STIMULUS TRAIN INDUCED FATIGUE IN A CORTICAL EVOKED POTENTIAL: THE EFFECT OF DIMETHOATE AND ETHANOL

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ABSTRACT

Whole populations can be exposed to a variety of neurotoxic substances which points to the need of search for means of early detection of harmful effects. Sensory evoked potentials are readily recorded in experimental animals and in humans and have been shown to be sensitive of toxic effects. Our aim was to see if the fatigue during a series of cortical somatosensory evoked potentials is reproducible and sensitive to the substances used. Evoked potentials recorded from rats treated with 5 % ethanol in the drinking water, with 1/25 LD_{50} dimethoate daily by gavage, or both, were re-evaluated. The first and last five potentials from a series of 50 were averaged and latency and amplitude of the main waves was measured. It was seen that while the latency showed minimal changes over the series, there was always a decrease of amplitude which was stronger in the treated animals.

KEY WORDS: organophosphate, alcohol, rat, biomarker

INTRODUCTION

Xenobiotics entering the human body from the environment and via food and drink are a major source of health risk. Although several environmental compounds are known to be neurotoxic, little is known about their possible population effects at low doses and long exposure times, first of all what concerns combined exposures.

Organophosphates (9) are used as insecticides and are emitted in the environment in large amounts. OPs are irreversible blockers of acetylcholinesterase (8) in a broad spectrum of organisms including humans. Intoxication with an OP results, beyond general symptoms like bradicardia, salivation

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etc.(8), in functional alterations of the central nervous system. EEG abnormalities have been described in human subjects (5) and in animals (2,6) together with alterations of the evoked cortical activity (1,3). The insecticide chosen for our studies, dimethoate (4) is an OP of moderate human toxicity registered and used presently in a number of countries, which increases the chance of repeated exposure for not only the users but also the general public.

The consume of different amounts of ethanol is a general phenomenon in modern societies. Although not overtly neurotoxic at low consumption, alcohol has been known to potentiate the toxic effects of certain other substances. In our previous studies it was found that subchronic ethanol treatment, in combination with different OPs and heavy metals, strengthened the alterations caused by the latter in the spontaneous and evoked cortical activity of rats (10).

The above-mentioned exposure of population calls for means of early detection of possible adverse effects. The use of biomarkers (7) is a novel way to do that, but most of the known biomarkers are based on chemical samples and hence not suited for the central nervous system. A consequent change in a form of nervous activity which is readily recordable also in humans, would be a possible candidate for such a biomarker. The aim of the present investigation was to see whether neurotoxic effect of dimethoate, ethanol and their combination is reflected in the fatigue of the somatosensory contical evoked potential of rats.

METHODS

The investigation was based on the re-evaluation of previously recorded activity. In those experiments, the rats (Wistar males, 10 weeks old) were treated for 12 weeks with 5 % ethanol in their drinking water, with 1/25 LD_{50} (= 20 mg/kg b.w.) dimethoate by gavage in a 5 times per week schedule, or with the combination of the two. Controls had tapwater, and distilled water in the gavage. At the end of the treatment, the animals were anesthetized with 1000 mg/kg urethane, the head was fixed and the left hemisphere exposed. Somatosensory cortical evoked potentials were recorded from the primary focus. The stimulus was an electric shock (ca. 3 V, 0.05 msec) delivered to the whiskery skin area in a sole series of 50 pulses at 1 Hz.

For the evaluation this time, "fatigue" was defined as the amplitude decrease and latency increase seen over the series of evoked potentials. Thus, the first 5 and the last 5 of the potentials (stored in a PC) was averaged, and amplitude and peak latency of the main negative and positive wave components was measured. The relative change ((average of the last 5)/ (average of the first 5)) representing the fatigue was calculated and again averaged for whole groups of animals (10 rats). It was finally checked if there is a correlation between the group-averaged fatigue and the neurotoxic exposure.

RESULTS AND DISCUSSION

Of the parameters investigated, the latency of the wave components of the evoked potential showed negligible changes during a stimulus series and this was not altered by dimethoate or alcohol treatment. The amplitude changes over the series were, however, more manifest and hence interpretable as fatigue.

There was a measurable decrease in the amplitude between the first and the last evoked potentials in each animal, control

or treated. This is represented by values below 1.00 in Table I. In the control rats, the decrease was moderate and was not much altered by alcohol treatment. In the rats given dimethoate, however, the decrease was significantly stronger. ($p<0.05$ vs. control, for the negative wave and the sum of both waves). In the dimethoate + alcohol combination group, the fatigue was not stronger than in the dimethoate-only group but still more than in the control. Four weeks without dimethoate administration ("wash out") after the 12 weeks of treatment resulted only in a partial recovery.

This kind of evaluation of the existing data showed that the fatigue of the sensory evoked potential, as defined here, can be calculated from simple measurements and seems to be sensitive to certain toxic influences. As different forms of evoked activity, including sensory potentials, are also easily recordable in humans, the measurement and calculation described above can be a promising candidate for a functional biomarker of neurotoxic effect.

	groups				
relative change (last/first)	**control**	**alcohol**	**dimethoate**	**dimethoate + alcohol**	**dimethoate wash out**
latency, negative wave	0.997 ± 0.009	0.981± 0.025	1.035 ± 0.031	0.997 ± 0.015	0.993 ± 0.030
latency, positive wave	0.993 ± 0.014	0.996 ± 0.014	0.837 ± 0.411	1.007 ± 0.029	1.008 ± 0.016
amplitude, negative wave	0.806 ± 0.231	0.819 ± 0.207	0.709* ± 0.285	0.852 ± 0.264	0.741 ± 0.244
amplitude, positive wave	0.905 ± 0.202	0.495 ± 0.633	0.612 ± 0.502	0.853 ± 0.552	1.072 ± 0.659
amplitude, summed	0.862 ± 0.210	0.860 ± 0.176	0.745* ± 0.359	0.804 ± 0.260	0.840 ± 0.252

Table I. Group averages of the calculated fatigue. Values above and below zero indicate that the given parameter was increased and decreased, respectively, in the last potentials of a series vs. the first ones. * = $p<0.05$

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OBOSEALA INDUSĂ DE STIMULI REPETITIVI ASUPRA POTENȚIALULUI CORTICAL EVOCAT: EFECTELE DIMETHOATULUI ȘI ETANOLULUI

REZUMAT

Întreaga populație poate fi expusă la o varietate de substanțe neurotoxice, fapt care evidențiază necesitatea căutării de mijloace de detecție precoce a efectelor nocive induse de acestea. Potențialele senzoriale evocate, care pot fi înregistrate atât la animalele de experiență, cât și la om, s-au dovedit utile pentru evidențierea efectelor toxice ale unor substanțe. Scopul cercetării noastre a fost de observa dacă oboseala dintr-o serie de potențiale somatosenzoriale evocate este reproductibilă și influențată de agenții utilizați. Potențialele evocate înregistrate la șobolani tratați zilnic prin gavaj cu etanol 5% în apa de băut sau/și cu 1/25 LD_{50} dimethoat au fost reevaluate. A fost calculată media primelor și ultimele cinci potențiale evocate dintr-o serie de 50, și au fost măsurate amplitudinea și latența principalelor unde. S-a observat că în timp ce latența a prezentat modificări minime în cadrul seriilor examinate, amplitudinea potențialelor a fost întotdeauna mai redusă, modificarea fiind mai accentuată la animalele tratate.

CUVINTE CHEIE: organofosfat, etanol, șobolani, biomarker.