Part II
Ischemia and the Blood-Brain Barrier Disorders
Experimental Cerebral Ischemia: The Contribution of the Bethesda Group

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Abstract Igor Klatzo started his research on cerebral ischemia at the NIH in the 1960s. The mechanism that produces the blood-brain barrier change after ischemia was a focus of interest in Klatzo’s experiments, which used larger mammals. Studies using Mongolian gerbils, started by U. Ito, resulted in several important findings, including observation of the maturation phenomenon in 1975. Using newly developed ischemia models, the mechanism of postischemic neuronal/tissue injury was extensively studied. The cumulative effect was observed after repetitive cerebral ischemia. The protective mechanism of cortical spreading depression after global ischemia was investigated. Projects including in vitro studies of human brain endothelial cells and mucosal tolerance to E-selectin were performed in the Stroke branch after Klatzo retired from the NIH. Klatzo published a biography of Cecil and Oskar Vogt after retirement. He passed away in May 2007 in Gaithersburg, Maryland a few months after he completed the first part of his autobiography.

Keywords Igor Klatzo • experimental cerebral ischemia • NIH

Igor Klatzo started his research on cerebral ischemia in the 1960s at the NIH. In the first series of studies, postischemic blood-brain barrier (BBB) changes as well as clinicopathological changes were the foci of interest. The first paper in this series of studies using larger mammals was published in 1970 in the first issue of Stroke journal (2), followed by reports on the ultra-structural changes and hemodynamic aspects of postischemic BBB changes (13). Biphasic opening of the BBB during the postischemic phase was reported in 1985 (10).

Research studies using Mongolian gerbils were started with U. Ito in the 1970s. Approximately one third of the gerbils developed ischemic symptoms such as circling hemiparesis and seizure after the occlusion of the unilateral common carotid artery (12). By selecting these sympto-positive animals (which will develop infarction), it is possible to have animals with a homogeneous intensity of tissue injury. In this series of investigations, the slow appearance of neuronal necrosis in the H2 (CA1) sector was observed. Shorter ischemic insults resulted in delayed appearances of necrosis (3). Blood-brain barrier disruption was also delayed as a result of milder ischemic insult (4). This facet of the response was named the ‘maturation phenomenon’. Energy failure after a short period ischemia also developed slowly over a few days of postischemia, with a tendency to be delayed in the areas suffering milder ischemic insults (11).

In Klatzo’s laboratory, several new animal models of cerebral ischemia have been developed and extensively tested. Studies using these new models of ischemia resulted in many interesting observations; after repetitive ischemic insults, a pronounced cumulative effect on brain edema and tissue injury was observed. The effect was most evident after 1 h interval ischemia, i.e. repetitive ischemia during the period of marked postischemic hypoperfusion (15). A model of complete global ischemia in a rat by Korpatchev (9) was introduced to Klatzo’s laboratory in the 1980s (6). This model is characterized by complete circulatory arrest, and it is much closer to clinical cardiac arrest than was previously employed in animal models. Postresuscitation pathophysiology was extensively investigated using this model. The protective effect of spreading depression was observed on the postischemic neurons (5).

Klatzo organized the first brain edema symposium with Franz Seitelberger from the University of Vienna Neurological Institute in 1965, and the proceedings were published by Springer Verlag (7) (Fig. 1). The succeeding international brain edema symposia were organized every 3 years in the USA, Europe, and Asia in rotation. Researchers who once worked in Klatzo’s laboratory organized most of the symposia. During Klatzo’s appointment at the Laboratory of Neuropathology and Neuroanatomical Sciences NINDS NIH, many researchers, including many neurosurgeons from Japan, visited his laboratory from all over the world.
Fig. 1  Inside cover of the proceedings of the First brain edema symposium. The symposium was organized by Klatzo and Seitelberger in 1965 in Vienna. The proceedings of the conference were published by Springer in 1967

After Klatzo retired from NIH, important projects including in vitro study of human brain endothelial cell (1) and mucosal tolerance have been performed. Hallenbeck succeeded Klatzo’s at NINDS, NIH, and continued his project on the mucosal tolerance to E-selectin (14). The project is very interesting from a clinical point of view, and it has resulted in important publications.

After retirement from the NIH in 1993, Klatzo focused his academic activity on writing a biography on Cecil and Oskar Vogt, the men who proposed the pathoclisis theory, and founders of the Brain Research Institute in Neustadt, Germany, where Klatzo started his academic career. The book was published by Springer Verlag in 2002 (8).

After publishing the biography, Klatzo started writing his autobiography. In October 9, 2006, he arranged a party in the Blue Ridge Mountains Virginia to celebrate his 90th birthday. His former collaborators, family members and friends gathered to celebrate the occasion. Several months after the party, his health conditions declined. He returned home and passed away on May 5, 2007 in Gaithersburg Maryland (Fig. 2).

Conflict of interest statement  We declare that we have no conflict of interest.

References


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Czernicki, Z.; Baethmann, A.; Ito, U.; Katayama, Y.;
Kuroiwa, T.; Mendelow, A.D. (Eds.)
2010, XIII, 403 p., Hardcover
ISBN: 978-3-211-98758-2