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Review Article

Neuronal basis of reproductive dysfunctions associated with diet and alcohol: From the womb to adulthood

Monika Gawałek, Joanna H. Sliwowska *

Laboratory of Neurobiology, Institute of Zoology, Poznań University of Life Sciences, Wojska Polskiego 71C, 60-625 Poznań, Poland

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ABSTRACT

The theory that individuals are born as *tabula rasa* and that their knowledge comes from experience and perception is no longer true. Studies suggest that experience is gained as early as in the mother's womb. Moreover, environmental stressors like alcohol or inadequate diet can affect physiological systems such as the hypothalmic-pituitary-gonadal (HPG) axis. The effects of these stressors can manifest as alterations in sexual development and adult reproductive functions. In this review, we consider and compare evidence from animal models and human studies demonstrating the role of environmental stressors (alcohol and under- or overnutrition) on the HPG axis. We review the role of alcohol and inadequate diet in prenatal reproductive system programming and consider specific candidate neurons in the adult hypothalamus through which reproductive function is being regulated. Finally, we review evidence from animal studies on the role that alcohol and diet play in fertility and reproductive disorders. We conclude that in order to better understand reproductive failure in animals and humans we need to consider *in utero* development and pay more attention to early life experience when searching for the origins of reproductive diseases.

1. "*Tabula rasa*" theory vs. the early programming hypothesis

It was long thought that individuals are born as *tabula rasa* or "clean slates". However, epidemiological data and animal studies suggest that experience and perception are gained as early as in the mother's womb. This led to the concept of fetal or early programming, according to which early environmental or nongenetic factors can organize or imprint physiological and behavioral systems [1–3]. A strong correlation has been shown between low birth weight, high cortisol levels and later development of hypertension and type 2 diabetes (DM2) [4,5]. A range of studies linked the intrauterine environment with

* *Corresponding author*. Tel.: +48 61 848 7866; fax: +48 61 848 7650.
E-mail addresses: mgawalek@gmial.com (M. Gawałek), joanna.sliwowska@gmail.com (J.H. Sliwowska).
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later hypertension, diabetes, high blood cholesterol, fibrinogen concentrations and polycystic ovary syndrome [1,6,7]. Thus, common adult diseases may originate during fetal development. The biological "purpose" of physiological and behavioral programming is not known. It has been suggested that environmental factors acting on the mother and fetus can alter the set point or responsiveness of physiological systems and thus prepare the organism for the environment into which it will be born. However, if there are adverse factors during pregnancy (e.g., over- or undernutrition, alcohol consumption) or if environmental circumstances later in life are different from what was anticipated, then the physiological adaptations may, in themselves, cause maladaptive responses and predispose the organism to later disease [2,3].

Importantly, some susceptibility to obesity and/or infertility may be transferred from parents to offspring *via* DNA imprinting (e.g., altered methylation pattern). Moreover, acquired instability may be carried onto the next generation and increase the risk of chronic diseases in adulthood [8]. Further, alteration in the epigenome extends beyond DNA methylation at imprinted loci; changes in histone modifications and localization genome-wide at a large number of loci were reported in infertile men [9].

This review is based on experimental studies and epidemiological data looking at the long-term effect of early life insults such as diet and alcohol on the development and functions of the hypothalamic–pituitary–gonadal (HPG) axis. The effects of poor diet and alcohol abuse in adulthood on reproductive functions will be also discussed.

2. Obesity, diabetes and alcohol abuse as major health concerns

Obesity is rising dramatically and is a major risk factor for diabetes. The World Health Organization (WHO) reported that at least 2.8 million people die earlier due to the consequences of being obese or overweight [10]. The severity of the problem is highlighted by the fact that in Europe, the Eastern Mediterranean and the Americas, over 50% of women are overweight [10]. Aside from primary metabolic health problems in people with obesity and diabetes, there are numerous secondary problems including disruptions of the reproductive system [11–13]. In the light of the early programming hypothesis, inadequate energy balance early in life may reprogram the neuroendocrine system, including the HPG axis, and manifest as obesity and diabetes later in life [14,15].

Alcohol abuse can also reset neuroendocrine systems, including the HPG axis. Women consuming alcohol during pregnancy may give birth to children with Fetal Alcohol Spectrum Disorder (FASD). In the most severe cases, children born with Fetal Alcohol Syndrome (FAS) have craniofacial malformations, growth deficiencies and central nervous system abnormalities [16,17]. Aside from the primary problems reported in children with FASD there is a wide range of secondary problems, including reproductive system defects. Despite overwhelming evidence about the harmful effects of alcohol on the fetus, FAS incidence remains high. In the U.S., during the 1980s and 1990s there were 0.5–2 FAS cases per 1000 births, and as many as 10 FASD cases per 1000 births [18]. Animal models of prenatal alcohol exposure (PAE), obesity and diabetes allow us to better understand the relationships between those insults and disruptions in the reproductive system.

3. The hypothalamic–pituitary–gonadal axis

Reproductive function in vertebrates is regulated by the cascade of events organized in the HPG axis. The hypothalamus is situated on top of the axis and produces gonadotropin-releasing hormone (GnRH). The anterior pituitary secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Gonadotropins regulate folliculogenesis in females, spermatogenesis in males, and steroid biosynthesis in both sexes. The gonads also release sex steroid hormones (estrogens, progestins, and androgens). Sex steroid hormones act at the peripheral target organs as well as the brain anterior pituitary, providing feedback in the HPG regulation. Although each level of the HPG axis is critical for regulation of reproductive functions, GnRH is the primary regulator of the entire system [19].

4. Early life insults and the HPG axis: potential players and their targets. Role of KNDy (kisspeptin/neurokinin B and dynorphin) neurons

It would be particularly helpful to identify the regions of the brain affected by early nutritional insults. The hypothalamus plays a role in controlling metabolic and reproductive functions and could be a key target for early life insults [20]. However, the role of altered neural organization within the overall effects of nutrients on prenatal programming has not been studied to the same degree of detail as the role of peripheral organ function. Insulin, which is elevated in offspring of fat-fed dams [21], and insulin-like growth factors are thought to be pivotal to neuronal differentiation, synapse formation and consolidation in the hypothalamus [22]. The latter plays a crucial role in regulating food intake [21,23]. Insulin and leptin, two important hormones secreted into the bloodstream in proportion to the amount of adipose tissue, are often studied in animal models of obesity, diabetes and undernutrition [24]. Those hormones are blood–borne and cross the blood–brain barrier to act upon the brain, including the hypothalamus's arcuate nucleus (ARC) [25]. In the ARC, neuropeptide Y (NPY), agouti-related peptide (AgRP) and proopiomelanocortin (POMC), which control metabolism, are synthesized and released [26–29]. In healthy organisms, adipocyte stores are correlated with the size of fat tissue. Secretion of insulin and leptin inhibits NPY/AgRP and stimulates POMC neurons, providing feedback that inhibits food intake [28]. However, offspring of diabetic pregnant rats displayed increased hypothalamic insulin levels. They had a higher number of NPY-positive neurons in the ARC at weaning [30] and as adults [22]. In addition, KNDy neurons (expressing kisspeptin, neurokinin B and dynorphin), which control reproductive functions were recently identified in the ARC [31]. Thus, the ARC seems to be a place where integration of metabolic and reproductive functions occurs. In this review we