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Review Article

PESTICIDES AS ENDOCRINE DISRUPTORS

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Summary: Several synthetic chemicals used as pesticides have the capacity to interfere with hormone action in the mammalian body. These chemicals are known as endocrine disruptors. Exposure to endocrine disruptors before birth can change the development of sexual organs, neuroendocrine system and behaviour. We are studying whether long term exposure to low doses of organophosphorus insecticide Chlormephos and herbicide Atrazine affects development and function of reproductive tract and brain. In Chlormephos study, adult male and female mice were exposed to 3,5 μg/ml and 0,35 μg/ml of Chlormephos in the drinking water. No statistically significant differences between treated and control groups were found in any of the observed parameters that included several indicators of testis development and blood levels of reproductive hormones, suggesting that Chlormephos does not act as an endocrine disruptor in reproductive tract. Elevated plus maze test revealed increased anxiety like behaviour in mice exposed neonatally to higher dose of Chlormephos. Microarray analyses revealed some differences in expression of genes that might be involved in the anxiety-like behaviour but we could not confirm several of them using quantitative RT PCR. On the other hand, studies with Atrazine did reveal some endocrine effects of prenatal and neonatal exposure to Atrazine, although these studies are still on-going and the results are not conclusive, yet.

Key words: endocrine disruptors; chlormephos; atrazine; reproductive tract; brain

Introduction

Several synthetic chemicals used as pesticides or pharmaceutical agents can possibly act as endocrine disruptors (ED), ED have the capacity to interfere with hormone action in the mammalian body. Exposure to ED before birth can change the development of sexual organs, neuroendocrine system and behavior. ED have low hormone activity in comparison to endogenous hormones, but their ability to accumulate in the body fat and long half-life of some of them could increase their concentrations in the animal body. Environmental chemicals could act as estrogens, antiestrogens or antiandrogens. Different EDs do not have structural similarities and therefore it is not possible today to predict which chemical could act as an endocrine disruptor (1).

Organophosphorus compounds (OPs) are a large class of chemicals used for various purposes like chemical weapons, pesticides and antiparasitics. At high doses, OPs are irreversible inhibitors of acetylcholinesterase, causing accumulation of acetylcholine in cholinergic nervous system. However, little is known about possible toxic effects of exposure to low doses of organophosphorous compounds.(2). Atrazine is one of the most widely used herbicides and as such, a very common water pollutant. Most EU countries set the limit for Atrazine contamination of drinking water at 0.1 μg/L, but in areas with intensive farming this limit is often exceeded and could reach up to 1 μg/L. Several studies have shown that Atrazine could affect the endocrine system, primarily the hypothalamic-pituitary-gonadal axis (3, 4), although there is still controversy whether the Atrazine really is an endocrine disruptor.

Organophosphorous compounds and endocrine disruption

Several studies examined whether OP substances could act as endocrine disruptors. Oka-

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hashi et al.(5) reported that high doses of fenitrotion decrease activity of brain cholinesterase in exposed animals, but does not affect reproductive performance, organ weights, histopathology of testes, accessory sex organs, pituitary, thyroid, ovaries, uterus and sperm parameters in rats. In the same study, no general toxicity or effect on anogenital distance, retention of areolae, onset of puberty, organ weights, histopathological findings and sperm parameters were observed in the F1 generation. Similarly, in our unpublished study, Chlormephos did not affect number of pups in litters, daily sperm production, weight of testes and seminal vesicles , number of apoptotic cells and fertility. However, in contrast to that, Narayana et al. (6) reported that injection of methyl parathion in Wistar rats at doses that are relevant to human exposures (0,5 – 1 mg/kg) caused decrease in sperm count and increase in morphological defects in semen, although the number of pups in litters from treated animals did not differ from control groups, suggesting that effect of methyl parathion is still small. Some OPs in high concentrations do have direct effect on reproductive and endocrine system in humans (7) and animals (6). In our study, we did not find any difference in daily sperm production and number of apoptotical cells in the offspring of treated animals, but we did not examine these two parameters in treated mice so we do not know whether there are any direct effect of Chlormephos on sperm development, although even if present, such effects would be small as we did not find any differences in the litter sizes between treated and control groups.

Several reports demonstrated that exposure to bisphenol A and metoxychlor before birth and during early postnatal period could affects sexual and non-sexual behavior (8, 9). In our study we observed increased anxiety-like behavior in adult mice that were exposed to Chlormephos only during neonatal period. OPs are soluble in lipids so they can pass through blood-brain-barrier and can get into direct contact with developing nerve cells and could therefore directly impact development of nerve cells in the brain. On the other hand, several studies have shown that OPs could disrupt blood-brain barrier (BBB) in mice and rats with long term exposure to low doses, and such disruption of blood brain barrier could enable other harmful substances to enter the brain and cause delayed behavioral effects observed in our study (10, 11)

Atrazine as endocrine disruptor

Atrazine is one of the most commonly used herbicides in the world and poses special concern because it is ubiquitous, persistent contaminant of groundwater and surface water that is active at low, ecologically relevant concentrations (12). Studies showed that Atrazine can affect the reproductive system in animals such as frogs and rats (13, 14). However, almost all studies examining Atrazine effects in mammals used large doses of Atrazine, which could mimic an exposure of workers working with Atrazine, but are usually not a concern for the general population. Atrazine does not act in the same manner as classical endocrine disruptors that influence estrogen or androgen receptors (15) but possibly induces expression of the CYP19 gene (16). Some studies have shown that, at least in vitro, Atrazine could increase the activity of P450 aromatase and thus elevate estrogen production. Most studies about the effects of Atrazine were described in females, but some studies demonstrated that it can affect male reproductive system. One recent study have thus shown that *in utero* and through milk exposure to Atrazine affects development of prostate and seminal vesicles, suggesting that Atrazine can pass through the placenta and/or into milk and can affect offspring of treated mothers (17). In our study we examined whether exposure to Atrazine *in utero* and during early postnatal period at doses relevant for the general human population, could affect reproductive tract development in male mice. Preliminary results do suggest certain affects especially on the development of male reproductive tract such as reduced daily sperm production and increased number of apoptotic cell in testes from neonatally treated mice, although further studies are now being conducted to confirm preliminary findings.

References:

1. McLachlan JA. Environmental signaling: what embryos and evolution teach us about endocrine disrupting chemicals. Endocr Rev 2001; 22(3): 319–41.

2. Weinbroum AA. Pathophysiological and clinical aspects of combat anticholinesterase poisoning. Br Med Bull 2004; 72: 119–33.

3. Villanueva CM, Durand G, Coutte MB, et al. Atrazine in municipal drinking water and risk of low birth weight, preterm delivery, and small-for-gesta-

tional-age status. Occup Environ Med 2005; 62(6): 400–5.

4. Cooper RL, Stoker TE, Tyrey L, et al. Atrazine disrupts the hypothalamic control of pituitary-ovarian function. Toxicol Sci 2000; 53(2): 297–307.

5. Okahashi N, Sano M, Miyata K, et al. Lack of evidence for endocrine disrupting effects in rats exposed to fenitrothion in utero and from weaning to maturation. Toxicology 2005; 206(1): 17–31.

6. Narayana K, Prashanthi N, Nayanatara A, et al. Effects of methyl parathion (o,o-dimethyl o-4-nitrophenyl phosphorothioate) on rat sperm morphology and sperm count, but not fertility, are associated with decreased ascorbic acid level in the testis. Mutat Res 2005; 588(1): 28–34.

7. Recio R, Ocampo-Gomez G, Moran-Martinez J, et al. Pesticide exposure alters follicle-stimulating hormone levels in Mexican agricultural workers. Environ Health Perspect 2005; 113(9): 1160–3.

8. Palanza P, Gioiosa L, vom Saal FS, et al. Effects of developmental exposure to bisphenol A on brain and behavior in mice. Environ Res 2008; 108(2): 150–7.

9. Panzica GC, Viglietti-Panzica C, Mura E, et al. Effects of xenoestrogens on the differentiation of behaviorally-relevant neural circuits. Front Neuroendocrinol 2007; 28(4): 179–200.

10. Song X, Pope C, Murthy R, et al. Interactive effects of paraoxon and pyridostigmine on blood-brain barrier integrity and cholinergic toxicity. Toxicol Sci 2004; 78(2): 241–7.

11. Gupta A, Agarwal R, Shukla GS. Functional impairment of blood-brain barrier following pesticide exposure during early development in rats. Hum Exp Toxicol 1999; 18(3): 174–9.

12. Solomon KR, Carr JA, Du Preez LH, et al. Effects of atrazine on fish, amphibians, and aquatic reptiles: a critical review. Crit Rev Toxicol 2008; 38(9): 721–72.

13. Cooper RL, Laws SC, Das PC, et al. Atrazine and reproductive function: mode and mechanism of action studies. Birth Defects Res B Dev Reprod Toxicol 2007; 80(2): 98–112.

14. Hayes TB, Collins A, Lee M, et al. Hermaphroditic, demasculinized frogs after exposure to the herbicide atrazine at low ecologically relevant doses. Proc Natl Acad Sci U S A 2002; 99(8): 5476–80.

15. Roberge M, Hakk H, Larsen G. Atrazine is a competitive inhibitor of phosphodiesterase but does not affect the estrogen receptor. Toxicol Lett 2004; 154(1-2): 61–8.

16. Sanderson JT, Letcher RJ, Heneweer M, et al. Effects of chloro-s-triazine herbicides and metabolites on aromatase activity in various human cell lines and on vitellogenin production in male carp hepatocytes. Environ Health Perspect 2001; 109(10): 1027–31.

17. Rayner JL, Enoch RR, Wolf DC, et al. Atrazine-induced reproductive tract alterations after transplacental and/or lactational exposure in male Long-Evans rats. Toxicol Appl Pharmacol 2007; 218(3): 238–48.

PESTICIDI KOT HORMONSKI MOTILCI

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Povzetek: Nekatere kemične snovi, ki jih uporabljamo kot pesticide, lahko motijo hormonsko ravnovesje v telesu. Imenujemo jih hormonski motilci. Izpostavljenost hormonskim motilcem pred rojstvom lahko vpliva na razvoj spolnih organov, na nevroendokrini razvoj in na obnašanje. V naši raziskavi proučujemo vpliv dolgotrajne izpostavljenosti nizkim dozam organofosfatnega insekticida klormefosa in pesticida atrazina na razvoj in delovanje spolih organov in možganov pri miših. Odraslim samcem in samicam smo smo v pitno vodo vmešali klormefos v koncentraciji 3,5 µg/ml in 0,35 µg/ml. Opazovali smo nekatere parametre dozorevanja mod in koncentracijo spolnih hormonov v krvi, vendar med poskusno in testnima skupinama nismo našli statistično značilnih razlik. Rezultati kažejo, da klormefos ne vpliva kot endokrini motilec na spolni sistem. Miši, ki so bile pred rojstvom in v zgodnjem poporodnem obdobju izpostavljene višji dozi klormefosa so v testu dvignjenega labirinta kazale povečano obnašanje podobno tesnobi. Analiza DNK mikromrež je pokazala razlike v izražanju nekaterih genov, ki so povezani z obnašanjem podobnim anksioznemu, vendar pa razlik nismo mogli potrdit z metodo kvantitativnega RT PCR. Raziskava izpostavljenosti miši nizkim dozam atrazina v obdobju pred in zgodaj po rojstvu je pokazala nekaj endokrinih vplivov, vendar pa rezultati še niso dokončni, saj raziskave še potekajo.

Ključne besede: hormonski motilci; klormefos; atrazin; spolni sistem; možgani