Chemical environmental factors: Can they affect acne?

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Introduction

Acne vulgaris represents a skin disorder characterized by chronic inflammation of the pilosebaceous units.[1] Acne affects nearly 80% of the adolescent population,[2] but persists into the 20s and 30s in 64% and 43% of adults respectively.[3] Furthermore, epidemiological evidence suggests that its prevalence is considerably higher in industrialized societies due to the changes in lifestyle and the influence of environmental factors on individuals with genetic predisposition.[4] Androgens have been long incriminated in the pathogenesis of acne as evidenced by onset at puberty (when excess androgen activity is observed)[5,6] and presentation in association with hyperandrogenism.[7] The relation of acne and androgens is further supported by studies showing that castrated men or eunuchs do not develop acne and that postadolescent resection of gonads or treatment with antiandrogens decreases sebum production and ameliorates acne.[8-10]

Endocrine-disrupting chemicals are defined as exogenous factors interfering with synthesis, secretion, transport, metabolism, binding or elimination of natural hormones. Endocrine-disrupting chemicals are widely used in the production of industrial, pharmaceuticals and personal care products. Exposure to endocrine-disrupting chemicals even in small concentrations can lead to endocrine disorders such as the imbalance of sex hormones.[11]

Several endocrine-disrupting chemicals which exist ubiquitously in the environment may induce excess androgenic stimulation or elevated androgen levels. Since androgens play a pivotal role in acne, the present article suggests that exposure to endocrine-disrupting chemicals, in combination with other agents, may be a crucial factor for acne pathogenesis.

Endocrine-disrupting Chemicals

Endocrine-disrupting chemicals interacting with androgen receptors

Endocrine-disrupting chemicals based on their interaction with androgen receptors, are classified into agonists and antagonists. Agonists bind to androgen receptors and mimic the biological activity of androgens leading to amplified cellular response. In the pilosebaceous units, androgen receptor agonists induce hyperplasia of the sebaceous gland, excessive sebum production, proliferation and cornification of keratinocytes.[12] Araki *et al*. were the first investigators who showed that two organic compounds, 2-tert-butyl anthraquinone and benzanthrone which are used in the manufacture of dyes and food package, were weak agonists of rat androgen receptors and their androgenic activity was 1000-10000 times less potent than that of dihydrotestosterone.[13] Relatively, recent studies suggested that brominated flame retardant used in construction materials may activate human androgen receptors with high potency.[14,15] Furthermore, particularly, important were the results of an *in vitro* study which identified six commonly used ultraviolet filters (benzophenone-2, isopentyl-4-methoxycinnamate, octyl methoxycinnamate, octocrylene, homosalate and octyl salicylate) acting as human androgen receptor agonists. Interestingly preparation of the cultures with the aforementioned ultraviolet filters and dihydrotestosterone resulted in the inhibition of dihydrotestosterone activity, indicating that ultraviolet filters may act as pure human androgen receptor agonists only in the absence of androgens.[16] Phthalates represent an additional group of chemicals for which there are numerous studies demonstrating their interference with endocrine system. Incubation of human cells with three broadly used phthalates (mono-n-butyl phthalate, dibutyl phthalate and di-2-ethylhexyl-phthalate) induced dose-dependent increase of androgenic activity, whereas the subsequent addition of flutamide reversed the aforementioned effects.[17]

Endocrine-disrupting chemicals acting without binding to androgen receptors

Ongoing research for endocrine-disrupting chemicals has revealed a novel class of chemicals which induce androgenic activity without being androgen receptors agonists. Triclocarban and other structurally similar urea compounds which are used in detergents and personal care products as antibacterial or antifungal agents have been found to amplify the cellular response and transcriptional activity induced by endogenous androgens without actually binding to the androgen receptors. No androgenic effect was observed

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when cells expressing human androgen receptors were incubated exclusively with triclocarban and neither did triclocarban compete with testosterone for binding to androgen receptors on a competitive binding assay.[18]

Pesticides are another group of endocrine disruptors which induce hormonal abnormalities by inhibiting aromatase activity. Aromatase which is a member of the cytochrome P450 superfamily is a determinant factor for sex hormones' balance because it converts androstenedione and testosterone to estrone and estradiol, respectively. Consequently, inhibition of aromatase activity results in the accumulation of androgens. Seven commonly used pesticides and glyphosate-based herbicides (prochloraz, imazalil, propiconazole, fenarimol, triadimenol, triadimefon and dicofol) were documented to significantly inhibit aromatase activity in human placental microsomes.[19-21]

Endocrine-disrupting chemicals acting through multiple pathways

Bisphenol A is an endocrine disruptor which has been incriminated in inhibiting aromatase synthesis as shown by the inverse correlation of aromatase mRNA and bisphenol A levels in the culture of rat ovarian granulosa cells.[22] *In vitro* studies on human cells have shown the inhibitory effect of bisphenol A on aromatase activity which depended not only on the concentration but also on time exposure.[23,24] Short time incubation (10 min to 6 h) enhanced aromatase activity, whereas long time incubation (18 h) caused dose-dependent reduction. Apart from aromatase, it was suggested that bisphenol A may reduce the activity of other male-specific P450 isoforms which play a crucial role in oxidative metabolism of androgens. Intraperitoneal treatment of rats with bisphenol A led to decreased hydroxylation and excretion of testosterone, resulting in increased levels of free testosterone.[25] Interference of bisphenol A with human sex hormone binding globulin is an additional mechanism leading to increased free testosterone. Bisphenol A was found to displace endogenous androgens from human sex hormone binding globulin binding sites, despite its low binding affinity.[26]

Some studies have demonstrated the androgenic potential of polychlorinated biphenyls which caused dose-dependent stimulation of rat androgen receptors.[27] Consistent with these results, a bioluminescent androgen screening assay showed that polychlorinated biphenyls may increase androgen receptor-mediated transcriptional activity.[28] In another *in vitro* study, very low levels of estradiol were found in the media of a culture of human placental cells treated with polychlorinated biphenyls mixture and dehydroepiandrosterone. The researchers suggested that polychlorinated biphenyls mixture abolished the conversion of dehydroepiandrosterone to estradiol by inhibiting aromatase activity.[29]

Tributyltin remains one of the most significant pollutants of the marine and aquatic environment despite its prohibited use. This endocrine disruptor inhibits aromatase activity as shown by the increased testosterone and decreased 17-β-estradiol levels in male rats treated with tributyltin.[30] The above findings were also confirmed by an *in vitro* study on human cells.[31] In addition, there are studies showing enhancement of the androgenic response after the incubation of cells with tributyltin and dihydrotestosterone, indicating a presumptive synergistic action.[32] Furthermore, it was suggested that tributyltin may elevate androgen levels by inhibiting the sulfur conjugation of testosterone and its active metabolites, resulting in its limited excretion.[33]

Discussion

Although research in the past years has significantly contributed to better insights into the pathogenesis of acne, there are still many pathways remaining to be elucidated. Persistently high prevalence, increase in chronic forms and poor response to treatment suggest the role of as yet unknown factors in its causation. As previously demonstrated, several endocrine-disrupting chemicals have the potential to increase levels of androgens or cellular response to them; however, not all of them are able to induce acne. Though it has been hypothesized that stimulation of androgen receptors by endocrine-disrupting chemicals may contribute to its pathogenesis, a definite causal relationship between such chemicals and acne is yet to be established. Exposure to these environmental agents may be a determinant factor which in combination with excess sebum production, altered follicular growth, *Propionibacterium acnes* colonization and inflammation, triggers the initiation and the development of acne.

The potential contribution of endocrine-disrupting chemicals to acne pathogenesis is important due to the widespread use of such chemicals in a huge variety of consumer goods and even children's toys.[34] Due to the high bioaccumulation and low biodegradation rates, endocrine-disrupting chemicals are found to persist in sediment, air, water and animals. It is worth noting that they have been easily detected in both human urine and plasma samples and in breast milk, clearly showing the extent of human exposure.[35,36] It is still debatable if the prevailing concentrations of endocrine-disrupting chemicals can cause androgenic effects in humans. This dose–response relationship has raised controversies because of the relatively low amounts of endocrine-disrupting chemicals in the environment. In addition, most of the data for endocrine-disrupting chemicals has been derived from *in vitro* and animals studies. Since acne is a skin disorder exclusively seen in humans, the effect of such chemicals on acne pathogenesis cannot be studied in animal models. On the other hand, simply extrapolating data from *in vitro* studies may be not be wise either. Accurate evaluation of the effects of endocrine-disrupting chemicals on pilosebaceous units requires human studies of long-term exposure to low concentrations and to mixtures of such compounds. The above review could serve as a stimulus to conduct *in vivo* human studies or epidemiological researches to assess the role of the environment on acne pathogenesis.

Conclusion

The present article emphasizes the constant interaction of humans with their environment. According to the results of *in vitro* studies, endocrine-disrupting chemicals are able to elevate androgen levels and consequently it is suggested that they may also contribute to acne. Due to the absence of clinical studies, it is not currently possible to draw conclusions regarding the importance of this hypothesis, but it might stimulate the design of large-scale studies to obtain an in-depth knowledge of acne.

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Conflicts of interest

There are no conflicts of interest.

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