Cyberspace Chat

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Part II: Beyond genetics—evidence suggests environmental endocrine disrupting chemicals (EDCs) impact our hormones and could provide epigenetic influence in AGA

In the last Cyberchat column, a discussion began with Mike Beehner's presentation of monozygotic female twins who, despite their identical genotype, had remarkably different degrees of hair loss. In a survey of monozygotic twins, differences in hair loss patterns were reportedly linked to smoking, alcohol consumption, stress, and sun exposure.[1] However, no scientific explanation was suggested for these findings. This engendered a conversation about epigenetic factors that may influence variant expression of androgenetic alopecia (AGA). In part II, the discussion of epigenetic influences continues with a review of the scientific evidence for environmental exposures shown to influence our hormonal and epigenetic homeostasis. In evaluating hair loss, it is important to recognize that although androgen metabolism and dihydrotestosterone (DHT) have been the recent focus for hair growth control and regulation, a comprehensive review of the research has shown that hormones previously considered to be "female," such as prolactin and estrogen, are important regulators of hair growth in both genders and are actually produced in the hair follicle. Furthermore, it appears steroid receptors are able to cross communicate with each other, underscoring the interdependent nature of these hormones.[2,3] Factors that up or down regulate or interrupt these hormone pathways could influence hair growth, and AGA. Therefore, as we look to answer the question whether environmental factors influence AGA, we must consider a complex, and as yet not fully described, interaction of androgens, estrogens, and progesterone. Additionally, the non-steroid hormones, thyroid and prolactin, also influence hair growth.[3,4] Steroid hormones and thyroid hormone belong to a family of hormones that signal through nuclear receptors to act as transcriptional factors. Epigenetics appears to be a common mechanism for regulating the expression of the nuclear receptors in hormone-sensitive organs.[5]

To review, epigenetics refers to the non-DNA cellular controls that regulate gene expression via activation/silencing of genes, or up or down regulation of genetic transcription. The agouti mice studies referred to in part 1 of this article captured the attention of geneticists and nutritional scientists by illustrating how dietary manipulation with specific nutrients (methyl donors) altered genotype expression causing dramatic phenotype variation in genetically identical mice.[6] When we consider dietary and environmental influence, we must understand this includes what we inhale, swallow, or, in some cases, touch and absorb—so food is not the only issue that matters. It is consumable exposures we don't know about that will be the focus of this column. Furthermore, it is important to consider the complexity of interpreting molecular and epigenetic effects. For instance, epigenetic regulatory controls can be inherited and passed transgenerationally—so some gene expression seen in adulthood occurs as a result of experiences or influences from a great-grandfather/grandmother.[7] Genetic variants can determine the effects of an external or epigenetic response. For example, certain Vitamin D receptor (VDR) polymorphisms can predispose to colon cancer, and nutritional supplements can eliminate the increased risk that manifests in colonic cells. Some dietary influences have also been shown to vary based on pre- or post-natal exposure, as well as duration of exposure to the activating/deactivating mechanism. These are often a methylation/demethylation or acetylation/deacetylation reaction.[8,9] The epigenetic methylation process described in part 1 appears to have a role in hair loss expression relative to the androgen receptor (AR) gene. Interestingly, the most recent gene to be proposed as part of the polygenic entity of AGA is the HDAC 9 gene on Chromosome 7.[10] The fact that this is a histone deacetylation gene suggests a possible epigenetic regulatory function. To further elucidate the complexity of epigenetic regulation, it must be remembered that each cell in our body has an identical genome, with variable gene expression to differentiate liver, pancreas, or dermal papilla cells. The variable gene activation may also determine whether or how an epigenetic effect occurs for a particular cell. Epigenetic science has unveiled many of the ways non-genomic controls create variable gene expression. This is important because epigenetic influences are modifiable. This provides perspective for reviewing evidence that points to a group of chemicals that act to modify hormonal and epigenetic influences known as endocrine disrupting chemicals (EDCs), which are ubiquitously used in the industrialized world and offer a common population exposure. These chemicals act with estrogenic, androgenic, anti-estrogenic, and anti-androgenic effects. Because of the ubiquitous nature of exposure to EDCs, they have become part of our consumption either directly or via the food chain. In the latter instance, it has been suggested we are what we eat-eats.

In 2009, an Endocrine Society Scientific statement was published following a comprehensive task force review of EDCs identified as able to disrupt the normal endocrine axis in both animals and humans. The result was a 50-page report identifying the chemicals or molecules, how the exposure occurs, and the scientific evidence that suggests that even in small amounts they are influencing our hormone and epigenetic homeostasis.[5,11] The hormonal effects of these EDCs are believed to cause increases in diabetes, obesity, prostate and testicular pathology, polycystic ovary syndrome as well as breast disease and cancer.

While the Endocrine Society statement was not designed to specifically address hair loss in AGA, among the substances included in this review are several that have an effect on the hormones involved in the hair growth paradigm. For those who would like a more comprehensive review, the entire report is referenced and easy to download in a PDF format.[11] As defined by the U.S. Environmental Protection Agency (EPA), an EDC is "an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process." Researchers now have a broader understanding of the ways EDCs work, including their action on nuclear receptors, such as androgen, estrogen, or thyroid receptors, and enzymatic pathways for synthesis and metabolism. EDCs can be natural or synthetic. The EPA estimates we are being exposed to hundreds of chemicals daily, which creates difficulties and limitations for interpreting the effects from a single EDC exposure.

The following is a list of some of the pertinent synthetic EDCs mentioned in the review article and information on how they are used to create an exposure, as well as the findings in animals and/or humans to document the hormonal effect:

Polychlorinated biphenyls (PCBs): These are synthetic, lipophilic, halogenated compounds used in electrical equipment such as transformers, capacitors, heat transfer and hydraulic systems, also cutting oils and lubricants. PCBs have also been used in products such as sealants, carbonless copy paper, paints, adhesives, plastics, flame retardants, and to control dust on roads. Although their production in the U.S. and Australia was banned in the late 1970s, and heavy restrictions have been imposed on their use in Europe since 1985, continued exposure occurs through ingestion of contaminated foods (fish, meat, dairy products, contaminated rice oil). PCBs can be transported long distances and have been identified in remote areas far from locations where they were manufactured or in use. Because PCBs bioaccumulate in adipose tissue, with a half life of 1-10 or more years, measurable levels are found in most of the U.S. population.[11] Epidemiological evidence across several different surveys including the U.S., Sweden, and Taiwan consistently showed an inverse relationship between PCBs and semen quality, with reduced sperm motility. Low levels were sufficient to have an effect.[12]

Hormonally, PCBs have been shown to have estrogenic and antiandrogenic activity. In animal models, PCBs reduce circulating levels of T4 and can interact with the thyroid receptor. They have been observed to cause both agonist and antagonist responses to the TR, with complex but deleterious effect. It is considered to be a neurotoxin in humans, with evidence of cerebellar sensitivity.

Plastics such as Bisphenol A (BPA): BPA is a synthetic monomer used in the production of polycarbonate plastics and epoxy resins and is produced at a rate of more than 800 million kg annually in the U.S. BPA has been used in the plastic that coats food cans, as well as in dental sealants and plastic bottles. It can be halogenated to produce a flame retardant (>60,000 tons/yr). Estimated consumption of BPA from epoxy lined food cans is estimated at 6.6ug/person/day. Levels in human serum in the U.S. have increased between 1977-1999, with concentrations ranging from 0.4-3.3ng/g in serum lipids. Infants were noted to have 1.6-3.5 times higher concentrations than adults. In a CDC survey of over 2,500 Americans, 93% were found to have BPA in their urine, with higher levels in adolescents and children. BPA readily crosses the placenta in rodents. Because of concerns about BPA toxicity, its use is banned in Canada, and in the EU for baby bottles. In 2011, China and Malaysia joined in banning the use of BPA in baby bottles. However, it is not clear how much of an effect this will have on overall population exposure to BPA.

Some of the effects of BPA observed in rodent models include increased prostate size, aberrant development of prostate and urethra, and prostate cancer. The proposed mechanism is increased ER alpha expression in the hypothalamus and increased AR expression in the prostate. Rat models reveal that early life exposure increases risk for prostate carcinogenesis, even at low doses. The result among BPA-exposed rats if exposed to estrogen later in life was that 100% developed intraepithelial neoplasia; while those who had not been exposed had only a 40% incidence. The BPA-exposed animals were shown to have permanent epigenetic changes, revealing altered DNA methylation patterns in multiple genes that altered gene transcription, apparently predisposing them to carcinogenesis. BPA also has the capacity to promote ER-dependent transcription, and while it may have significantly less potency than endogenous estrogens, it is a full agonist for ER alpha and ER beta.[11] It appears to have an antagonistic effect on the thyroid receptor (TR beta). In rats this has been shown to produce an endocrine profile similar to thyroid resistance syndrome where T4 levels were elevated but TSH remained normal. It was concluded that BPA in this setting inhibits TR beta negative feedback, and reduces T3 mediated gene expression by enhancing activity between nuclear receptors and corepressors. The neuroendocrine effect of BPA-exposed rats was a thyroid resistance syndrome that looks similar to ADHD in humans.[14] BPA is speculated to have effects on the female reproductive system with increased mammary gland density and early puberty. Potential mechanisms of action include an increased number of progesterone receptor positive epithelial cells and reduced sulfotransferase inactivation of estradiol.

The following EDCs have an impact on androgen homeostasis:

Plasticizers (Phthalates): These are used in the manufacture of flexible, vinyl plastic in consumer products such as flooring, wall coverings, food contact and medical devices. Also used in lacquers, varnishes, and coatings including some time-released pharmaceutical preparations. Phthalates can be found in personal care products such as perfumes, lotion, hair gels, and cosmetics that may include phthalates as a solvent. Phthalates have been combined with PVC, a more brittle plastic, to produce a softer plastic for toys. However, the phthalate chemical can slough off increasing the risk of contamination when handled. According to the most recent population survey of chemical exposures, the CDC reported that virtually 100% of persons studied revealed evidence of phthalate exposure.[15]

Concerns about phthalate exposure as an EDC focused on its effect in the male reproductive tract. In a recent study looking at the impact of phthalate exposure on over 100 three-month-old baby boys in Denmark and Finland, findings included reduced testosterone production and other endocrine abnormalities.[16] These data on reproductive hormones provides additional evidence that human testicular development and function may be vulnerable to perinatal phthalate exposure.

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In human males, a phenomenon known as testicular dysgenesis syndrome (TDS) arising from disturbed prenatal development results in cryptorchidism, hypospadias, oligospermia, and testicular cancer. Epidemiological data directly linking TDS to EDCs is lacking; however, in rodent models, a TDS-like condition has been found after fetal exposure to phthalates. The mechanism of action is believed, as previously noted, to be decreased testosterone synthesis.[11]

Polybrominateddiphenyl ethers (PBDEs): These are widely utilized as flame retardants and have been used as additives to polyurethane foam in furniture and carpet padding. Some formulations were used in electronics including televisions and computers. Concerns about physiologic effects have reduced the number of formulations available in the U.S., and some have been banned in the EU since 2004. Despite various plans and efforts to phase out these compounds, as a result of widespread consumer use they are an ubiquitous contaminant of residential indoor air and dust globally. Products containing PBDEs remain, and because of the long half-life, it is expected that human exposure to this compound will continue for years. Exposure in the U.S. study in terms of serum body burden was higher than in Japan, China, Belgium, and Australia reflecting various formulations. The CDC reported that among 1,985 participants in the National Health and Nutrition Examination Survey (NHANES) in 2003-2004, measurable levels of PBDEs were found in 60% of participants.[17]

Many animal studies have reported behavioral and neurostructural brain abnormalities in animals exposed to PBDEs.[18] PBDEs are known to bind to the thyroid hormone receptor and that two hydoxylated molecules of PBDE can bind to both TR alpha and beta receptors.[10,18] Recent experimental data also indicates anti-androgen properties of certain molecular compounds using PBDEs.[20]

Non-persistant pesticides (Organophophates, Atrazine-Carbamates, Pyrethroids, Methyl Bromide, Vinclozolin): These are insecticides, herbicides, and fungicides. Because they are widely used, most of the general population is exposed through ingestion of foods that contain low levels of residue, or through inhalation or dermal exposure from home or commercial contact.

Female reproductive disorders in humans have shown an association with pesticides, revealing persistent organochlorine chemical isolated from ovarian follicular fluid of women undergoing *in vitro* fertilization (IVF). There is also epidemiologic evidence of increased female infertility in women occupationally exposed to pesticides.[11] Similarly, several epidemiological studies support an association between these pesticides and altered semen quality, though often collected in the setting of multiple, simultaneous pesticide exposure.[21] The fact that living in an agricultural area increases risk for cryptorchidism and hypospadias offers support to the observed link between EDCs such as organochlorine pesticides to genital anomalies in men.

Methyl bromide is a fungicide used in farming. In 1993, a collaborative study from the National Cancer Institute and National Institute of Environmental Health Sciences evaluated 90,000 participants from an agricultural lifestyle and health survey and found a definite association with development of prostate cancer. While some of these chemicals were not found to have a direct estrogenic or androgenic action, they were found to inhibit the cytochrome P450 enzymes, which metabolize estradiol, estrone, and testosterone. It is hypothesized that these compounds exert their influence by interfering with steroid metabolism increasing the bioavailability of estrogens. In men, these estrogenic EDCs have been linked with an increased risk for prostate cancer through ER activation.[11]

Vinclozolin is a fungicide used to treat wine grapes and other fruits and vegetables. It is considered to be an anti-androgen. In fetal rats, exposure was related to hypospadias, undescended testes, delayed puberty, and prostate disease in subsequent generations. The apparent mechanism of action is altered DNA methylation in germ cell lines,[22] and reduced ER alpha.

Triclosan is an antibacterial chemical found in detergents, soaps, skin cleansers, deodorants, lotions, creams, toothpastes, and dishwashing liquids. In a 2003-2004 survey by the CDC of more than 2,500 people, 75% of participants had urinary levels of triclosan.[23] Animal studies indicate that triclosan disrupts steroidogenesis and has antiandrogenic properties that reduce testosterone production.[24,25]

Some EDCs are natural compounds, and among the most frequently consumed are the phytoestrogens, from soy products. A chemical called Genistein is a phytoestrogen that binds to ER-alpha and ER-beta, and at low concentrations is estrogenic with an inhibitory effect on lipogenesis. At higher concentrations, however, it promotes lipogenesis via the PPAR gamma pathway, which is independent of ER. Gender differences on the effect of genistein occur, which involve ER-beta and adipose deposition and insulin resistance. It has been suggested that soy isoflavones are thyroid peroxidase inhibitors preventing the organification of iodine for thyroid activity. Human infants fed soy formula had twice the rate of autoimmune thyroid disease as teens.[11] In the U.K., soy formula requires a prescription due to concerns about its effects on developing infants. However, in a 2-year controlled study in post-menopausal women on isoflavone supplementation, there was no evidence of thyroid or other hormonal disturbance.[26]

Metalo-estrogens are naturally occurring EDCs.

Arsenic is a heavy metal found in water in many areas of the country. A recent report from the AMA indicated higher than recommended levels in some infant formula and in some breakfast bars.[27] Studies have reported arsenic disrupts glucocorticoid receptor mediated transcription, with low levels stimulating transcription while higher levels are inhibitory. New findings also indicate progesterone receptors display a similar response. The exact mechanism is not clear, but it is not due to altered steroid or receptor levels.[28]

Metalloestrogens refer to a group of metal ions that have been shown to have estrogenic activity. In fact, it is now known that divalent cadmium, copper, cobalt, nickel, lead, mercury, tin, and chromium ions, as well as arsenite, selenite, and vanadate, activate responses mediated by estrogen receptor (ER). It is of great interest to note the estrogenic potencies of metal ions were 25-100% of the activity of 17β-estradiol, making metalloestrogens more potent than phytoestrogens, and most xenoestrogens of concern.[29]

Discussion

Levels of circulating and active steroid and thyroid hormones depend on the rate of biosynthesis, as well as the amount of protein bound hormone, and balance between activation and break

down in target tissues. They also depend on the functionality and binding at the hormone nuclear receptor. As previously noted, epigenetics appears to be a common mechanism by which hormone sensitive organs are regulated.[5] An unexpected regulatory micro RNA or promoter methylation of the receptor gene can greatly affect end organ sensitivity for an endocrine axis. EDCs work by mimicking or antagonizing function of a particular hormone or its receptor to disrupt the pathway or effect. The previous list of EDCs represents a short list of environmental exposures that is considered to be much more extensive. Among the EDCs listed, in addition to their hormonal effect, there are documented epigenetic effects as follows: BPA (hypomethylation in prostate tissue), BPDEs (decrease in global gene methylation), Vinclozalin (altered DNA methylation patterns), phytoestrogens (hypomethylation), heavy metals such as cadmium (hypermethylation).[29] Not all EDCs have been studied for their epigenetic effects, and some are the subject of ongoing investigation. Many EDCs were in use for decades before their physiologic potential came to light. Based on the hormonal milieu of the hair follicle, and the known interaction between estrogens and androgens, it seems likely the hormonal and epigenetic effects of these chemicals are in a position to influence the cascade that controls AGA. Estrogen appears to modify androgen metabolism, and the reverse is also apparent.[2] Therefore, EDCs that either promote or inhibit estrogen or androgen may up or down regulate hair growth cycling and their epigenetic influences may activate or repress regulatory genes for hair growth. It is also appreciated that extrapituitary prolactin is produced in hair follicles and may work with estrogen to regulate transcription of important hair growth modulatory genes. Some of the EDCs mentioned are known to impact thyroid hormone function and hair growth. One of the ways they may do this is by the interaction between prolactin and TRH. In hypothyroid states, TRH, which is elevated in the normal HPA axis, stimulates and can cause hyperprolactinemia, which is associated with prolonged catagen in the hair follicle.[30] The role of estrogen in hair growth cycling is incompletely identified; therefore, it is not currently possible to predict all effects that various EDCs may have on accelerating or attenuating AGA. What can be anticipated is that as we further elucidate the role of these hormones and the epigenetic effects of EDCs, we can better identify how they impact hair loss or growth. Based on many of the adverse affects these chemicals appear to have on male and female reproduction, finding a way to detoxify or avoid them seems daunting, and will need to be the subject of a different discussion.

So with all these EDCs, is there any evidence for an impact on AGA? Perhaps. Consider the fact that we now see early development of AGA reported in up to 14% of Caucasian teen males. With age, the incidence rises to include nearly 80% of men and between 29-42% of Caucasian women over 70 years of age.[31] We can see there is high genotype prevalence in Caucasian men. What isn't known is whether a greater percentage of the population may be losing hair sooner or later, and in a greater or lesser pattern than expected by genetics alone. Findings in the recently reported epidemiology of AGA in Asia may be more revealing. In a large population survey of Chinese men and women (n > 15,000), only 2.8% of men in their 20s were affected, which increased to 41.4% of men affected over age 70. In women, AGA was observed in only 1.8% of women in their 20s, rising to 11.8% of women affected in those over 70 years old. Korean AGA prevalence was similar: in young men, 2.3% were affected in their 30s and 46.9% over 70 years old. In Korean women, again prevalence was low, 0.2% in their 30s and 24.7% in those over 70 years. However, a surprising and unexplained finding in both the Korean and Chinese surveys was a large number of affected individuals who reported no family history of hair loss: 29.7% of men and 19.2% of women in the Chinese survey, and 48.5% of men and 45.2% of women in the Korean study.[32,33] This perplexing finding raises the question of whether the hair loss was actually AGA; and, if so, was this the result of genetic mutation? Given the rarity of gene mutation, and the large percentage affected, this is unlikely. Notably in the Korean survey, many of the men had thinning but were not bald or exhibiting the usual patterned hair loss. As we have been discussing, another intriguing possibility is that epigenetic factors are activating and silencing genes in response to dietary or environmental exposures. The new science of epigenetics is expected to account for much of the variable changes in the genetic expression of hormonally mediated entities such as AGA.

Conclusion

The subject of environmental chemicals capable of disrupting complex endocrine pathways via direct or epigenetic mechanisms requires a rethinking of genotype as the overriding determinant of cellular function and activity. Epigenetic influences are surfacing as real mediator of variations in function and phenotype. Until we have answered the questions of how each of the androgen, estrogen, progesterone, and prolactin mediated genes, receptors, and various molecular components and pathways interact, we cannot predict with certainty how or if certain EDCs will affect AGA. But it seems highly likely these environmental chemical exposures with their endocrine influences are changing cellular activity, and are influencing hair cycling in AGA. In part 3 of this series, we will take a closer look at the subject of nutrigenomics, stress, cigarettes, and alcohol to review the scientific evidence to support these factors as determinants of hair loss in AGA.

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