CHEMICALLY INDUCED MYOTONIA IN MAMMALIAN AND AMPHIBIAN SKELETAL MUSCLE

by

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April, 1979.

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SUMMARY

This thesis contains two experimental sections: Section A is concerned with changes that occur in the twitch response and electromyogram (EMG) of mammalian muscle, and Section B is concerned with changes that occur in the twitch response of amphibian muscle, when certain chemical agents are applied to the muscle.

GENERAL INTRODUCTION

Hereditary myotonia and myotonia induced by chemical agents in man and other animals are reviewed.

SECTION A

The isolated rat diaphragm, extensor digitorum longus and soleus muscles were used as the test preparations and bathed in Synthetic Interstitial Fluid. The muscle was stimulated by a short train of three one-millisecond pulses at 225 Hertz and rested 10 minutes between each stimulation to avoid the "warm up" phenomenon of myotonic muscle.

A number of auxin-like substances, currently used as herbicides and previously untried for their myotonic activity, were tested. Almost all of them, when appropriately chloro or methyl substituted, except the phenylacetic acids, produced myotonic responses in isolated mammalian muscle at 2.5 mmol l^{-1}. A subgroup of the myotonia-producing substances had significant antimyotonic activity under certain conditions. Other synthetic auxin-like substances, notably the phenylacetic acids, were unaccountably inactive as myotonic or antimyotonic agents.

The commonly used loop diuretics, ethacrynic acid, furosemide and mersalyl acid, tested on the basis of the similarity of their chemical structure to that of known myotonic agents, were found to induce myotonia in isolated mammalian muscle. Furosemide injected intravenously into the rat induced a myotonic EMG similar to that produced after intraperitoneal injection of the potent myotonic agent, anthracene-9-carboxylic acid (A-9-C).

Muscle spasms and cramps seen as side effects of high doses of furosemide may therefore be induced myotonia caused by the diuretic and not just increased excitability due to electrolyte shifts as previously believed. The new loop diuretics, indapamide, bumetanide and piretanide, did not induce myotonia directly in vitro but seem capable of interacting with subthreshold concentrations of A-9-C to produce myotonic responses. Because of their lower myotonic potency their use may be preferable to that of the more myotonic diuretic agents.

All of these agents are presumed to produce myotonia by blocking muscle membrane chloride channels. Therefore several potent anion channel blockers in red blood cells were also tested on mammalian muscle. They were found to be inactive as myotonic agents.

Chronic administration of hypocholesterolemic agents such as 20,25-diazacholesterol have been reported to induce myotonia in man and other animals. I tested rats fed 20,25-DAC for the EMG "divebomber" volleys characteristic of myotonia. 20,25-DAC treated muscles were observed in vitro and were not myotonic but responded to what on normal muscles were subthreshold concentrations of A-9-C. Muscles dissected from rats injected i-p with A-9-C, on the other hand, were myotonic in vitro.

SECTION B

It has been reported that the potent myotonic agents in mammals are inactive in amphibians thereby implying significant differences between amphibian and mammalian muscles. However in my study A-9-C at 2.25×10^{-3} mol l^{-1} induced myotonic responses in amphibian sartorius muscles *in vitro*. A-9-C also induced myotonia in amphibians *in vivo*. Some of the RBC anion channel blockers and loop diuretics induced myotonic responses in amphibian muscle *in vitro*. Amphibian muscle made myotonic could be warmed up by exercise to alleviate the myotonia as in mammalian muscle.

Amphibian muscle can therefore be made myotonic although the conditions necessary are different from those of mammalian muscle. Amphibian muscle is thus not so different from mammalian muscle as has sometimes been suggested.

DECLARATION

I declare this thesis to be a record of original work containing no material that has been accepted for the award of any other degree or diploma in any University.

To the best of my belief and knowledge, no material previously published or written by another person has been included without due reference in the text of the thesis.

Susan R. Dawe.

ACKNOWLEDGEMENTS

In particular, I thank my co-supervisors, Dr. D.I.B. Kerr, from the Department of Human Physiology and Pharmacology of the University of Adelaide, and Dr. A.H. Bretag, from the School of Pharmacy of the South Australian Institute of Technology, for suggesting this field of study and for their continued support and guidance throughout the period of my candidature.

I am indebted to Dr. A.H. Bretag for his enthusiastic and optimistic encouragement and advice in all aspects of this work.

I thank Dr. A.H. Bretag and Dr. A.G. Moskwa for their participation in some experiments particularly involving the diuretics and electromyography.

I am grateful to Miss Sue Jenkin for her patient help in the preparation of this thesis.

For the supply of drugs listed in the Materials and Methods, I gratefully acknowledge the following companies: Lilly Industries, Sydney; Upjohn Company, Michigan, U.S.A.; Farm Chemicals, Hamilton, Queensland; Chemical Industries (Kwinana), Fremantle, Western Australia; Dow Chemical, California, U.S.A.; Winthrop Laboratories, Sydney; Leo Laboratories, Ballerup, Denmark; Hoechst Australia, Melbourne; Servier Laboratories, Hawthorn, Victoria.

I would also thank my husband, Malcolm, for his support and my employer, Professor B.J. Christie, of the School of Pharmacy, S.A.I.T., for the opportunity to undertake this study.