Action of Histamine on Procaine Nerve Block

In a communication in *Nature* of October 22, 1949, Bárány and Nordquist[1] reported certain observations on the action of histamine on nerve block caused by procaine and pyribenzamine. They were led to perform these experiments because histamine has been found in nerves[2,3], because most antihistaminic drugs are local anæsthetics, and because it has been shown that the local anæsthetic procaine also has an antihistaminic action[4,5]. Bárány and Nordquist found that, using the gastrocnemius muscle as an index of conduction in the frog sciatic nerve, histamine antagonized the local anæsthetic action of procaine and pyribenzamine. But it must be remarked that the concentration of histamine used, 0·4–0·6 per cent histamine dihydrochloride, was very large and unlikely to be encountered under physiological conditions.

We have repeated the experiments of Bárány and Nordquist, using the isolated frog sciatic nerve and testing conduction by recording the action potentials with an amplifier and cathode-ray oscilloscope. The nerve was stimulated supramaximally by 100–200 microsecond pulses at a frequency of 4–10 per second from a square-wave stimulator. We tested the effect of 0·3 per cent procaine hydrochloride in frog Ringer alone and of mixtures of 0·3 per cent procaine hydrochloride and 0·4 per cent histamine dihydrochloride in frog Ringer, and confirmed the results of Bárány and Nordquist to the extent that the blocking activity of the two solutions is different. The solution of procaine completely blocked the nerve in four to six minutes, whereas the mixture of procaine and histamine took much longer to block the nerve or merely reduced the size of the action potential without abolishing it.

It is well known that the free base is the active constituent of a local anæsthetic salt such as procaine hydrochloride; the effect of the drug is greater at an alkaline *p*H, whereas the activity is less as the *p*H becomes lower[6–8]. The *p*H of our frog Ringer solution was 7·4, of the 0·3 per cent procaine hydrochloride in Ringer 6·8–7·0, and of the mixture of 0·3 per cent procaine hydrochloride and 0·4 per cent histamine dihydrochloride about 4·8, since the histamine salt is strongly acid. It therefore occurred to us that the apparent inhibition of local anæsthetic action by histamine might be due to the difference in *p*H. Experiments were carried out testing the blocking effect of procaine hydrochloride alone and of mixtures of procaine hydrochloride and histamine dihydrochloride at *p*H 3, *p*H 5 and *p*H 7. The *p*H was adjusted with hydrochloric acid or sodium bicarbonate and was tested with a *p*H meter.

The results of these experiments are as follows:

(*a*) *Effect of p*H *on the anæsthetic potency of* 0·3 *per cent procaine hydrochloride alone.* The *p*H of the unadjusted solution was 6·8–7·0; in this *p*H range, the nerve was completely blocked in four to six minutes. At *p*H 5, it took twelve to fourteen minutes. At *p*H 3, the nerve was not blocked.

(*b*) *Effect of p*H *on the anæsthetic potency of mixtures of* 0·3 *per cent procaine hydrochloride and* 0·4 *per cent histamine dihydrochloride.* The *p*H of the unadjusted solution was 4·4–5·0, usually 4·8. This mixture either merely reduced the spike height or took ten to forty minutes to cause complete block. At *p*H 3, the nerve was not blocked. At *p*H 7, conduction was blocked in two to five minutes, slightly more rapidly than by procaine alone.

From these observations we suggest that the apparent inhibition of procaine block by histamine dihydrochloride is due primarily to the effect of the acid *p*H of this solution in depressing the dissociation of the anæsthetic salt, and hence reducing the amount of free base present.

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Fluoroacetate and the Tricarboxylic Acid Cycle in Nematode Parasites

Conceptions of the mode of action of fluoroacetate are varied and conflicting, according to the biological material studied[1–5]. Another reaction of fluoroacetate, in nematode parasites, in which it appears to inhibit oxidation within the Krebs tricarboxylic acid cycle, is reported here.

In the experiments outlined below, the action of the sodium salt to monofluoroacetic acid on the nematode parasites, *Nematodirus spathiger*, *Nematodirus filicollis* and *Ascaridia galli*, is described. Respiration studies were carried out using the direct manometric technique of Warburg, and citrate estimations were performed by the method of Pucher, Sherman and Vickery[6] as modified by Krebs and Eggleston[7]. The parasites were either ground to a *brei* with sand or minced in a mincer of the type of Seevers and Shideman[8]. Pigeon breast muscle and pigeon liver, treated in the same way, were used for comparison.

Fluoroacetate of concentration 0·01 *M* had a marked inhibitory effect on the respiration of the parasites. *Nematodirus* spp. was most affected; its respiration was inhibited 70 per cent by 0·01 *M* fluoroacetate. In contrast, this concentration of the poison had no effect on the respiration of pigeon breast muscle.

The inhibition of respiration caused by 0·01 *M* fluoroacetate was decreased and in some cases abolished by the addition of the tricarboxylic acid cycle intermediates, α-ketoglutarate, succinate, fumarate, malate and oxaloacetate. In a typical experiment, in which 0·01 *M* fluoroacetate inhibited 60 per cent, 0·01 *M* succinate and 0·01 *M* α-ketoglutarate completely abolished this inhibition; 0·01 *M* fumarate decreased the inhibition to 20 per cent, and 0·01 *M* malate and 0·01 *M* oxaloacetate each decreased the inhibition to 15 per cent.

Acetate could be utilized in the parasites by means of the tricarboxylic acid cycle. Acetate, or its products, condensed with oxaloacetate to form citrate, and the citrate so formed was metabolized, at least partially, by way of the tricarboxylic acid cycle[9]. The addition of fluoroacetate caused increased yields of citrate in this condensation. This is probably due to inhibition of aerobic citrate utilization by fluoroacetate in the parasites. Under aerobic conditions, 0·01 *M* fluoroacetate caused complete