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Central effect of paraoxon in diabetic rats

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THE PHARMACOLOGICAL effects of certain substances are modified by the administration of insulin[1,2] or the presence of a diabetic state.[3] Organophosphate compounds cause accumulation of acetylcholine in the brains of rats[4,5] and rabbits.[6] There have, however, been no reports on the central effects of these compounds in diabetic animals or animals receiving insulin. We accordingly report the effect of paraoxon on the brain acetylcholine content of diabetic rats.

Male albino rats, 150 ± 15 g, were injected subcutaneously with paraoxon (0·4 mg/kg). Diabetes was induced by the intraperitoneal injection of alloxan (100 mg/kg) two or three times at 3-day intervals. Blood was collected from the tail and blood sugar levels were estimated according to the Somogyi–Nelson method.[7] A "diabetic" animal had a blood sugar level above 175 mg per cent. Insulin (0·5 and 1·0 U/kg) was injected intraperitoneally.

Healthy animals with blood sugar levels of less than 120 mg per cent were taken as controls. The animals were decapitated 30 min after receiving paraoxon or insulin. The brains were removed quickly; total acetylcholine was extracted by the method of Smallman and Fisher[8] and assayed on the isolated guinea pig ileum. Statistical evaluations were performed by the Student's *t*-test.

The acetylcholine content of the brains of normal and diabetic rats was 2·72 and 2·81 μg/g of wet weight respectively. In insulin-treated diabetic rats, the brain acetylcholine content was 2·79 μg/g. After the administration of paraoxon, the acetylcholine content of the brain of diabetic animals was 3·78 μg/g while in normal animals, this figure was 4·87 μg/g (Table 1).

TABLE 1. EFFECT OF PARAOXON AND INSULIN ON THE BRAIN ACETYLCHOLINE CONTENT OF DIABETIC RATS

Group	Substance	Dose	No. of rats	Normal or diabetic	Brain acetylcholine content (μg/g, mean ± S.E.)	P value*
1	Saline (s.c.)†		10	Normal	2·72 ± 0·16	
2	Saline (s.c.)		8	Diabetic	2·81 ± 0·03	NS
3	Paraoxon (s.c.)	0·4 mg/kg	5	Normal	4·87 ± 0·02	< 0·01
4	Paraoxon (s.c.)	0·4 mg/kg	6	Diabetic	3·78 ± 0·04 (P < 0·01)‡	< 0·05
5	Paraoxon (s.c.) + insulin (i.p.)	0·4 mg/kg + 0·5 U/kg	6	Diabetic	4·33 ± 0·04	< 0·01
6	Paraoxon (s.c.) + insulin (i.p.)	0·4 mg/kg + 1·0 U/kg	6	Diabetic	4·82 ± 0·05 (P < 0·01)§	< 0·01
7	Insulin (i.p.)	1·0 U/kg	5	Diabetic	2·79 ± 0·04	NS

* P values in each case represent comparisons with group 1.
† Abbreviations used: s.c. = subcutaneous; i.p. = intraperitoneal; NS = not significant.
‡ Represents the value obtained by comparing groups 3 and 4.
§ Represents the value obtained by comparing groups 4 and 6.

When paraoxon was injected with insulin, 0·5 and 1·0 U/kg, the brain acetylcholine content of diabetic rats was 4·33 and 4·82 μg/g, respectively, while in diabetic rats treated with paraoxon only, the level was 3·78 μg/g (Table 1).

The acetylcholine content of the brain is not changed in diabetic rats nor in diabetic rats receiving insulin (Table 1). However in the saline-treated control animals, the brain acetylcholine content was 2·72 μg/g, while after paraoxon this increased to 4·87 μg/g. In contrast, in diabetic rats paraoxon increased the brain acetylcholine level to only 3·78 μg/g. This indicates that the ability of paraoxon to increase brain acetylcholine is markedly impaired in diabetic animals. When paraoxon was administered simultaneously with insulin (0·5 or 1·0 U/kg) in diabetic animals, the acetylcholine content of the brain was 4·33 and 4·82 μg/g respectively (Table 1).

It has been reported that insulin increases the permeability of various biological membranes to carbohydrates[9,10] and amino acids,[11,12] and also increases the potency of various drugs.[13–15] In alloxan diabetes where there is a deficiency of insulin the permeability of various membranes to paraoxon might be impaired. This may cause reduced access of paraoxon to brain cholinesterase and, since the level of brain acetylcholine is related to the inhibition of cholinesterase by paraoxon,[16] a decrease in the acetylcholine content of brain.

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