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The Local Anticonvulsive Action of Calcium Salts.*

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Using Beutner and Miley's method,[1] it was found that 200 mg per kg of procaine HCl injected intramuscularly into 56 guinea pigs caused clonic and tonic convulsions in all of the animals. The convulsions lasted 51 minutes on the average, and were preceded by hind leg stiffness. One hundred mg per kg of procaine HCl produced convulsions in 84% of 204 observations, with an averge duration of 12 minutes, while 50 mg per kg acted in only 8% of the animals with an average duration of 8 minutes.

If $CaCl_2$ was added to the procaine HCl solution and injected simultaneously, a marked decrease in the incidence of these convulsions was invariably observed. Thus, 200 mg per kg of $CaCl_2$ with 200 mg per kg of procaine HCl reduced the incidence of convulsions to 43% in 30 trials. Similarly, 100 mg per kg of $CaCl_2$ added to 100 mg per kg of the procaine solution reduced the incidence to 14% in 122 cases. This inhibiting effect of $CaCl_2$ on procaine convulsions is much less if $CaCl_2$ is injected separately from procaine.

The nature of the local action of $CaCl_2$ in reducing procaine convulsions may be clarified if one notes the effect of $MgCl_2$ added to the procaine-$CaCl_2$ mixture. Two hundred mg per kg of $MgCl_2$ was added to and injected intramuscularly in guinea pigs with 100 mg per kg of both procaine HCl and $CaCl_2$. In 137 experiments, the incidence of convulsions was 33%, or more than twice what we found it to be without $MgCl_2$. This indicates that $MgCl_2$ counteracts $CaCl_2$ locally, probably by altering membrane permeability as in the case of calcium-magnesium antagonism in the Meltzer-Auer phenomenon.

Since the locally irritating properties of $CaCl_2$ on intramuscular administration might have been a factor in the observations, we studied the effects of the less irritating organic calcium compounds by the same methods. Out of several organic calcium salts tested

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1 Beutner, R., and Miley, PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 279. (See also Beutner, Miller and Prussmack, *J. Pharm.*, 1936, **57**, 116.

only calcium gluconate was found to have no significant effect in inhibiting procaine or butyn convulsions. This can be correlated with the complete non-ionization of this compound, since calcium gluconate was found to be the *only* calcium salt the solutions of which are non-conductors of the electrical current. Calcium lactate, however, which is about as good a conductor as $CaCl_2$ in watery solution, appears to surpass calcium chloride, on the basis of calcium content, in power to inhibit these local anesthetic convulsions. Similarly, calcium salicylate, which is a good conductor, surpasses calcium chloride in reducing the incidence of procaine or butyn convulsions when injected simultaneously. Calcium gluconate is inefficient only when mixed and injected simultaneously with procaine. On separate injection it has some anticonvulsive action probably due to chemical decomposition.

By the same methods one may estimate the anticonvulsant effects of epinephrin HCl when given with local anesthetics. Thus, in a concentration of 1:50,000 in a procaine solution administered in a dose of 100 mg per kg, the incidence of convulsions was lowered from an expected 84% to 8%. This is, of course, a strictly local effect, as can be readily demonstrated by failure to observe a lowering of expected incidence of convulsions when relatively large doses of epinephrine HCl are injected into one leg and the procaine into the other. Ephedrine was found to be devoid of any such anticonvulsive action, even when given in relatively high doses simultaneously with procaine.

Camp[2] has called attention to the epinephrine-like action of large doses of potassium salts. When added to solutions of procaine HCl and injected with it, KCl was found to have anticonvulsant action. Thus, 100 mg per kg of KCl given with 100 mg per kg of procaine HCl reduced the expected incidence of convulsions from 84% to 59% in 48 experiments.

Tatum[3] and others have shown that the convulsant action of local anesthetics can be inhibited by various centrally acting depressant drugs, such as the barbiturates. This anticonvulsive action can, however, only be demonstrated if the barbital is administeed 15 or 30 minutes before the local anesthetic. We found that if pentobarbital, or phenobarbital, are mixed with procaine solutions and injected simultaneously, the incidence of expected convulsions is higher than if the procaine is given alone. Thus, 100 mg per kg

2 Camp, W. J. R., and Higgins, J. A., *J. Pharm.*, 1936, **57**, 376.

3 Tatum, A. L., Atkinson, A. J., and Collins, K. M., *J. Pharm.*, 1924-5, **26**, 325; Knoefel, P. K., Herwick, R. P., and Loevenhart, A. S., *J. Pharm.*, 1930, **39**, 397.

of procaine HCl with 20 mg per kg of either barbital gave an incidence of 91% convulsions in 60 cases, instead of the expected 84% found for procaine alone. However, if these same amounts of these barbitals were injected half an hour earlier than the procaine, no convulsions appeared at all. The barbitals therefore seem to have no *local* action in inhibiting local anesthetic convulsions.

Full details of these experiments will be published later. Meanwhile, it may be concluded that $CaCl_2$ tends to inhibit local anesthetic convulsions when administered in the same solution by altering permeability, as indicated by the fact that the addition of $MgCl_2$ to the solution counteracts this anticonvulsant action. The anticonvulsant effect of calcium salts seems to be proportional to the extent of ionization. Epinephrine and potassium ions tend to inhibit local anesthetic convulsions when administered in local anesthetic solutions by local constricting effects. Barbiturates inhibit local anesthetic convulsions *only* by central depressant action.

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Production of Pyrogen in Sera by Bacteria.

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The occurrence of fever and chills is a relatively frequent phenomenon following intravenous serum therapy. Among the many writers calling attention to this reaction, it suffices only to mention Bullowa[1] who speaks of its high incidence in the use of refined and unrefined pneumococcus sera. The subject has been a fruitful field of research and speculation. The cause of this reaction has been variously attributed to hemolysis, to the use of anti-coagulants, to the presence of toxic fractions of proteins, and to bacterial contamination.

Felton[2] has shown the reactive principle to be in the acid precipitate of the water-insoluble protein of the sera, and intimates that it may

[1] Bullowa, J. G. M., *Management of the Pneumonias*, Oxford Press, 1937, p. 317.

[2] Felton, L. D., and Kauffman, G., *J. Infect. Dis.*, 1931, **49**, 335.