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The epigenetic adaptation hypothesis

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Editorial

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Central hypothesis

What if epigenetic mechanisms could help explain the rising prevalence of obesity, autism-related diagnoses, and infertility in humans? And what if some of these changes reflected maladaptive consequences of an environmental response that once helped preserve species survival? This editorial advances a hypothesis rather than a conclusion: several lines of evidence now link civilization-driven environmental change, both associatively and causally, to the emergence of new human phenotypes.

Dietary change and metabolic programming

Something has changed in our environment that resulted in epidemic of obesity. Amongst the main diet changes that occurred in the last 80 years, the increase of sugar and more importantly fructose is significant. Fructose primarily came from fruit, and fruit is most abundant in the fall. In human diets, this seasonal exposure may have supported energy storage before winter, when food availability was lower. The liver rapidly converts fructose into fat, and one way to maintain this reserve over time is to store it as abdominal fat, which is less readily mobilized under ordinary metabolic conditions.[1,2]

For most of human history, fruit was the main dietary source of fructose. However, beginning in the 1960s, high-fructose corn syrup was increasingly used to sweeten soft drinks. At the same time, fruit juice consumption in children, especially orange juice, increased markedly. As a result, infants, children, and adults began receiving substantial amounts of fructose throughout the year rather than mainly during a seasonal window.

This first dietary shift has lasted for approximately 80 years and continues today. It may have acted additively with other features of modern nutrition, including ultra-processed foods, fast foods, and diets high in both fat and sugar. This new environment contributed to the emergence of a generation of children with obesity, early insulin resistance, and high blood glucose levels, some of whom became parents and may have transmitted altered metabolic responses to the next generation[3,4]

This raises an important paradox in developmental nutrition: how could obesity program obesity as effectively as starvation? Starvation before and during pregnancy is known to influence offspring development, particularly when children are later born into an energy-rich rather than energy-poor environment. This phenomenon is generally interpreted as a short-term adaptive response to anticipated food scarcity.[5,6]

Historically, during winter or other periods of limited food availability, saturated fatty acids/ketone bodies increase in the blood as fat reserves are mobilized to compensate for reduced intake. In that context, the ovary/oviduct/uterus may detect the metabolic state and program the oocyte or embryo for a low-energy environment.[5] But what if these tissues interpret the elevated fatty acids and ketone bodies observed in maternal obesity as a starvation-like signals? And what if this effect accumulates from one generation to the next, until descendants become programmed for obesity even on a normal diet and are then exposed to a high-fructose, high-fat diet?

Evidence from experimental and animal models

This scenario has been reproduced experimentally in mice, supporting the broader idea that maternal undernutrition and overnutrition can both shape offspring metabolic risk through developmental programming, although the precise degree of mechanistic overlap remains to be defined.[7,8] What also remains to be clarified is the early molecular signature of metabolic programming in the oocyte and early embryo that characterizes intergenerational, and possibly transgenerational, effects.

This description is, of course, an oversimplification of the complexity of metabolic programming in gametes and maternally inherited mitochondria. The early embryo also senses its energetic environment as early as the four-cell stage, adapting its metabolism in ways that may influence epigenetic establishment throughout pregnancy.

A major challenge in human studies is that the mother typically provides both the oocyte and the gestational environment, making causal relationships difficult to disentangle. In animals in

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which one female provides the oocyte and another carries the pregnancy, such as dairy cattle, it is easier to distinguish gamete-mediated effects from gestational effects.

In these species, researchers can also obtain valuable biological material, including gametes and embryos, to investigate the molecular pathways involved in parental programming. In dairy cattle, large postnatal datasets can be analyzed for body weight disease outcomes such as infertility, and production traits. When offspring are compared across in vitro fertilization, embryo transfer, and insemination, the programming effect of the gamete donor can be separated from the effect of the gestational carrier. Detailed genetic information extending up to three generations upstream further helps correct for genetic effects and assess the impact of the conception environment on offspring outcomes.[9]

These observations suggest that negative energy balance around conception in high-producing dairy cows may be associated with altered offspring performance, including production and reproductive traits, although the direct causal links requires careful experimental confirmation.[10]

Human fertility, obesity, and neurodevelopmental observations

In humans, fertility is decreasing in both males and females, although several confounding factors remain, including the age at which couples try to start a family. Semen analyses nonetheless suggest that male fertility has declined over the past 50 years.[11] Parental obesity is also associated with lower fertility in both sexes[12,13]

Recent studies also associate autism-related diagnoses with paternal and maternal age at conception[14] and, in some cases, maternal obesity.[15] In addition, exposure to toxicants and endocrine disruptors has increased over the past 50 years and may contribute to human neurodevelopmental outcomes.[16]

This creates a broader paradox in epigenetic research: distinct stressors – including nutritional imbalance, toxicological exposure, and psychological stress – may converge on similar outcomes, including obesity, infertility, and neurodevelopmental differences. Perhaps biological systems have a limited repertoire of adaptive responses to rapidly changing environments and therefore recruit overlapping pathways in response to different forms of stress.

Discussion and conclusion

This leads to a provocative and explicitly speculative question: could autism-related traits, in some contexts, reflect part of a broader biological response to starvation or environmental instability? Autism is associated with behavioral differences and, in some individuals, distinctive cognitive abilities and divergent thinking. Some First Nations perspectives describe autistic children as having special gifts.[17] If starvation was the relevant environmental pressure, could reduce fertility and reduced social behavior be interpreted, cautiously and hypothetically, as potentially adaptive at the species level? This interpretation is not directly demonstrated by the current references and should be treated as a hypothesis-generating idea rather than an established conclusion.

This topic remains sensitive in contemporary society, but emerging evidence may justify careful scientific discussion. The purpose of this editorial is not to offer a definitive answer, but to frame a testable hypothesis linking metabolic programming, fertility, and neurodevelopment within a broader DOHaD perspective.

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