Streptozotocin model of Alzheimer's disease: source of artifacts or food for thought?

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The major fuel for a healthy resting human brain is glucose. The molar ratio of oxygen to glucose consumption (Oxygen-Glucose Index, OGI) is 5.2-5.5, indicating that ~15% of glucose is metabolized anaerobically. OGI remains stable across adulthood.

Glucose hypometabolism is an early sign of Alzheimer's disease (AD). In 1996 Ogawa et al. reported on OGI of a small group of patients in the early stage of AD and age-matched controls. Whereas the mean OGI of controls was 5.63, the mean OGI of patients was 9.86. The difference (p<0.005) was striking and undeniable. This report was neither the first, nor the only one showing brain hypometabolism of glucose (but not oxygen) in the early AD.

Streptozotocin (STZ), a toxin from soil bacteria, is upon systemic application selectively toxic toward glucose-sensing and insulin-producing pancreatic beta cells, following cellular uptake with glucose transporter 2 (GLUT2) protein located in cell membranes. Brain is not affected because blood-brain barrier lacks GLUT2. However, intracerebroventricular (icv) STZ injection(s) chronically decrease cerebral glucose uptake and produce multiple other effects that resemble molecular, pathological, and behavioural features of AD. This „metabolic" model of AD, introduced by Sigfried Hoyer in 1990-s, become quite popular. Most authors assume that icv STZ produces cerebral glucose hypometabolism through desensitizing brain insulin receptors. However, such mechanism is certainly not possible.

Our experiments showed that icv STZ injections evoke liberation of lipid compounds to blood. We propose the following hypothesis: STZ applied to lateral ventricles reaches tanycytes, GLUT2-expressing cells involved in glucose sensing, located in the vicinity of lateral ventricles. When their input is reset to zero, sympathetic nervous system causes mobilization of lipids to immediately replace glucose as the main fuel for the brain. Some of these compounds are toxic to the brain, e.g. ceramides. A possible relevance of this mechanism to human AD deserves further study.