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Inhibition of Carnitine Palmitoyltransferase by Malonyl-CoA in Human Muscle is Influenced by Anesthesia

To the Editor:—Recently in this journal, Katsuya *et al.* reported a patient with postanesthetic acute renal failure due to carnitine palmitoyltransferase (CPT) deficiency.[1] Since the original description of CPT deficiency in 1973, it had been an open question why: (1) patients with CPT deficiency suffer from intermittent attacks of rhabdomyolysis, whereas carnitine deficiency shows a fixed or progressive muscle weakness; and (2) why so little lipid accumulates in muscle in CPT deficiency.[2] An answer to these questions has come from a study by Zierz and Engel,[3] which had demonstrated that CPT deficiency is not due to a lack of catalytically active CPT I, CPT II, or both, but is caused by altered regulatory properties of CPT that is abnormally inhibited by increasing substrate/product concentrations and by malonyl-CoA. This suggests that the patient's enzyme is most vulnerable when lipid metabolism is stressed.

The notion that anesthesia might be a precipitating factor for rhabdomyolysis in patients with CPT "deficiency"[1] is supported by the following data on CPT in normal human muscle. CPT was studied in fresh muscle biopsies obtained during general anesthesia (thiopental, succinylcholine, enflurane, and nitrous oxide) from four orthopedic patients and during local anesthesia (lidocaine 1%) from four patients who underwent biopsy for diagnosis of neuromuscular disease but were ultimately found to have no disease. CPT was measured in muscle homogenate by the isotope forward assay.[3] Total CPT activity was not different in the two groups (0.81 ± 0.10 and 0.89 ± 0.14 $\mu mol \cdot min^{-1} \cdot g\ protein^{-1}$ from patients anesthetized with local or general anesthesia, respectively). After local anesthesia, the malonyl-CoA insensitive fraction of CPT was about 40% of total CPT. After general anesthesia, however, the insensitive fraction was only 20% ($P < 0.001$) (fig. 1). In contrast, the malonyl-CoA insensitive fraction of CPT in muscle obtained in local anesthesia from patients with CPT "deficiency" is only 5–15%.[3]

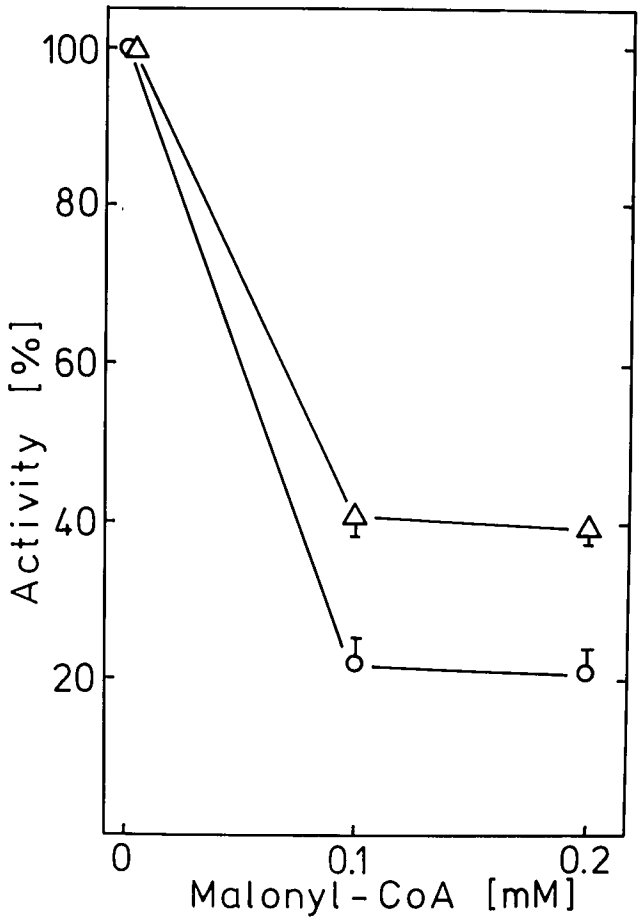

FIG. 1. Inhibition of CPT from normal human skeletal muscle by malonyl-CoA. CPT was measured by the isotope forward assay in homogenates from muscle obtained during general anesthesia (○) or local anesthesia (△). Malonyl-CoA was present in the assay as indicated. Values are expressed as percent of initial activity. Symbols and vertical lines represent means and one standard deviation of four muscles. The differences were significant with $P < 0.001$.

It is reasonable to assume that, during general anesthesia, the lipophilic drugs also accumulate in muscle mitochondria, whereas, during local anesthesia, the drug administered subcutaneously does not reach the muscle. Due to their lipophilic properties, drugs used in general anesthesia interact with the phospholipid bilayer of biological membranes.[4] Because the inhibition of CPT by malonyl-CoA requires membrane association of CPT,[5] the effect of general anesthesia on the malonyl-CoA sensitivity of CPT might be caused by a local disordering of the lipid matrix.

The data indicate that the effect of general anesthesia on the inhibition by malonyl-CoA is a tendency of the normal CPT to react like the abnormally regulated enzyme of patients. The physiological significance of this effect in normal muscle remains obscure. However, it may be inferred that, in patients with CPT "deficiency," the already abnormally regulated enzyme is additionally stressed by the general anesthesia. This might explain why general anesthesia is a precipitating factor for rhabdomyolysis in patients with CPT "deficiency."

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