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Pointing to Intrauterine Growth Restriction (IUGR)

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One of the most puzzling epigenetic effects on intrauterine growth could be the restriction of nutrients, which we consider one of the most insidious stress for developing organisms. One obvious and efficient mechanism to produce nutritional stress is the impossibility to obtain nutrients, that, paradoxically happens, in distinct human populations in the World, affecting not only adults, but many children, including those unborn, who will not get the chance to develop properly and are born with evident somatic abnormalities, when they reach birth, particularly with faulty brains. Being good land to be discriminated for they does not always perform in human duties as their mates. Not less important is another deficiency they are subjected to which is the lack of the affective nutrient and a proper education, when they get any.

We initiate long before a lasting research Project. with the idea to study the effects of prenatal undernutrition on brain development. To gain access to brain tissue, we set up some experimental models that hopefully could reproduce similar clinical conditions, like the picture known as Placental Insufficiency, which is, in humans, another cause of nutrients passing deficiently to fetal circulation conditioning Intrauterine Growth Restriction (IUGR). As its name suggests, fetal growth and development is restricted, with underdeveloped fetuses. Another experimental approach consisted to subject pregnant rats to a protein-calorie malnutrition, as a different approach of provoking the nutritional stress. And, strictly supervising normally growing controls and experimental subjects, we were able to run a long lasting Project to study the effect of prenatal nutritional stress on a specific neuronal system, taking the advantage that some neurotransmitters, biogenic amines, are synthesized from specific nutrients which are their metabolic biosynthetic precursors.

We first observed that the most reactive brain system to changes in the availability to its precursor nutrient, by undernutrition, was the brain serotonergic system (brain 5-HT). As it is well known the 5-HT system is a very relevant one for brain function, not only in the adult brain, but as we have obtained and published complementary results, also during embryonic life, identifying first several functional properties of the 5-HT system in the rat fetal brain. As Gene Lauder, has long stated, the 5-HT system has important brain morphogenetic functions: We, besides, observed that L-tryptophan (L-Trp, the 5HT precursor aminoacid) not only passes through the placental membranes, which is well known, as the other nutrients do, but we observed that when doing so it is efficiently taken up by the fetal brain and does stimulate, in it, the 5-HT synthesis effectively, significantly activating the limiting enzyme (Tryptophan-5-Hydroxylase) in the IUGR fetal brain, . This

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enzyme remains activated in IUGR rat brains, over control values, even up to the postnatal period and up to adulthood, and the plasma free fraction of L-Trp, remains elevated up to 3 months postnatally in the human baby, who suffered IUGR. We described how 5HT is recognized and taken up by specific differentiating rat fetal brain structures, like axonal growth cones (AGC) E17, supporting their role in brain axogenesis in normal rat brain. Results also were obtained about how 5-HT is synthesized in fetal brain tissues and released from AGC´s, in a K+ and Ca++ dependency. And our lab also published interesting results on the kinetics (mol to mol) of plasma L-Trp binding to plasma albumin, free of fatty acids, in rats and in human nursing babies, which has not been studied in normal or in IUGR albumin. Interestingly in the latter, binding kinetics is different that in normal albumin, binding significantly less plasma LTrp, than in the albumin of normal controls, up to 3 months of postnatal age. Therefore these babies carry an elevated Plasma Free L-Trp fraction sign of an abnormal metabolic trait. The L-Trp binding to plasma albumin seems to be a very relevant regulatory mechanism for the control of the precursor´s amino acid free plasma fraction, for its transport through the Brain Blood Barrier to brain tissues, where it participates in the serotonin biosynthetic path in 5-HT neurons. In IUGR rats, as mentioned, the Plasma Free Fraction of L-Trp passes through BBB (Blood Brain Barrier) in a higher amount, activating and accelerating 5-HT brain synthesis. Which gave us a possible explanation of why the 5-HT morphogenetic function is not performing properly and it alters its normal physiological role in the structural maturation, particularly of the sensory cortices. With this and other information, that we put together, we were able to acknowledge better, how the fetal brain is altered when subjected to IUGR.

Prenatal undernutrition, whether from the mother´s protein calorie restriction or through placental insufficiency, alters mainly the corticogenesis. In particular seems to damage the sensory cortices which are particularly innervated and their development regulated by serotonergic terminals. Several lines of evidence from our Research Group, showed that in the offspring of rats that suffered of IUGR, the somatosensory cortex had an altered development, as well as the auditory cortex. With clear morphologic changes at the 3rd;5th ant 7th postnatal days. And, in human babies and rats too, a functional significant altered response to specific stimuli, from the auditory cortex, up to 3 months of postnatal age, in suckling babies, when the amplitude of the N1/P2 segment of the long latency wave response to Auditory Evoked Potentials, was dramatically decreased, translating a poor reactivity of the auditory cortex to specific stimuli in IUGR babies. Which in turn, it translated a significant drop of sensitiveness of the auditory cortex responses to serotonergic regulation.

In Prenatal Malnutrition, whether Protein-Calorie or IUGR, the morphogenetic role of 5-HT seems to be significantly altered during cortical formation, by all the metabolic alterations in the 5-HT brain biosynthetic path, which is overactivated and seems to modify its developmental functions during embryonic life. Other groups have confirmed that prenatal alterations of the serotonin synthesis in the rat, are able to significantly alter barrel´s conformation in S1. Or conformation and function of the visual cortex.

We. may confirm that there is a functional fetal serotonergic system, and that it is quite susceptible to be damaged when altering the availability of precursor nutrients like L-Trp, in the case of the 5-HT system early in life. Or other important metabolic precursors involved in specific brain biosynthetic paths. Affected subjects would be dealing with a metabolic serotonergic brain disfunction, since the prenatal life. It remains to follow those IUGR babies, to find out how they would perform adapting or maladapting to their environment, using their developmentally obtained neurologic resources, carrying a subtle neurometabolic disfunction that could befuddle them.