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CHANGES IN THE CENTRAL NERVOUS ACTIVITY OF RATS TREATED WITH DIMETHOATE IN COMBINATION WITH OTHER NEUROTOXICANTS IN DIFFERENT PHASES OF ONTOGENESIS*

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Organophosphates are usually found in the environment with other pesticides and with pollutants of industrial origin can cause combined exposure involving unknown interactions between the agents. In this study, female Wistar rats were given 1/25 LD_{50} of dimethoate by gavage, combined with the same LD_{50} fractions of propoxur and cypermethrin or with arsenic (6.66 mg kg^{-1}). The doses were given from day 5 to 15 of pregnancy, or that plus for the 4 weeks of lactation, or that plus 8 weeks for the male offspring after weaning. Control rats received distilled water. Electrophysiological recording was done when the male offspring reached 12 weeks of age. Spontaneous activity and evoked potentials from the somatosensory, visual and auditory cortex; and conduction velocity and absolute and relative refractory periods of the tail nerve were measured. The general trend was a shift of the spontaneous cortical activity to higher frequencies and increase in the evoked potential latency. The results showed that combined exposure to several environmental toxicants could be more harmful than the effects of each substance alone, indicating the importance of combination toxicology in modelling human effects. Furthermore, these results emphasize the importance of avoiding toxic exposures in pregnant and nursing women.

KEY WORDS: *development, heavy metal, insecticides, neurotoxicity, rat*

Human production, including industrial and agricultural production, has led to considerable environmental pollution, and to human exposure to a number of xenobiotics. Insecticides have had a large-scale application in agriculture and in vector control. The selectivity of insecticides is imperfect, so that their presence in the environment, and consequently in food and drink, can result in human toxic exposure.

Organophosphates (OPs) (1) are known to permanently inhibit acetylcholinesterase (2). In human OP poisoning, a variety of nervous system effects have been observed, including abnormal EEG (3) and peripheral neuropathy (4). The EEG effects of OPs in humans have been confirmed in animal experiments (5, 6) and effects on the evoked cortical activity have been also found (7, 8). Dimethoate (DIM), the OP used in this study, is moderately toxic for humans (9) and has been in use in many countries. In our earlier experiments, low dose DIM was applied in different administration modes and timing schemes, including three-generation model (6, 10), and was found to alter neurophysiological parameters in the exposed generation and their offspring.

Carbamates are another group of insecticide agents acting on the cholinesterase (11). However, their effect is reversible (12). In accidental poisonings, propoxur (PRP), the carbamate used in this study, elicited typical symptoms of cholinergic hyperactivity,

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although atropine-like effects following PRP exposure are also known (13). Further mechanisms to be taken into consideration are the effect of PRP on ATP-dependent ionic balance (first of all, calcium) (14), leading to synaptic dysfunction. In animal experiments, a single dose of ca. 1/10 LD_{50} caused a 60 % drop in cholinesterase activity and marked disturbances in higher nervous functions (15). PRP is primarily an agent of domestic insect control and anti-malarial measures (12), often resulting in direct human contact. Pyrethroids, synthetic analogues of the insecticide component of *Pyrethrum* plant extract, are widely used as insecticides because of their high insecticidal potency, low mammalian toxicity and biodegradability (16). The primary target of pyrethroids are Na^+ channels (17, 18), but Ca^{2+} channels are also affected (19). Pyrethroids also inhibit ATPases (20, 21), and various receptors (22–25). Cypermethrin (CYP), the substance used in this study, belongs to type II pyrethroids exhibiting central neurotoxicity (26). Poisoning by type II pyrehtroids is manifested in hypersensitivity, choreoathetosis, tremors and paralysis (27, 28).

Anthropogenic environmental arsenic originates mostly from mining and smelting of certain ores and also from coal burning (29). The principal source of non-occupational arsenic intake are food, drinking water and air (30). Inorganic arsenic is a well-known human poison (31). Arsenic affects the central and peripheral nervous system of humans (32), producing neuropathy manifested in electromyographic and nerve conduction velocity alterations (33). Children living near an arsenic-emitting coal-fired power plant exhibited a moderate hearing loss (34). Exposure to elevated levels of arsenic in drinking water increases the risk of cerebrovascular disease and cerebral infarction (35). Altered transmitter levels, abnormal behaviour (36), and electrophysiological and motility changes (37) were observed in rats treated chronically with inorganic arsenic.

Combined exposure to the above mentioned xenobiotics is not unlikely. Exposure to several insecticides is possible in those who apply them professionally or at home, or through residues in food. For arsenic, a typical source of population exposure (e.g. in south-east Hungary) is the natural As in drinking water (38). Therefore, rats in this study were exposed to a combination of DIM+PRP+CYP (DPC combination), or DIM+arsenic (AsD combination) in a scheme involving the phases of ontogenesis.

METHODS

One group of pregnant female Wistar rats of ca. 250 g body weight was orally receiving a combination of 1/25 LD_{50} doses of dimethoate (28.2 mg kg^{-1} b.w.) plus propoxur (3.4 mg kg^{-1} b.w.) and cypermethrin (22.2 mg kg^{-1} b. w.) in sunflower oil (DPC combination), and another group a combination of 1/25 LD_{50} doses of dimethoate (28.2 mg kg^{-1} b. w.) and arsenic ($NaAsO_2$, 6.66 mg kg^{-1} b. w.) in distilled water (AsD combination). Control groups (CON) received the vehicle, oil or water alone. The substances were applied daily by gavage, from the 5th to 15th day of pregnancy (P protocol), or from the 5th to 15th day of pregnancy + for 4 weeks of lactation (P+L protocol), or from the 5th to 15th day of pregnancy + for 4 weeks of lactation + male offspring (F1 generation) treated for another 8 weeks after weaning (P+L+PLP protocol). This treatment scheme, based on the OEDC Guideline No. 414, includes the period of organogenesis (P protocol), and simulates milk-borne exposure of babies from exposed mothers during rapid postnatal development (P+L protocol) and later exposure experienced after weaning. It proved to be usable in detecting the developmental effects on the nervous system by several environmental chemicals including dichlorvos (8), the combination of DIM and lead (39), and mercury (40).

The neurophysiological parameters were investigated in F1 male offspring (10 animals per group, see Table 1 for all groups) at 12 weeks of age. Their body weight was recorded weekly and used as indicator of development.

In urethane anaesthesia (1000 mg kg^{-1}), the animal's head was fixed in a stereotaxic frame, the skull was opened and the left hemisphere exposed. Following ca. 30 min recovery, a silver recording electrode was placed on the primary somatosensory (SS), visual (VIS) and auditory (AUD) areas and electrocorticogram (ECoG) was recorded simultaneously from these sites for 6 minutes. Sensory stimuli (in a series of 50 with 1 Hz repetition frequency) were then applied and the cortical evoked potentials (EPs) recorded from the same sites. For somatosensory stimulation, a pair of needles were inserted between the contralateral whiskers and fine electric shocks were delivered. For visual stimulation, flashbulb flashes (1 Hz, 60 lx) were directed to the contralateral eye via an optical conductor. Acoustic stimulation was performed by clicks (1 Hz, 40 dB), led through the hollow ear bar into the contralateral ear of the rat.

Table 1 *Relative organ weights of animals in different combinations and treatment protocols. DPC, dimethoate-propoxur-cypermethrin combination; AsD, dimethoate-arsenic combination. CON, untreated; P, treated during pregnancy; PL, treated during pregnancy and lactation; PLP, treated during pregnancy, lactation and in the post-weaning period (see Methods for details of treatment).*

Groups		Brain[a]	Liver[b]	Lungs[b]	Heart[b]	Kidney[b]	Spleen[b]	Thymus[b]	Adrenal glands[b]
DPC subgroups	CON	0.453 ±0.029	6.711 ±0.604	0.997 ±0.067	0.657 ±0.0499	1.4613 ±0.133	0.375 ±0.033	0.260 ±0.047	0.036 ±0.005
	P	0.509* ±0.031	6.396 ±0.623	1.201 ±0.422	0.666 ±0.099	1.399 ±0.099	0.242 ±0.055	0.221 ±0.054	0.039 ±0.006
	PL	0.491* ±0.036	6.050* ±0.815	1.066 ±0.129	0.595* ±0.072	1.327* ±0.145	0.320 ±0.046	0.263 ±0.036	0.036 ±0.004
	PLP	0.563* ±0.045	5.159* ±0.547	0.961 ±0.146	0.572* ±0.063	1.224* ±0.094	0.256* ±0.032	0.214* ±0.032	0.034 ±0.005
AsD subgroups	CON	0.498 ±0.040	7.170 ±0.642	0.993 ±0.113	0.708 ±0.066	1.271 ±0.085	0.307 ±0.036	0.260 ±0.050	0.031 ±0.005
	P	0.495 ±0.019	6.729 ±0.668	1.007 ±0.059	0.592* ±0.039	1.289 ±0.105	0.255* ±0.048	0.202* ±0.041	0.028 ±0.005
	PL	0.455 ±0.034	7.122 ±0.425	1.0676 ±0.130	0.67407 ±0.048	1.357* ±0.118	0.308 ±0.048	0.260 ±0.060	0.035 ±0.006
	PLP	0.468* ±0.034	8.384* ±1.212	0.951 ±0.099	0.721* ±0.077	1.345* ±0.114	0.318 ±0.064	0.277 ±0.061	0.029 ±0.004

Mean±SD, n=10. *p<0.05 treated vs. control.
[a] brain weight related to 100 grams of body weight.
[b] organ weight related to brain weight.

The ECoG analysis provided the frequency power spectrum by bands (delta to gamma). On the cortical EPs, latency and duration of the main waves were measured manually after averaging. Following electrophysiology, the animals were sacrificed by an overdose of urethane, dissected, and organ weights measured. Relative organ weights were calculated on the basis of brain weight.

From the primary data, group averages were obtained and compared by one-way ANOVA with LSD post hoc test, after the Kolmogorov-Smirnov normality check.

This study has been carried out under GLP conditions (certificate No. 3011/48/2003). The principles of the Ethical Committee for the Protection of Animals in Research of the University were strictly followed.

RESULTS

General effect on the development

The development of the F1 generation male rats, monitored by the body weight gain, is shown in Figure 1. In the DPC treated groups, a slight, apparently treatment-protocol-dependent weight loss developed when compared to the controls, but the weight differences were significant only in the last two weeks. In the AsD treated groups, the treatment had no noteworthy effect on the body weight gain.

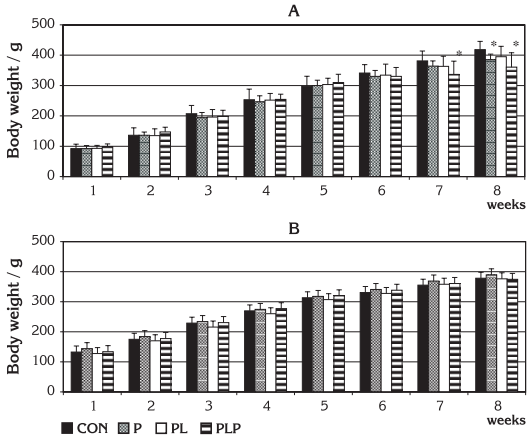

Figure 1 *Body weight gain of the control and treated F1 male rats (A: dimethoate+propoxur+cypermethrin [DPC] combination; B: dimethoate+arsenic [AsD] combination). Abscissa: postnatal weeks. Ordinate: body weight gain in grams (group mean+SD, n=10). Insert: bar pattern for the treatment groups (CON, control; P, treated during pregnancy; PL, treated during pregnancy and lactation; PLP, treated during pregnancy, lactation, and in the post-weaning period for the male offspring; see Methods for further explanation). *p<0.05 treated vs. control.*

The organs measured, most notably the liver, the kidneys and the heart, showed significant weight alterations in both combinations (Table 1). However, DPC-treated rats seem to have suffered greater organ damage because the trend of alterations showed clearer dependence on the treatment protocol. The changes in brain weight (shown as relative brain weight in Table 1) were significant in the PLP protocol with AsD treatment and in all DPC-treated groups.

Effects on the ECoG

The insecticide combination (DPC) caused a moderate increase in the activity of the fast (beta 2 and gamma) bands (Figure 2, left bars), which was significant only in the auditory cortex. A corresponding decrease in slow activity was the most marked in the visual area, where the treatment protocol-dependent trend was also the clearest. The effect of the AsD combination (Figure 2, right bars) was an increase in delta and decrease in alpha and beta 1 bands, with no change in the fastest two bands. The changes were significant mostly in the somatosensory and visual areas where the proportionality of the changes and the treatment protocol, which determined the summed dose, was also the clearest.

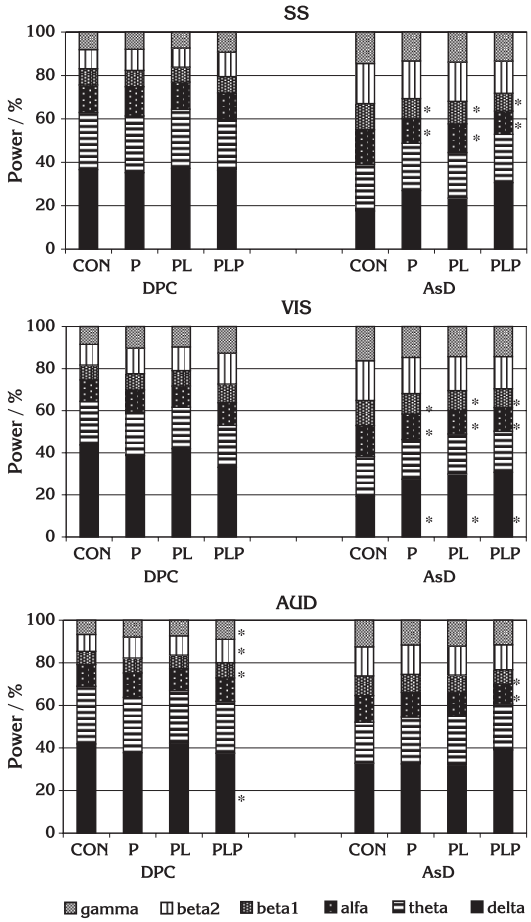

Figure 2 *Frequency distribution of the spontaneous cortical activity (ECoG) in the three cortical areas recorded (SS, somatosensory; VIS, visual; AUD, auditory cortex). Abscissa: control and treated groups, marked as in Figure 1. Left bars, DPC (dimethoate+propoxur+cypermethrin); right bars, AsD (dimethoate+arsenic). Ordinate: relative power of the frequency bands (insert: bar pattern for the bands). *p<0.05 vs. the same band in the control group.*

Effect on the cortical EPs

DPC treatment changed the parameters of the EPs in all three cortical areas (Figure 3). The latency of the somatosensory EP decreased and its duration increased. The latency of the visual EP increased, showing clear treatment protocol dependence, and significance in case of PLP treatment. Here, the change of the duration was less characteristic. In case of the auditory EP, the latency increase was significant without any treatment protocol-dependence, and the duration increase was significant only in the P+L+P treatment group. In the groups receiving AsD combination treatment, the changes in the parameters of the cortical evoked potentials were equivocal (not shown).

DISCUSSION

The effects of the applied combinations on the body weight gain and on the organ weights were generally mild, indicating low general toxicity of the doses applied. Arsenic in the same dose, given to young adult rats for up to 12 weeks, failed to cause significant organ weight alterations (39). In an experiment involving 6-week exposure, PRP and the OP methyl parathion had no effect on weight gain and a moderate effect on liver and kidney weight (42).

The effect of the DPC combination on the ECoG, decrease of the slow and increase of the fast waves, was in accordance with previous observations. With DIM alone, used in the same dose as in this work, increasing ECoG mean frequency was seen in dependence of treatment protocol, that is, summed treatment time (6). *Dési and Nagymajtényi* (8) described the same effect with another OP, dichlorvos. The known common target of OPs and carbamates, acetylcholinesterase, would suggest a common

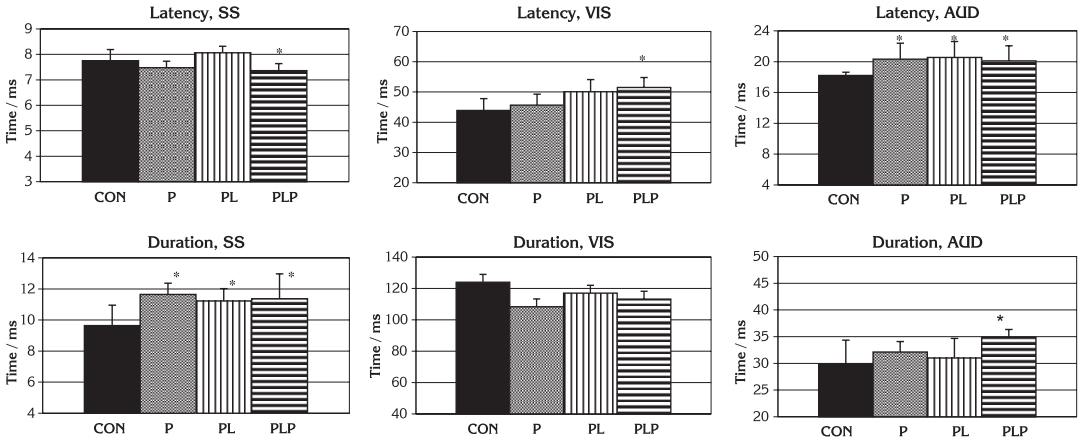

Figure 3 *Latency and duration of the evoked potentials from the three cortical areas (SS, somatosensory; VIS, visual; AUD, auditory cortex) in the DPC treated rats. Abscissa: treatment groups. Ordinate: milliseconds (group mean+SD, n=10; note different scales). *p<0.05 treated vs. control.*

mechanism on cortical functions (1, 12). Regarding the cholinergic mechanism of the ascending cortical activation system (43), cholinesterase inhibitors increased cortical activity, which was observed in the form of a shift to higher frequencies in ECoG waves. The effect of CYP, a pyrethroid, cannot be linked with one transmitter system (22-25) so it can only be said that the ECoG frequency shift in the DPC-treated rats probably reflected the effect of DIM and PRP. Moreover, CYP and OP have been reported not to interact (44).

Arsenic has an additional effect on the cholinergic system. The inhibition of muscarinic receptors (45) and the interference of As with dopaminergic neurotransmission (45) may have contributed to the slowing of ECoG seen in our study, and these effects were apparently not counteracted by DIM.

The increase in the EP latency upon OP administration was described in several of our laboratory studies (8, 10). This time, the effect in the DPC-treated rats was absent in the somatosensory EP, possibly due to the presence of CYP.

Given alone during ontogenesis, the effect of As on the EPs was slight (37). This time, the AsD combination had no noteworthy effect on the evoked activity. This may partly be due to the opposite effect of OPs and As on cholinergic modulation of cortical activity.

Combined experimental exposure of rats to the mentioned environmental pollutants during ontogenesis affected several endpoints. Body weight and organ toxic effects were minor, indicating that the observed actions on the nervous system were target-specific and not secondary to a general toxic effect. Within them, spontaneous cortical activity seemed to be a better indicator of the neurotoxic effect of these substances than the forms of evoked activity studied. Indicators of this kind can be developed into biomarkers, applied in the assessment and follow-up of human risk from environmental xenobiotics, above all in more vulnerable groups within the population such as pregnant women, babies or small children.

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Sažetak

PROMJENE U AKTIVNOSTI SREDIŠNJEGA ŽIVČANOG SUSTAVA ŠTAKORA TRETIRANIH TIJEKOM FAZA ONTOGENEZE DIMETOATOM, ORGANOFOSFORNIM INSEKTICIDOM U KOMBINACIJI S DRUGIM TOKSIKANTIMA

Organofosfati su u okolišu obično prisutni zajedno s drugim pesticidima i mogu uzrokovati uz onečišćivače industrijskog podrijetla, kombiniranu izloženost koja uzrokuje interakcije među spojevima. U radu su ženke štakora soja Wistar tretirane oralnom intubacijom s 1/25 LD_{50} dimetoata kombiniranog s 1/25 LD_{50} propoksura i cipermetrina ili s arsenom (6,66 mg kg^{-1}). Tretmani su bili: od 5. do 15. dana trudnoće; ili od 5. do 15. dana trudnoće i 4 tjedna za vrijeme laktacije; ili od 5. do 15. dana trudnoće, 4 tjedna za vrijeme laktacije i 8 tjedana potomcima mužjacima nakon polijeganja. Kontrolna skupina štakora tretirana je samo destiliranom vodom. Na potomcima mužjacima je nakon 12 tjedana provedeno elektrofiziološko snimanje. Mjerena su spontana i podražajno izazvana aktivnost iz somatosenzorskih, vizualnih i auditivnih kortikalnih područja, brzina provođenja i apsolutni i relativni periodi otpora repnog živca. Opće promjene bile su pomak u spontanoj kortikalnoj aktivnosti na više frekvencije te povećanje latentnog perioda kod podražajno izazvanog potencijala. Rezultati su pokazali da izlaganje kombinacijama toksikanata iz okoliša može biti štetnije od učinaka svakog od toksikanata zasebno, upućujući na važnost ispitivanja učinaka kombinacija različitih toksikanata na ljudsko zdravlje. Rezultati osobito upućuju na važnost izbjegavanja izlaganja trudnica i dojilja toksikantima.

KLJUČNE RIJEČI: *insekticidi, neurotoksičnost, razvoj, štakor, teški metali*

REQUESTS FOR REPRINTS:

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