Letter to the Editor

Effects of Free Fatty Acid Metabolism Derangement

To the Editor,

The article by Dr. William Shaw in Vol. 3, No. 3 JOM provides us with yet another example of how derangement of free fatty acid metabolism can cause a series of brain impairments like schizophrenia, Reyes' Syndrome hepatic coma, etc. We see this same process in our studies of brain injury due to ischemia-reperfusion here at Dr. David Gilboe's Lab. We have measured free fatty acid during our perfusion studies of isolated dog brain. After a 14 minute ischemia, followed by a one hour reperfu-sion period, we have drawn simultaneous arterial and venous samples for analysis to determine the flux of FFA in and out of the brain. Ischemia results in a marked rised in plasma FFA and we feel that this is caused by Ca2+ ion influx into the cells that activates phospholipase A2. Membrane phospholipids are broken down and FFA is released. Low cell ATP levels prevent the quick repolarization of the cell and closing of Ca2+ ion channels and the removal of excess Ca2+ from inside the cell. Overactivation of the phospholipase A2 enzyme is the result of cell ischemia and this generates the excess FFA. Mitochondria are inactivated by the excess FFA and energy production shifts to other pathways like fermentation of glucose to lactic acid and the hexose monophosphate shunt pathway. This adds to the injury because the hexose shunt makes more FFA. Perhaps the short chain FFAs are markedly increased in these instances due to synthesis by the overactive hexose shunt. Fatty degeneration results from the overproduction of FFA in cells that have overactive hexose shunt and recovery depends on the restoration of mitochondrial oxidation.

Reperfusion after ischemia can cause further damage because the sudden influx of oxygen into a cell low on energy can generate, by xanthine oxidase, the very damaging superoxides. This can result in the activation of poly (ADP-ribose) synthetase that splits NAD and again the mitochondria are inactivated. Superoxides can cause peroxidation of lipids in the membranes and thus further impair cell function. It is interesting to note that various therapeutic agents that are used to prevent damage and restore function after ischemia-reperfusion insult to the brain are free radical scavengers, like vitamin E, phenytoin, glutathione, and the new Lazaroid compounds from Upjohn; or they are xanthine oxidase inhibitors like allopurinol; or they are antilipolytic agents like insulin, chlorpromazine and nicotinic acid. Some agents have a dual function, for example the coenzymes generated from nicotinic acid, NADH and NADPH, can act as part of the free radical scavenging system in addition to the antilipolytic action of nicotinic acid. Chlorpromazine is a free radical scavenger as well as an antilipolytic.

After ischemia in the dog brains, the EEG goes flat, evoked potentials lost, and we see a sudden drop in extracellular Ca2+ ion concentration. This Ca2+ ion drop is due to the influx of Ca2+ ion into the cells. Perfusion pressure and intracranial pressure gradually go up and FFAs are markedly increased in our venous samples. Recovery is rare in control brains that have no therapy. Decrease in FFA caused by uptake of the FFA into the brain precedes the return of evoked potentials and EEG. It is interesting to note that hyperglycemia is more protective than euglycemia, but we have not tried giving insulin along with the excess glucose.

I wonder if recovery from excess FFA could predispose to superoxide damage because the cells are suffering from low energy? Could the xanthine oxidase pathway be making superoxides in Reyes' Syndrome just as we see in ischemia-reperfusion injury of the brain? If this is true, then the use of vitamin E, allopurinol, and nicotinic acid would be very helpful.

Sincerely,

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