Short Communication

Decreased Toxicity of d-Tubocurarine after Pretreatment with Drugs Elevating the Intracellular Level of c-AMP in Mice

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Summary. The toxicity of d-tubocurarine in mice was slightly but significantly reduced after pretreatment with drugs which are known to increase the intracellular level of c-AMP. Papaverine, theophylline and ephedrine elevated the LD₅₀ values of d-tubocurarine by 12 to 26%. The dibutyryl derivative of c-AMP as well as c-GMP were also active in this respect.

Key words: d-Tubocurarine — Cyclic AMP — Cyclic GMP — Phosphodiesterase Inhibitors.

Introduction

Catecholamines are known to facilitate neuromuscular transmission (Krnjević and Miledi, 1958; Jenkinson et al., 1968) and to promote the accumulation of cyclic adenosine-3',5'-monophosphate (c-AMP) in the brain (Klainer et al., 1962). Since c-AMP mediates many of the physiological effects of catecholamines (see Robison et al., 1968), it appears possible that the effects of catecholamines on neuromuscular transmission are also mediated by c-AMP.

This suggestion is supported by the observation of Breckenridge et al. (1967) that theophylline, an inhibitor of phosphodiesterase, augmented the increase in tension of the cat gastrocnemius muscle caused by adrenaline. Furthermore, Singer and Goldberg (1970) demonstrated that the dibutyryl derivative of c-AMP (DBA) and methylxanthines mimic the effects of catecholamines on neuromuscular transmission. These observations have provided evidence that c-AMP can promote neuromuscular transmission, obviously by facilitating the release of acetylcholine from motor nerve endings.

Recently Varagić and Žugić (1971) reported that aminophylline and caffeine are able to augment the twitch response of the isolated phrenic
nerve-diaphragm preparation caused by direct or indirect stimulation. The effects of xanthine derivatives were well correlated with the action of glucose-6-phosphate.

Based on our recent observation (Vapaatalo and Anttila, unpublished results) that some PDE-inhibitors as well as c-AMP and cyclic guanosine-3',5'-monophosphate (c-GMP) reduced the action of d-tubocurarine (d-TC) on isolated rat diaphragm, it was studied, whether these agents are able to modify the toxicity of d-TC in vivo.

Material and Methods

d-Tubocurarine chloride (Orion Ltd., Helsinki) was given to white male mice (22–26 g) into a tail vein in a volume of 0.11–0.13 ml. The toxicity of d-TC was estimated according to Miller and Tainter (1944) and the results are given as LD₅₀ of 24 h. For the determination of LD₅₀ values 3 to 10 groups of mice were used, and in each group there were 10 to 20 animals. The animals were pretreated either with saline, papaverine hydrochloride, theophylline (aminophylline, dissolved in water with ethylenediamine-HCl, 14 mg/ml) or ephedrine chloride (Medica Ltd., Helsinki), N⁶-2'-O-dibutyryl adenosine-3',5'-monophosphate sodium (DBA) or cyclic guanosine-3',5'-monophosphate sodium (c-GMP) (Boehringer Mannheim GmbH, Mannheim) as indicated in detail in the table. The doses are given in salts except that of theophylline, which refers to the base. The solvents used did not modify the toxicity of d-TC. Student's t-test was used for statistical analysis.

Results

The LD₅₀ of d-TC was 113 ± 2 μg/kg (Table 1). The PDE inhibitors, papaverine and theophylline, decreased the toxicity of d-TC by 26% and 12%, respectively. Ephedrine and c-GMP were active, too. Also DBA diminished the toxicity of d-TC (11%), but the level of significance was lower (P < 0.05). Papaverine, in a dose of 2 mg/kg, most effectively protected the animals against d-TC. The drugs were also tested in somewhat higher and lower doses than those given in the Table 1; their effects were about the same. In a dose of 0.5 mg/kg papaverine was no more active and in much higher doses papaverine, theophylline and ephedrine even increased the toxicity of d-TC, obviously due to their own toxicity.

Discussion

There are strong reasons for believing that c-AMP plays an important role in the function of the nervous system and also in neuromuscular transmission (for review see: Greengard and Costa, 1970). In accordance with this suggestion it was found that drugs known to increase the intracellular level of c-AMP, such as papaverine, theophylline and ephedrine, were able to diminish the toxicity of d-TC but not that of succinylcholine (Vapaatalo and Anttila, unpublished results). Two cyclic nucleotides, DBA and c-GMP were active, too.