This Week's Citation Classic®

Sokoloff L, Reivich M, Kennedy C, Des Rosiers M H, Patlak C S, Pettigrew K D, Sakurada O & Shinohara M. The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. *J. Neurochemistry* 28:897-916, 1977.

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By the use of 2-[^{14}C]deoxyglucose and quantitative autoradiography, glucose utilization is measured simultaneously in all structures of the brain of conscious and anesthetized rats. [The *SCI*® indicates that this paper has been cited in over 1,765 publications.]

Localization of Metabolic and Functional Activities in Brain

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March 30, 1989

The deoxyglucose method, which measures local cerebral glucose utilization (LCGU), has had a long gestation. In 1949, following two years of service as a neuropsychiatrist in the US Army Medical Corps, I joined Seymour S. Kety at the University of Pennsylvania to learn and apply his then recently developed N_2O method for measurement of average blood flow and metabolic rate in the brain as a whole in man.[1] Although the method demonstrated lowered cerebral metabolic rate in conditions associated with reduced levels of consciousness, it revealed no changes in cerebral energy metabolism during normal alterations of mental function or in functional psychoses. This suggested that normal mental functions and cerebral energy metabolism were not related, or else regions of brain involved in specific mental functions were too small or localized to be detected in measurements of average metabolic rate in the brain as a whole. What was needed was a method to measure energy metabolism simultaneously in all the local regions of the brain in the conscious state. The first step in this direction was the [^{131}I]trifluoroiodomethane method, which was based on Kety's[2] principles of inert gas exchange and was developed by Kety and his associates in 1955.[3] This method measured local cerebral blood flow, which normally correlates closely with local energy metabolism. A unique feature of the method was a quantitative autoradiographic technique that provided the anatomic localization. In 1956 I tried to use the autoradiographic technique to measure LCGU with [^{14}C]glucose, but the rapid loss of labeled products of its metabolism necessitated experimental periods too short to allow accurate assessment of precursor glucose specific activity in the tissue because of the lag of the tissue behind the blood or plasma. I, therefore, shelved the project. Soon thereafter, I learned of 2-deoxyglucose (DG), a hexose that in large doses causes coma like that in hypoglycemia but with normal or elevated blood glucose levels. A. Sols and R.K. Crane[4] had shown that DG, like glucose, was phosphorylated by hexokinase to deoxyglucose-6-phosphate (DG-6-P) but could not be metabolized further down the glycolytic pathway. It was subsequently shown that the coma was due to the accumulation of DG-6-P, which then competed with the relatively low glucose-6-phosphate (G-6-P) concentrations and blocked its further metabolism. DG-6-P accumulated because it was a poor substrate for enzymes in brain that metabolized G-6-P. These properties suggested that the use of radioactive DG might avoid the problems with labeled glucose and could be used to measure LCGU.

In 1964 M. Reivich and J. Jehle joined Kety and me at the National Institute of Mental Health (NIMH) and adapted the [^{131}I]trifluoroiodomethane method for use with [^{14}C]antipyrine. With quantitative ^{14}C autoradiography now available, the idea of measuring LCGU with [^{14}C]DG was resurrected. In 1968 Reivich, now back at the University of Pennsylvania, and our laboratory at NIMH began the collaboration that led to the DG method. We were fortunate to have a wonderfully competent, enthusiastic, and dedicated team, consisting of C. Kennedy, M.H. Des Rosiers, Jehle, O. Sakurada, M. Shinohara, C.S. Patlak, and K.D. Pettigrew.

Numerous experiments with the method provided unequivocal evidence of a close relationship between local cerebral functional and metabolic activities.[5] Indeed, the effects of altered functional activity on metabolic rate were often so pronounced that they could be visualized directly in the autoradiograms.

A "stain" for local functional activity in the nervous system has proved to be a powerful tool for physiological, pharmacological, and behavioral studies in many areas of neuroscience.[5,6] Also, the method has been adapted for human use with positron emission tomography. These are probably the reasons for the paper's frequent citation. The work has been recognized by the F.O. Schmitt Award in 1980, the Lasker Award in 1981, the US National Academy of Sciences Award in the Neurosciences in 1988, and the Georg von Hevesy Award in 1988.

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2. **Kety S S.** The theory and applications of the exchange of inert gas at the lungs and tissues. *Pharmacol. Rev.* 3:1-41, 1951. (Cited 1,000 times.) [See also: **Kety S S.** Citation Classic. *Current Contents/Life Sciences* 32(27):12, 3 July 1989.]
3. **Landau W H, Freygang W H, Rowland L P, Sokoloff L & Kety S S.** The local circulation of the living brain: values in the unanesthetized and anesthetized cat. *Trans. Amer. Neurol. Assn.* 80:125-9, 1955. (Cited 275 times.)
4. **Sols A & Crane R K.** Substrate specificity of brain hexokinase. *J. Biol. Chem.* 210:581-95, 1954. (Cited 440 times.)
5. **Sokoloff L.** Localization of functional activity in the central nervous system by measurement of glucose utilization with radioactive deoxyglucose. *J. Cerebr. Blood Flow Metabol.* 1:7-36, 1981. (Cited 170 times.)
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