development is a complex process and is regulated by a number of signaling molecules and transcription factors.

Over the past few years, it has become clear that insulin has profound effects in the development and function of CNS, where it regulates several neuronal functions, including regulation of synaptic

plasticity, dendritic outgrowth, and involvement in neuronal survival, life span, inhibition of neuronal apoptosis, learning and memory, and neurological disorders.<sup>16-20</sup> Moreover, the role of InsR signaling in controlling structure and function of CNS has not yet been widely explored *in vivo*. The InsR is also a component of synapses, where it concentrates at the postsynaptic density in cultured hippocampal neurons.<sup>21</sup> These data together suggest that the insulin receptor is in the right place at the right time to regulate the initial neuronal development by regulating synaptic function in the CNS.

The Insulin receptor (InsR) is expressed in various areas of the developing and adult brain,<sup>20,22-25</sup> and its functions have become the focus of recent research. The expression of the InsR in the brain was discovered decades ago. This receptor is developmentally regulated, being higher at early stages and lower in the adult and is distributed in a widespread, but selective, pattern in the brain, including cerebral cortex, hippocampus, olfactory bulb, and cerebellum as reported in rodents.<sup>20,22,23</sup>

The hippocampus—a brain structure vital for spatial learning and memory—is particularly vulnerable to changes in glucose concentration, particularly during the development.<sup>23,26,27</sup> Considering the developmental and functional roles of insulin in the CNS, recent investigations hypothesized that the insulin may be one of the possible mechanism involved in the cognitive abnormalities observed in offspring of diabetic mothers.<sup>28,29</sup>

## Discussion

The expression of the InsR in the brain was discovered decades ago. For the first time, Havrankova et al.<sup>23</sup> localized the InsR in the CNS. The origin of insulin in the brain has been explained from

peripheral or central sources, or both.<sup>25</sup> It was found that the Insulin enters the central nervous system (CNS) by crossing the blood–brain barrier through a receptor-mediated transport mechanism.<sup>30–32</sup> However, the molecular identity of this transport mechanism remains unclear. Margolis et al.<sup>31</sup> demonstrated that peripheral infusion of insulin leads to an increase in insulin levels in cerebrospinal fluid, suggesting that insulin can indeed cross the blood–brain barrier. These findings were later confirmed in studies indicating that less than 1% of the peripherally administered insulin reaches the CNS in rodents.<sup>32</sup>

The InsR belongs to the family of tyrosine kinase receptors. Binding by insulin leads to rapid auto phosphorylation of the receptor, followed by activation of downstream pathways such as the PI3K and the MAPK.<sup>16,18,20,23,25</sup>

Accumulating data support the idea that InsR signaling plays a prominent role in both developmental and functional aspects of CNS.<sup>16–18,20</sup> In addition, emergent evidence suggests an association of InsR signaling with several neurological and neurodegenerative disorders, for example Schizophrenia, Parkinson's disease and Alzheimer's disease.<sup>33–36</sup> InsR signaling, therefore, might participate at both ends of the story: early development as well as later neurodegenerative and psychologic disorders. Interestingly, a study By Hami et al.<sup>37</sup> showed that there are prominent gender-and laterality- differences in expression and distribution pattern of InsR in the developing rat hippocampus. The authors concluded that these differences may be a probable mechanism for the control of sex and laterality differences in development and function of the rat hippocampus.<sup>37</sup>

Gestational diabetes is one of the most common metabolic disorders in pregnancy period and is associated with a higher risk of short- and long-term neurocognitive abnormalities in the offspring.<sup>1,2,4,5,7–9,28,29,38,39</sup> Diabetes during pregnancy period as a result of metabolic abnormalities and perinatal complications may be associated with developing brain abnormalities in offspring, including long-lasting neurological impairment, impairments in attention and memory, hyperactivity, poorer general cognitive function and altered social behaviors.<sup>1,2,6,39–45</sup> As yet, no distinct molecular mechanism has been identified to explain the reasons for the wide range of CNS abnormalities observed in the infants born to diabetic mothers.

To elucidate the negative impacts of gestational diabetes on cognitive functioning in the children, several researchers have been reported that diabetic mothers had offspring with significantly lower mean IQs than control infants.<sup>1–4,10–13</sup> Moreover, many of the developmental effects of gestational diabetes on the fetal CNS can be attributed to maternal hyperglycemia and fetal hyperglycemia/hyperinsulinemia.<sup>5,38,39</sup> In diabetic pregnancies, the fetal blood glucose concentration is fairly high as the glucose in the mother's blood crosses the placenta freely. Therefore, *In Utero* hyperglycemia stimulates the pancreas of the fetuses, leads to beta-cell hyperplasia and hypertrophy with increased insulin secretion and results in fetal hyperinsulinemia.<sup>46,47</sup>

The hippocampal formation sub serves important physiological and behavioral functions including spatial learning and memory and is a part of brain that particularly vulnerable to changes in blood glucose level.<sup>4,8,26,27</sup> Tehranipour et al.<sup>48</sup> were examined the effects of maternal diabetes on density of hippocampal pyramidal cells immediately after birth and indicated that diabetes in pregnancy period can decreased the numerical density of pyramidal cells in the hippocampus of rat newborns.<sup>48</sup> Recent studies have also clearly established that gestational diabetes in pregnancy disrupts the regulation of InsR in the hippocampus and cerebellum of neonatal rats. Hami et al.<sup>29</sup> evaluated

the effects of diabetes in pregnancy on gene expression and protein concentration of InsR in the developing rat hippocampus at postnatal days 0, 7, and 14. In that study, the researchers found a markedly up-regulation of InsR expression in the hippocampus of newborns born to diabetic dams at first postnatal day. At the same time point, they showed only slight changes in their hippocampal protein transcripts. In two weeks old of age rats, the InsR gene expression was strikingly declined in the hippocampus of diabetic newborns. The authors claimed that maternal diabetes strongly altered the regulation of InsR during development of rat hippocampus.<sup>29</sup>

## Conclusion

The Incidence of neurocognitive anomalies in offspring born to diabetic mothers is more common in comparison to children of normal population. Nevertheless, the exact mechanism by which gestational diabetes affects the developing CNS remains to be defined. There are multiple lines of evidence that suggest the disturbances in intellectual functioning observed in the children of diabetic women are accompanied by modification of hippocampus structure and function. The etiology and pathogenesis of these impairments induced by gestational diabetes have spurred considerable efforts for clinically and basically researches. The final goal at these studies was to find the teratogenic factors, which may enable preventive or protective measures to be taken in pregnancies with diabetes. The new researches on genetic predisposition involves in teratogenicity of diabetes in pregnancy starts to define new genes and their products involved in the etiology of CNS malfunctions and malformations observed in children born to diabetic mothers. Recent evidence clearly indicated that maternal diabetes markedly influences the regulation of InsR-as an important regulator of development and function of CNS-in the developing rat hippocampus. Dissecting out the mechanisms responsible for gestational diabetes-related changes in the development of CNS is helping to prevent from impaired cognitive and memory functions in offspring.

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## Conflict of interest

Author declares that there is no conflict of interest.

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