Tryptophan metabolism in pregnancy

The amino acid tryptophan (Trp) is essential for protein synthesis and produces many important chemicals in the body, including: serotonin in brain which controls appetite, behaviour, cognition, emotion and mood; melatonin in the pineal gland which controls our body rhythm and sleep and acts also as antioxidant; nicotinic acid (niacin or vitamin B_3) in liver which is the pellagra preventing factor; coenzymes for many reactions throughout the body and for DNA repair; and a number of metabolites known as kynurenine metabolites that are involved in normal metabolism, and nervous system function in health and in modulating the immune system in infectious and neurological diseases.

Trp is in high demand during pregnancy to meet the increased protein formation by the expectant mother and growth and development of the fetus. Tolerance of the fetus during pregnancy has been a puzzle for scientists for many decades. During the 1980s, research has shown that, during bacterial, parasitic and viral infections, the immune system is activated to combat infection. This activation stimulates an enzyme called IDO (indoleamine dioxygenase) to break down Trp, resulting in a decrease in its plasma levels. Researchers suggested that depriving the infectious agent of this essential Trp nutrient by its depletion explains the ability of the immune system to combat infection. The same depletion idea was then proposed in 1998 to explain why the mother does not reject the fetus. The rationale was that activation of the immune system during pregnancy can also accelerate the breakdown of Trp. Thus, the “Trp depletion concept in pregnancy” was proposed based on an animal model and the decrease in plasma Trp during pregnancy. However, far from being depleted, another form of Trp, known as free Trp, has been known for some considerable time to be increased in pregnancy. The researchers who suggested the depletion concept relied only on measuring the whole of plasma Trp. Trp exists in plasma mainly (90-95%) bound to the plasma protein albumin, with the remaining 5-10% being unbound and so is freely and immediately available for organs and tissues. Thus, (free) Trp availability to the fetus is actually increased and this is reflected in high levels of Trp in umbilical cord blood and fetus in both humans and animals, consistent with the increased demand for Trp by mother and fetus.

Accordingly, I proposed a “Trp utilisation concept” in pregnancy that satisfies the increased requirements for this essential amino acid by both mother and fetus and at the same time guarding against fetal rejection. These requirements are manifold: (1) the need for increased protein synthesis by mother and for fetal growth and development; (2) serotonin for signaling pathways aiding fetal development and protecting the mother against depression; (3) the Trp metabolite kynurenic acid for protecting the nervous system of the fetus; (4) the Trp metabolite quinolinic acid for ensuring adequate levels of coenzymes for various metabolic reactions; (5) protection of the fetus against rejection by suppressing the immune response of the mother through the kynurenine metabolites of Trp, whose levels are also increased during pregnancy. It is hoped that applying the Trp utilization concept to pregnancy will stimulate further research to identify missing gaps in our knowledge of the Trp status in pregnancy and its complications and thus suggest intervention strategies aimed at ensuring a successful pregnancy outcome.

In the case of infections, both immune suppression by kynurenine metabolites and Trp depletion can work together to combat the infection. However, in pregnancy, only immune suppression is involved in conjunction with the increased need for Trp to ensure a successful outcome.

Publication

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