The effect of potassium antimonyl tartrate on the γ-aminobutyric acid and acetylcholine contents in the cerebral hemispheres of normal and *Schistosoma mansoni* infected mice

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Potassium antimonyl tartrate (PAT) is commonly used in the treatment of schistosomiasis. Although being effective, it produces severe side effects. Toxic effects of the drug have been reported on liver (Tribouley & Duret, 1963) spleen (Abdalla & Saif, 1967) and heart (Tarr, 1947; Mainzer & Krause, 1960). However there is little information on the central effect of the drug. Zohdy & Nooman (1968) have shown that PAT causes cerebral stimulation, as evidenced by e.e.g. changes, and in large doses may cause convulsion. However, Shou Pai (1962) has reported that the drug may exert a central depressant action.

As acetylcholine and γ-aminobutyric acid (GABA) are believed to be important transmitters in the cerebral cortex and may be involved in the control of cerebral activation we have examined the effect of PAT on their concentrations in normal and in *Schistosoma mansoni* infected mice.

Adult male albino mice, 20–25 g, in groups of 36 were used, one group as control, others received PAT injected in an isotonic, sterile, 0·6% solution intraperitoneally in doses of 2 and 20 mg kg^{-1}. The latter dose is within the range usually used in the treatment of experimental schistosomiasis in mice (Standen, 1963) while the smaller dose is usually employed in man.

The acute effect was studied in a group of mice 1 h after one injection of the drug. The chronic effect was determined in 4 groups of mice given daily injections of the drug. Two groups were killed and examined 1 h after the fifth and tenth injections respectively, while the other two groups were killed 5 and 10 days respectively after the tenth injection.

Mice were infected by *Schistosoma mansoni*, by exposing each tail to 200 cercariae of an Egyptain strain of the parasite using the method of Stirewalt & Fregeau (1965).

After 8 weeks, daily examination of the stools allowed the selection of those animals passing a large number of ova. The infected mice were divided into groups of 36 and a similar study to that with normal mice was made.

The mice were decapitated, the cerebral hemispheres isolated, rapidly cooled and each was divided into two halves, one half for GABA determination and the other for acetylcholine. For each determination, the halves from six animals were pooled. GABA was estimated using a chromatographic colorimetric method (Saad, 1970) which is sensitive to 1 μg. Acetylcholine was estimated by initial extraction according to Beani & Bianchi (1963), then assayed biologically using the four-point assay on eserinized frog rectus abdominis (Gaddum, 1934; Feldberg, 1945). The method is sensitive to 1 ng ml^{-1}.

Student's *t*-test was applied at $P = 0.05$ to evaluate the significance between the means.

The normal GABA content in cerebral hemispheres of normal adult male mice was 3·3 μ mol g^{-1}, while the acetylcholine content was 5·5 μg g^{-1}. There was no significant change in the GABA content in the *S. mansoni* infected mice (3·0 μmol g^{-1}), while a small but significant rise was observed in the acetylcholine content (6·8 μg g^{-1}).

Tables 1 and 2 summarize the percentage changes induced by PAT in doses of 2 and 20 mg kg^{-1} on the cerebral hemisphere GABA and acetylcholine contents respectively. PAT consistently caused a decrease in GABA content while raising the acetylcholine content in the cerebral hemispheres of both normal and infected mice. Generally the effect was more pronounced in the latter and with the higher dose of PAT than with the lower one. In acute experiments (1 h after one injection) PAT, in a high dose, induced a significant fall in GABA content of 23% while significantly raising the acetylcholine content to nearly 20%.

The effect in normal mice, although qualitatively similar, was not statistically significant. The low dose of PAT had no marked effect on GABA content, but raised significantly the acetylcholine content of infected, and not of normal mice. On continued administration

Table 1. *The mean cerebral GABA contents (± s.e. mean) in normal and* S. mansoni *infected mice after treatment with PAT in does of 2 & 20 mg kg^{-1}, i.p. daily.*

Time of Autopsy	2 mg kg^{-1} of PAT		20 mg kg^{-1} of PAT	
	Normal	Infected	Normal	Infected
1 h after 1st Inj.	3·2 ± 0·1 (−3·03)	2·8 ± 0·2 (−6·66)	2·8 ± 0·05 (−15·15)	2·3* ± 0·1 (−23·33)
5th Inj.	3·8 ± 0·2 (−9·03)	2·6 ± 0·1 (−13·33)	2·6* ± 0·07 (−21·21)	2·4* ± 0·3 (−19·99)
10th Inj.	2·66* ± 0·13 (−19·39)	2·2* ± 0·2 (−26·66)	2·3* ± 0·1 (−30·30)	2·1* ± 0·2 (−30·00)
Days after the 10th injection				
5th day	2·8 ± 0·5 (−15·15)	2·4* ± 0·15 (−22·00)	2·5* ± 0·4 (−24·42)	17·7* ± 0·1 (−40·97)
10th day	2·90 ± 0·4 (−12·12)	2·90 ± 0·1 (−3·33)	2·80 ± 0·2 (−15·15)	2·6 ± 0·1 (−13·33)

The GABA content in normal untreated mice was 3·3 ± 0·3 and 3 ± 0·2 μmol g^{-1} in infected untreated mice. *Significant difference rom the control ($P < 0.05$). % change from control is in parentheses.

Table 2. *The mean cerebral acetylcholine contents (± s.e. mean) in normal and* S. mansoni *infected mice after treatment with PAT in doses of 2 and 20 mg kg^{-1} i.p. daily.*

Time of Autopsy 1 h after	2 mg kg^{-1} of PAT		20 mg kg^{-1} of PAT	
	Normal	Infected	Normal	Infected
	5·94 ± 0·3 (8·06)	8·37* ± 0·3 (23·13)	6·2 ± 0·5 (13·63)	8·14* ± 0·9 (19·85)
5th Inj.	6·45 ± 0·5 (17·37)	8·80* ± 0·2 (29·44)	6·47 ± 0·4 (17·71)	8·53* ± 0·7 (25·55)
10th Inj.	6·77* ± 0·8 (23·24)	9·46* ± 0·8 (39·13)	7·27* ± 0·9 (32·35)	9·27* ± 0·9 (36·47)
Days after 10th Injection				
5th day	6·55 ± 0·6 (18·48)	7·96 ± 0·5 (17·14)	6·84*8 ± 0·8 (24·52)	8·74* ± 0·7 (28·64)
10th day	6·16 ± 0·6 (12·12)	7·83 ± 0·5 (15·22)	6·37 ± 0·1 (15·82)	8·67* ± 0·7 (27·54)

The acetylcholine content in normal untreated mice was 5·5 ± 0·45 and 6·8 ± 0·38 μg g^{-1} in infected untreated mice.* Significant difference from control ($P < 0·05$). % change from control is in parentheses.

for 10 days, PAT induced a progressive rise in acetylcholine content reaching up to 39% in infected mice with the low dose, and up to 36·5% with the higher dose level. The effect in normal mice was smaller.

The GABA content of the cerebral hemispheres of infected mice showed a progressive decline from its respective control value, reaching 30% after 10 days of daily administration with the high dose level of PAT.

After treatment had stopped the changes in both GABA and acetylcholine contents tended to return to normal. This was seen particularly with the GABA contents 10 days after cessation of therapy when the values were not significantly different from normal. The changes in acetylcholine content were more persistant, especially with the high dose of PAT, such that there was still a 27·5% rise in acetylcholine content 10 days after completion of treatment.

The present results show that PAT significantly increases the cerebral hemisphere acetylcholine content and significantly decreased the cerebral hemisphere GABA content. There was no significant difference in the concentration of the transmitters studied following infection with *S. mansoni* showing that the infection as such had no marked influence on either. However, the presence of infection seemed to influence the effects of PAT such that the drug action was more pronounced in infected animals. This may be due to hepatic dys-function, partly produced by the infection (Abdalla, Saif & Abdel Fatah, 1969) and partly from repeated Sb^{3+} administration. The maximal effect of PAT on the tenth day of medication, is probably the result of accumulation of Sb^{3+} coupled with its poor excretion from the body (Lippincott, Hess & Ellerbrack, 1947).

The cumulative effect of the drug may contribute to its delayed effect after stoppage of medication (Schulert, 1964).

The present results suggest that PAT should perhaps be avoided in cases of epilepsy where the brain GABA content is low (Elliot, Roberts & Baxter, 1959) and GABA's formation from glucose is decreased in the brain of idiopathic epileptics (Kokudo, 1959).

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