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Role of Glucose or Potassium Lack in Nerve Block

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Potassium and glucose are usually lacking in solutions employed for nerve conduction block. The significance of this for impulse conduction was studied in rabbit vagus nerve *in vitro*, incubated for 2 h in Ringer's-bicarbonate solution containing or lacking 5 mM glucose and 4 mM potassium chloride (n = 5 for each condition). The C-fiber action potential was recorded by periodic stimulation and the Na and K content of the desheathed nerve core was determined at the end of the incubation. In the presence of glucose, apparently normal conduction persisted for at least 2 h, even though the nerves incubated in potassium-free medium lost 20 per cent of their potassium. In the absence of glucose, reversible extinction of conduction was complete in 78 ± 9 min when external potassium was present, and in 110 ± 10 min when external potassium was absent. The data suggest that lack of glucose may reinforce C-fiber inexcitability during conduction block and that inclusion of a physiologic amount of potassium chloride in the solution may also be desirable. (Key words: Metabolism: glucose. Nerve: axon; block; conduction; depolarization; metabolism; potential. Ions: potassium; sodium.)

INJECTABLE LOCAL ANESTHETIC PREPARATIONS generally contain enough sodium chloride to assure isotonicity with body fluids. However, they are usually lacking in potassium and glucose, two physiologic solutes that are necessary for the maintenance of normal excitability of nerve fibers. Although the effect of excess of these substances in local anesthetic solutions has been well studied,[1–3] relatively little is known about the effect of the corresponding deficiencies. This study reports on the ability of mammalian nerve to withstand glucose and potassium deprivation *in vitro* and briefly discusses the clinical implications.

Methods

Rabbits were killed by injection of air into the marginal vein of the ear and perfused with oxygenated Ringer's lactate solution (Travenol Laboratories) via the left ventricle. The cervical vagus nerves were excised, care being taken not to damage the perineurial sheath. One nerve of a pair was stored at 38° C in modified Earl's basic salts solution. The other nerve was immobilized on stimulating and recording electrodes in a water-jacketed chamber at 38° C as previously described,[4] and incubated in various solutions continuously bubbled with O_2 95 per cent–CO_2 5 per cent. For observation of the time course of changes in the C-fiber component of the compound action potential, the nerve was periodically raised out of the solution and cathodally stimulated with two supramaximal (twice maximal) 0.3-ms 1-Hz pulses from a Grass S44 stimulator, applied every 5–10 min via a capacity-coupled stimulus isolation unit. The amplified potentials were displayed and photographed at successively higher levels on the screen of a Tektronix 532® cathode ray oscilloscope, 6–8 traces being photographed on each Polaroid® picture. Generally, the two nerves of each pair were studied consecutively, but in some of the later experiments, the second nerve was mounted in a separate incubation chamber and studied concurrently with the first. The unmodified incubation medium was a Ringer's - bicarbonate solution containing NaCl 144, $CaCl_2$ 2.2, $MgSO_4$ 0.8, and $NaHCO_3$ 24 mmol/l. The four experimental modifications of the incubating solution consisted of omitting or including 4 mM potassium chloride, and of omitting or including 5 mM glucose (five different nerves with each of the modifications). Sodium chloride in lieu of potassium chloride or sucrose in lieu of glucose was added to preserve isotonicity. At the conclusion of the electrophysiological observations the nerve was desheathed, the core was weighed, and the residual

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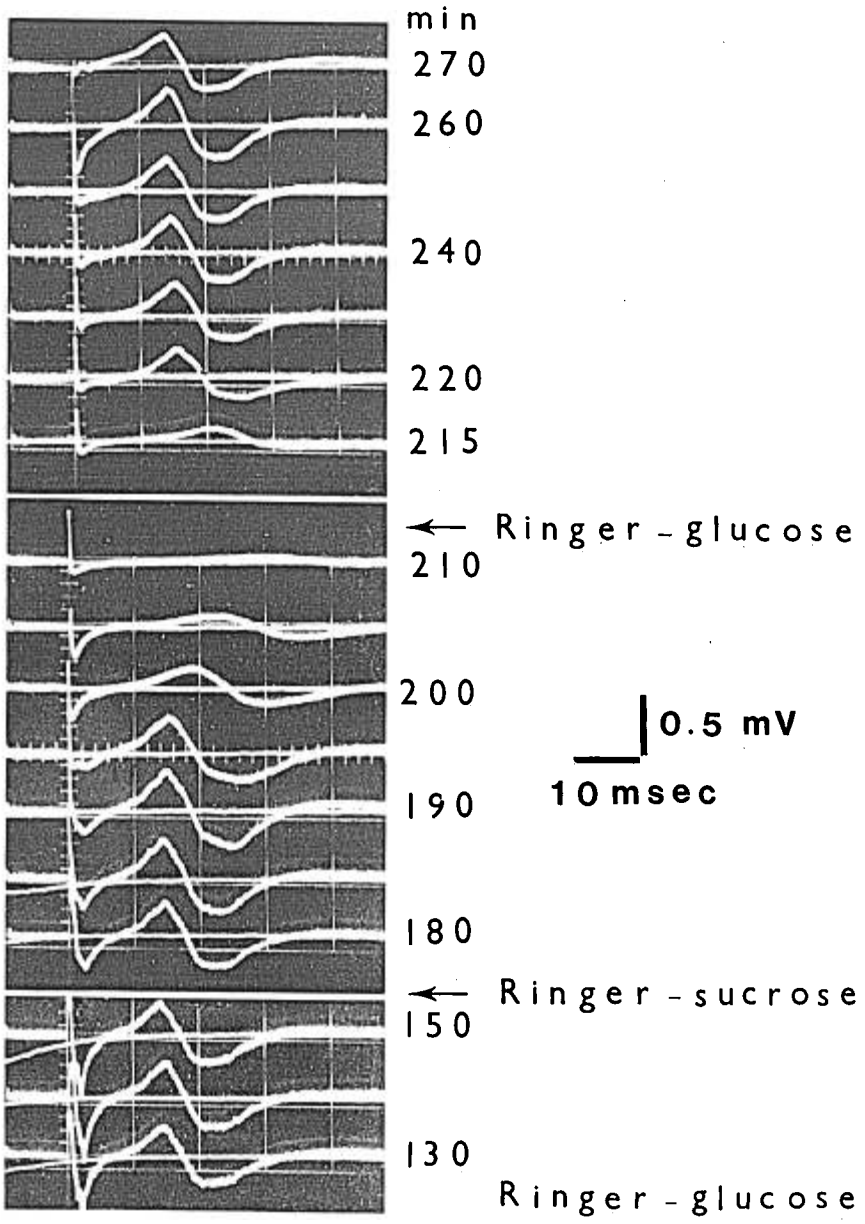

FIG. 1. Photographic record of an experiment in which the nerve was incubated for 150 min in Ringer's-bicarbonate medium containing 5 mM glucose (bottom three traces) followed by incubation for 60 min in glucose-free medium (next seven traces from the bottom) and finally again in Ringer's-bicarbonate-glucose (top seven traces). The nerve was briefly raised out of the solution and stimulated once for each record, but rested undisturbed in the solution during the intervening periods. Note the delayed concomitant decrease in amplitude and conduction velocity of the C-fiber potential when the nerve was deprived of glucose, and the relatively prompt recovery when glucose was restored.

K^+ and Na^+ content of the core was determined by flame photometry. Results are expressed as means ± SD. The statistical significance of differences was evaluated by analysis of variance and by Student's *t* test for unpaired samples, $P < 0.05$ being regarded as probably significant. Three additional nerves underwent further electrophysiological study after desheathing instead of being analyzed.

Results

Glucose Absent from Medium

The C-fiber potential began to decline in amplitude 30–40 min after the start of the incubation in the glucose-free solution, and was generally extinguished after another 30 min (fig. 1 and table 1). The extinction of the C-fibers as tested in three nerves not included in table 1 was completely reversible; the action potential gradually returned to normal within 30 min of raising the concentration of glucose to 5 mmol/l (Fig. 1). The minimum concentration of glucose required to restore conduction in C-fibers was between 0.6 and 2.4 mmol/l (n = 2). Desheathing a nerve immediately after extinction of conduction in glucose-free medium resulted in prompt recovery of excitability (n = 3). In the sheathed state extinction of C-fiber conduction required 78 ± 9 min when external potassium was present in the bathing solution, in

TABLE 1. Effects of Lack of External Glucose and/or K^+ on C-Fiber Excitability (n ≥ 5)

Extraneural Glucose (mmol/kg)	Extraneural K^+ (mmol/kg)	Time to Nonconduction (min)	Core Na^+ (mmol/kg)	Core K^+ (mmol/kg)
0	0	110 ± 10*	117 ± 5	47 ± 5‡
0	4	78 ± 9‡	134 ± 13‡	57 ± 6†
5	0	>120§	110 ± 6	49 ± 5†
5	4	>120§	117 ± 8	62 ± 3
Unincubated control¶			110 ± 9	63 ± 4

* Values are means ± SD.

† $P < 0.05$, ‡ $P < 0.01$ (analysis of variance and unpaired t test with unincubated control).

§ C-fiber potential normal for >120 min.

¶ n = 13. All other nerves underwent preliminary incubation in Ringer's-bicarbonate-glucose for 60–150 min.

contrast to 110 ± 10 min when potassium was absent ($P < 0.01$), even though in the latter case much more potassium had been lost from the core (table 1).

5 mM Glucose Present in Medium

In the presence of glucose C-fiber conduction remained normal for at least 2 h, irrespective of the presence or absence of external potassium. However, when 4 mM potassium was present external to the nerve, the core content of potassium was unchanged (62 ± 3 mmol/kg wet tissue), whereas when potassium was absent the core potassium decreased to 49 ± 5 mmol/kg wet tissue ($P < 0.05$). Incubation in glucose-free solution containing potassium increased the core content of sodium from the control value of 110 ± 13 mmol/kg wet tissue to 134 ± 13 mmol/kg wet tissue ($P < 0.01$), but other changes in sodium content were unremarkable.

Discussion

During *in vitro* incubation the nerve was of course deprived of nutritional support from the neuronal soma and from the blood. Nevertheless, preliminary observations showed that during incubation at 38° C in Ringer's-bicarbonate-glucose, the electrophysiological behavior was stable for at least 17 h, with less than 20 per cent decline in the amplitude or velocity of conduction of the C-fiber component of the compound action potential during this time.

During the first 30–40 min of glucose deprivation there was no demonstrable electrophysiological change in C-fibers. Evidently, in the absence of external glucose, the plasma membrane Na^+- and K^+-dependent ATPase continued to function at normal capacity until the glucose level in the nerve fell below a critical concentration, after which point the leakage of potassium out of the cells[5] (and the leakage of sodium into the cells) was increasingly uncompensated by pumping.

It is interesting that the maintenance of normal C-fiber excitability with glucose did not in itself ensure normal conservation of potassium by the sheathed fasciculus. In the presence of an outward potassium concentration gradient across the perineurium, the plasma membrane pumps of the cells in the fascicular core were unable to retrieve all the potassium that leaked out through the cell membrane. That is, some of the potassium that leaked out of the cytoplasm of the Schwann cells and axons went on to leak out of the fasciculus through the perineurium. Thus, *in vitro* the presence of a physiologically adequate concentration of potassium outside the fasciculus is essential to conservation of potassium by the axons.

Somewhat paradoxically, under conditions combining glucose-lack and absence of external potassium, extinction of conduction was significantly slower than when glucose alone was lacking and ambient potassium concentration was normal. This suggests that escape of potassium from the fasciculus was the principal factor responsible for prolonging the period of excitability. This interpretation is supported by the observation of prompt recovery of excitability upon desheathing. Desheathing the nerve removed the accumulated extraneuronal potassium and allowed the intra- to extracellular gradient to be restored to a functional level, even though the intraneuronal potassium level had fallen considerably below normal.

It is known that extinction of conduction can be accelerated by raising the extraneural potassium concentration, and several attempts to exploit this property in order to accelerate clinical nerve block have been made.[6,7] More recently, Bromage and Burfoot[8] used 120 mM potassium chloride in conjunction with epidural anesthesia, but abandoned the study after untoward reactions were observed following inadvertent perforation of the spinal dura mater. However, in peripheral nerve block, this particular danger is absent. Aldrete *et al.*[9] showed that inclusion of 180 mM potassium chloride nearly doubled the duration of peripheral nerve block obtainable with 2 per cent lidocaine. The risk of cardiac arrhythmias has presumably discouraged routine use of such potassium-rich solutions. Our results suggest that inclusion of a low, physiologically safe concentration of potassium chloride in local anesthetic solutions might be of some benefit and probably deserves further study.

The absence of glucose from the bathing solution

tends to deprive the nerve of an essential energy substrate and, as shown in these experiments, to produce a reversible conduction block in the unmyelinated C-fibers, which, if it occurs clinically, may be considered advantageous. Nevertheless, it cannot be assumed that the effect of omission of glucose on the nerve is necessarily always innocuous, since information on the corresponding recovery rate of conduction in the myelinated A-fibers is not yet available. Until it is, search for a substitute for glucose in hyperbaric spinal anesthesia would be premature.

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