Hyperinsulinemia and Insulin Resistance: What Comes First?

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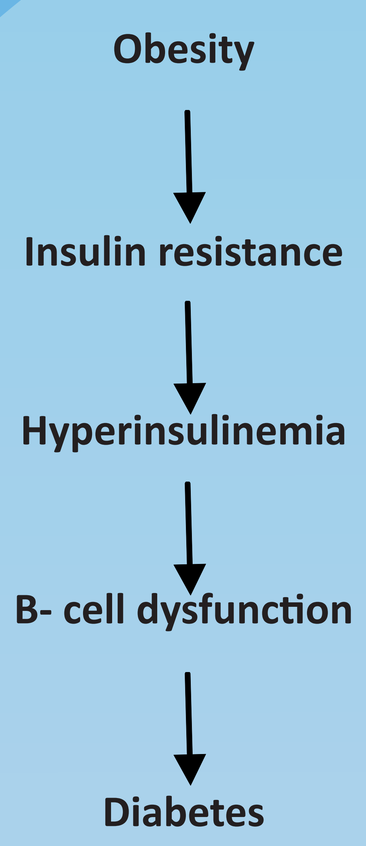
Background

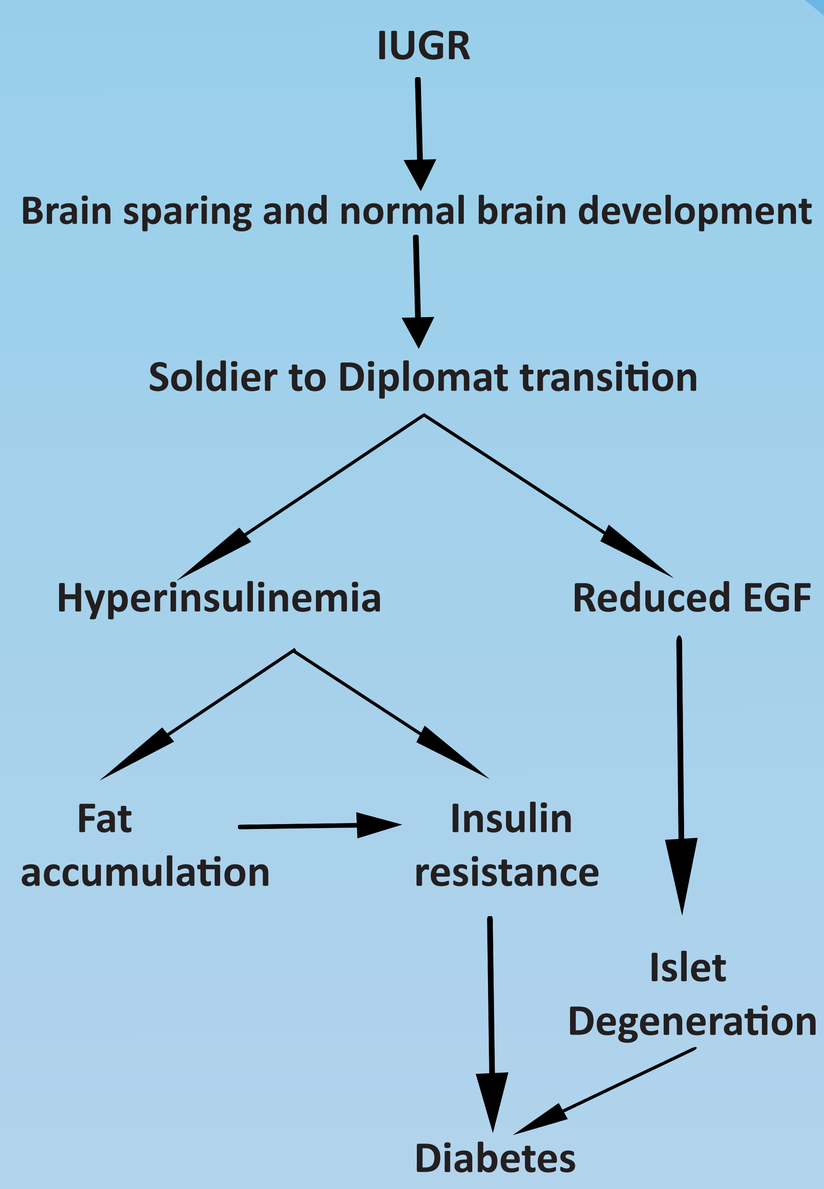
1. Classical explanation:
Classical explanation of diabetic pathophysiology states that obesity induced insulin resistance develops first and is followed by compensatory hyperinsulinemia[1]. Further insulin resistance leads to prolonged, increased secretary demand on beta cells leading to subsequent secondary beta cell failure, giving rise to hyperglycaemia and diabetes[2].

2. Neurobehavioral origin hypothesis:
The Neurobehavioral origin hypothesis suggests that insulin resistance mediates a shift from muscle dependent (soldier) to brain dependent (diplomat) strategies of making a livelihood. If nutrient limitation affects intrauterine development, brain development is the least affected among all the organs[4][5]. As a result, in IUGR babies muscle weight is poor but the brain is relatively well developed. Such a person is more likely to be a successful diplomat rather than a soldier and insulin resistance is adaptive for such an individual[3]. Since insulin is involved in brain development and cognitive functions, higher levels of insulin are needed. As insulin is having strong anti-lipolytic effect,
hyperinsulinemia is followed by subsequent excess fat accumulation. Also compensatory insulin resistance is needed to avoid hypoglycemia. This hypothesis predicts a reverse order of pathophysiology i.e. primary hyperinsulinemia followed by compensatory insulin resistance[3]

Classical Explanation



Neurobehavioral origin hypothesis



Objective:
To determine in diabetes whether hyperinsulinemia develops first or insulin resistance develops first.

Methods:
We searched literature for studies that investigated directly or indirectly the sequence of development of hyperinsulinemia and insulin resistance in humans and animal models from an early stage. Meta-analysis was conducted on published data.

Results:
1. In low birth weight neonates in humans as well as in rat models, hyperinsulinemia is found at very early stage.[6]

2. Development of insulin resistance is preceded by hyperinsulinemia in mice, rats as well as in humans.[7][8]

3. In normoglycaemic hyperinsulinemia state if insulin production is suppressed insulin sensitivity increases rapidly maintaining the normoglycaemic state.[9][10]

4. Beta cell expansion beginning in intrauterine life is independent of glucose, Insulin and Insulin receptors.[6]

Conclusion:
All the four lines of evidence indicate that hyperinsulinemia precedes insulin resistance supporting the predictions of neurobehavioral origin hypothesis over the orthodox view.

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