Possible role of γ-aminobutyric acid in paraoxon-induced convulsions

The convulsions caused by organophosphate compounds have been attributed to inhibition of cholinesterases and a concomitant increase in the concentration of endogenous acetylcholine which excites the whole cholinergic nervous system (Stewart, 1952; Nachmansohn, 1959). Woodbury & Esplin (1959) found that there was a significant correlation of γ-aminobutyric acid (GABA) content in brain and electroshock seizure threshold, the reduction in brain GABA content being accompanied by an increase in brain excitability. There are no reports on the effect of organophosphates on GABA content of brain. We have examined the effect of paraoxon on the GABA content of rat brain.

Phenobarbitone sodium, which is effective against grand mal epilepsy, has also been used to control convulsions caused by insecticides (Hayes, 1967). Isoniazid produces a decrease in brain GABA content (Sugawara, 1958; Bukin, 1959). The effects of phenobarbitone and isoniazid on paraoxon-induced convulsions and changes in brain GABA level have also been examined.

Adult male albino rats, 150–200 g, were divided into 6 groups. One group of animals was used as control. A second group was killed ½ h after the subcutaneous injection of paraoxon (0·1 mg/kg). A third group was injected with phenobarbitone sodium (50 mg/kg, i.p.) 2 h and with paraoxon (0·1 mg/kg, s.c.) ½ h before death. Isoniazid and phenobarbitone (50 mg/kg) were administered intraperitoneally separately into groups of rats which were killed after 1 and 2 h respectively. Animals in the last group had isoniazid (50 mg/kg, i.p.) 1 h and paraoxon (0·1 mg/kg, s.c.) ½ h before death.

GABA was determined according to the method of Maynert, Klingman & Kaji (1962).

Phenobarbitone sodium protected all animals from paraoxon-induced convulsions while the animals without phenobarbitone treatment showed convulsions. The animals injected with phenobarbitone alone were markedly depressed before death. The animals treated with isoniazid and paraoxon showed severe convulsions and two of them died.

The results indicate that paraoxon reduces the brain GABA content (Table 1). A decrease in brain GABA level has been held responsible for certain drug induced convulsions (Killam & Bain, 1957) and increased brain excitability (Woodbury & Vernadakis, 1958). According to Roberts, Rothstein & Baxter (1958), the excita-

Table 1. *Effect of paraoxon, phenobarbitone and isoniazid on GABA content of rat brain.* The animals were killed ½ h after paraoxon (0·1 mg/kg, s.c.), 2 h after phenobarbitone (50 mg/kg, i.p.) and 1 h after isoniazid (50 mg/kg, i.p.). The figures in parentheses indicate the number of animals used in each experiment.

	GABA content (mg/100 g wet tissue)				
Controls	Paraoxon	Phenobarbitone and paraoxon	Phenobarbitone	Isoniazid	Isoniazid and paraoxon
32·1 ± 1·1 (10)	22·8 ± 1·0 (7)	30·9 ± 0·1 (6)	40·3 ± 1·5 (6)	23·2 ± 0·8 (5)	18·3 ± 0·7 (5)
*P**	<0·01	N.S.	<0·01	<0·01	<0·01
*P***		<0·01			<0·05

* The difference between the mean GABA content and the controls.
** The difference between the mean GABA content and that after paraoxon treatment.

bility of brain neurons depends on the level of acetylcholine (excitatory) and GABA (inhibitory). Paraoxon-induced reduction in brain GABA level (Table 1) may disturb this balance and increase the brain excitability resulting in convulsions.

The protection of rats from paraoxon-induced convulsions by phenobarbitone was accompanied by a return to almost normal of the brain GABA level which had been reduced to 22·8 mg/100 g by paraoxon administration (Table 1). There was no significant difference between the mean GABA content of control animals (32·1 mg/100 g) and those that received paraoxon and phenobarbitone (30·9 mg/100 g).

The potentiation of paraoxon-induced convulsions by isoniazid was accompanied by a small but significant decrease in GABA content from the already lowered level of GABA induced by paraoxon (Table 1). The degree of convulsive activity also increased as the GABA level fell. According to Maslova (1964), the GABA level in brain is changed according to the phases of neuronal excitability.

Since there is a striking and highly significant correlation of GABA content in brain and excitability (Woodbury & Vernadakis, 1958; Woodbury & Esplin, 1959) and because there is a change in GABA content in protection from or potentiation of paraoxon-induced convulsions, it is possible that paraoxon-induced reduction of brain GABA content may be an additional and contributory factor in the convulsions caused by it.

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