Effects of nonylphenol on hyperadrenalism and metabolism in male rats

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Nonylphenol (NP) is an environmental endocrine-disrupting chemical (EDC) that has been detected in human cord blood and milk. It is unavoidable that human fetus and infant exposure to this environmental contaminant. We previously observed that developmental NP exposure led to increased body weight, elevated plasma adrenocorticotropin (ACTH), higher production and concentrations of corticosterone and aldosterone, and more 11β-hydroxysteroid dehydrogenase I (11β-HSD1) expression/activity during the first generation at the adult stage. The “fetal origins of adult disease” phenomenon appears to be based on epigenetic modifications during the sensitive developmental period. Epigenetic modifications during development can be “inherited” after differentiation by DNA methyltransferases. Without intervention, NP-induced Cushing’s syndrome can impact the health of an individual for life. We have reported that recovering from NP-induced Cushing’s syndrome requires one full generation for male rats (F2 generation recovers from the NP-affected F1 generation). The logical treatment plan for the F1 generation consists of counteracting the elevated 11β-HSD1 activity because epigenetic modifications cannot be effectively reversed. The inhibition of 11β-HSD1 activity has become a potential treatment plan. PF915275 (PF; 4-cyano-biphenyl-4-sulfonic acid (6-amino-pyridin-2-yl)-amide) is a selective inhibitor of 11β-HSD1, and an initial clinical trial has proven its safety and efficacy. We have reported that PF915275 can reverse/alleviate NP-induced Cushing’s syndrome. This study showed a potential direction for the treatment of ENDR-induced Cushing’s syndrome and pandemic metabolic syndrome.

Keywords: nonylphenol; hyperadrenalism; metabolism

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Since the book “Silent Spring” [1] was written, people have realized that the man-made chemicals that are intended to benefit humans, such as dichlorodiphenyltrichloroethane (DDT), diethylstilbestrol (DES), and bisphenol A (BPA), also have a negative impact on the environment, on wildlife and on public health. The main mechanism by which these chemicals have influence is that they interfere or disrupt normal endocrine regulation, especially the estrogen...
pathway. Due to previous tragedies that have been observed in human reproductive integrity, namely DES \[2, 3\], studies have focused on the impact of endocrine disruptors (ENDR) on reproduction \[9\], teratology, and reproductive oncology. Pandemic metabolic syndrome, which encompasses obesity, diabetes, and hypertension, is a global public health concern \[5, 6\]. Convincing evidence suggests that caloric intake and physical activity are not the only factors responsible for metabolic syndromes around the world \[7\]. Baillie-Hamilton \[8\] theorized that metabolic disease, namely obesity and hypertension, coincided with the introduction of synthetic organic chemicals, many of which are ENDrs. Nonylphenol (NP), an ENDR which has been reported to have weak estrogenic activity \[9\] is also a nonylphenol ethoxylate degradation product as well as a widely used non-ionic surfactant in agriculture and industry. It is also used in household products such as detergents, cleaners, indoor pesticides, cosmetics, and food packaging (US EPA RIN 2070-ZA09). Chronic human adrenal glucocorticoid hormone elevation can lead to Cushing’s syndrome, which is associated with abdominal obesity, glucose intolerance, and hypertension. These symptoms are similar to those of metabolic syndrome. In our previous study, NP stimulated glucocorticoid and mineralocorticoid release from cell cultures \[10, 11\]. NP stimulating adrenal activity to increase adrenal corticoid hormone might lead to Cushing’s syndrome from these in vitro studies.

Such wide application and use in household exposure makes NP detectable in urine samples worldwide \[12, 13\]. NP accumulation in human adipose tissue has also been observed \[14, 15\]. Moreover, recent attention has been given to the detection of NP in human cord blood \[16\] and in human milk \[17, 18\], making fetus and infant exposure to this contaminant unavoidable. By the concept of “fetal origins of adult disease” \[19\], the developmental exposure to ENDrs can have wide and long lasting consequences. The impact of NP exposure during developmental period needs careful examination for public health concern. In the study \[20\], male adult offspring (F1) developmental exposure NP water showed (1) hyperadrenalism was observed in the form of elevated plasma ACTH, corticosterone, and aldosterone levels, and by a decrease in hypothalamic-pituitary-adrenal (HPA) negative feedback system sensitivity. (2) Elevated 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) activity is associated with obesity and metabolic syndrome \[21-23\], and the increased liver 11β-HSD1 protein expression. (3) Increased aldosterone synthase activity, 11β-hydroxylase activity and steroidogenic acute regulatory (StAR) protein expression in adrenal. This observation supported Barker’s hypothesis of the “fetal origins of adult disease” \[19\]. Increases in 11β-HSD1 activity are associated with obesity and metabolic syndrome which has been identified as an intracellular Cushing’s state \[24\]. The “fetal origins of adult disease” phenomenon appears to be based on epigenetic modifications during the sensitive developmental period. Epigenetic modifications during development can be “inherited” after differentiation by DNA methyltransferases \[25\]. Without intervention, NP-induced Cushing’s syndrome can impact the health of an individual for life. We have reported that recovering from NP-induced Cushing’s syndrome requires one full generation for male rats (F2 generation recovers from the NP-affected F1 generation) \[26\]. The logical treatment plan for the F1 generation consists of counteracting the elevated 11β-HSD1 activity because epigenetic modifications cannot be effectively reversed.

Recently, the amplification of glucocorticoid action within the adipose tissue by the intracellular enzyme 11β-HSD1 has been suggested to be involved in the development of central obesity \[27, 28\]. 11β-HSD1 regenerates active glucocorticoids (cortisol in humans and corticosterone in rodents) from inactive 11-keto forms in the liver, adipose tissue and brain, and this regeneration amplifies local glucocorticoid action. Masuzaki et al. \[27\] created transgenic male mice that overexpress 11β-HSD1 in adipose tissue to increase the adipose levels of corticosterone; these mice developed visceral obesity and exhibited pronounced insulin-resistant diabetes and hyperlipidemia. 11β-HSD1 knockout mice are protected from insulin resistance, hyperglycemia, and dyslipidemia \[29\]. Logically, the inhibition of 11β-HSD1 activity has become a potential treatment plan. PF91-275 (PF; 4’-cyano-biphenyl-4-sulfonic acid (6-amino-pyridin-2-yl)-amide) is a selective inhibitor of 11β-HSD1 \[30\], and an initial clinical trial has proven its safety and efficacy \[30, 31\]. Developmental exposure to NP results in Cushing’s syndrome/metabolic syndrome symptoms in male adult rats. The dysregulation of glucocorticoid regeneration from its inactive to its active form by 11β-HSD1 in tissues appears to be responsible for this effect. In our study \[32\], the activity of 11β-HSD can be inhibited by a specific inhibitor (PF915275). The results showed that treatment with the 11β-HSD1 inhibitor PF915275 reversed/alleviated NP-induced hyperadrenalism via the following mechanisms: (1) decreasing serum corticosterone, 11β-hydroxylase, and aldosterone synthase levels; (2) significantly increasing PPARγ protein and mRNA expression, in adipose tissue, NP significantly increased PPARγ mRNA expression, whereas PF915275 significantly decreased the level of mRNA expression; and (3) the expression of key regulators/enzymes in the adipogenesis metabolic pathway was also modulated. These results show a potential direction for the treatment of ENDR-induced Cushing’s syndrome and pandemic metabolic syndrome.
Conflicting interests

The authors have declared that no conflict of interests exist.

Abbreviations

ACTH: adrenocorticotropic; BPA: bisphenol A; DDT: dichlorodiphenyltrichloroethane; DES: diethylstilbestrol; EDC: endocrine-disrupting chemical; ENDR: endocrine disruptors; 11β-HSD1: 11β-hydroxysteroid dehydrogenase I; NP: nonylphenol; PF915275: PF; 4′-cyano-biphenyl-4-sulfonic acid (6-amino-pyridin-2-yl)-amide); PPARα: peroxisome proliferator-activated receptor α; PPARγ: peroxisome proliferator-activated receptor γ; StAR: steroidogenic acute regulatory protein.

References


