Introduction

Ongoing interest in brain ischemia research has provided data showing that ischemia may be involved in the pathogenesis of Alzheimer’s disease; Transient brain ischemia in the rat produces a stereotyped pattern of selective neuronal degeneration, which simulates early Alzheimer’s disease pathology. Some animals that survive 1 year after brain ischemia developed brain atrophy, which is indicative of an active, slowly progressing neuropathological process; More recently, it has become recognized by us that neuropathological processes continue well beyond the acute stage. The profile of microvascular pathology that is observed in an experimental rat model of global brain ischemia shares a commonality with neurodegeneration processes in Alzheimer’s disease. The objective of this study was to further develop and characterize cardiac arrest model in rats, which provides practical way to analyze Alzheimer’s-type neurodegeneration.

Main aim

Our focus here will be to present a brief description of major pathological events that occur within the microvascular compartment (BBB, platelets & APP changes) as a consequence of ischemia-reperfusion brain injury with long-term survival.
Methods

Using female Wistar rats, blood-brain barrier changes, distribution of different fragments of amyloid precursor protein and platelets pathology were examined after 5-10 min global brain ischemia with survival time until 1 year; Rats were perfusion fixed for light and electron microscopic analysis

Experimental protocol

- Cardiac arrest:
  5 - 10 min
- Survival period:
  1, 7 Days
  6, 12 Months
Ischemic Blood-Brain Barrier and Alzheimer’s Amyloid Plaques Development

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Results
Postischemic rats with short and long-term survival demonstrated chronic dysfunction and random blood-brain barrier changes; Permeability alterations were spotty and dispersedly in cortex, hippocampus, thalamus, basal ganglia, cerebellum and white matter; Horseradish peroxidase extravasations involved capillaries, venules, veins and arterioles; Plenty of different fragments of amyloid precursor protein deposits were associated with the capillaries; Perivascular deposits of amyloid took the same form as extravasated peroxidase; Our investigation revealed numerous platelet aggregates of varying sizes within microvessels; Aggregates of platelets like blood-brain barrier changes and amyloid deposits were focal, random and dispersedly; Some platelets were found outside the brain microvessels in the perivascular space; Blood-brain barrier changes and platelet aggregation correlated well with amyloid deposits in perivascular space;
Ischemic Blood-Brain Barrier
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Recent studies have postulated an association between the blood-brain barrier and vascular sequestration and perivascular accumulation of β-amyloid peptide in brain parenchyma. This stimulated us to study whether experimental opening of the blood-brain barrier by global brain ischemia in the rat, may influence transport of circulating β-amyloid peptide and deposition of β-amyloid peptide in the brain as plaques.
Experimental procedures

Group 1
Single global brain ischemia - 10 min
- 1st injection: 5 mg of human β-amyloid peptide 1-42 i.v during 15 min after ischemia
- Next 3 times/week, 1 mg of human β-amyloid peptide 1-42 i.v.
- 3 months survival
- Adequate controls
- 4G8 antibody for identification movement of human β-amyloid peptide 1-42 across ischemic blood-brain barrier

Group 2
Repeated global brain ischemia
1st – 10 min interval 1 month
2nd – 3.5 min interval 1 month
3rd – 3.5 min
- After all ischemic insults, injection 5 mg of human β-amyloid peptide 1-42 i.v during 15 min after ischemia
- Next 3 times/week, 1 mg of human β-amyloid peptide 1-42 i.v.
- 3 months survival
- Adequate controls
- 4G8 antibody for identification movement of human β-amyloid peptide 1-42 across ischemic blood-brain barrier
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Conclusion

Chronic ischemic blood-brain barrier dysfunction, platelet-vessel wall interactions, and platelets in the perivascular space with different fragments of amyloid precursor protein accumulation, may be involved in the gradual maturation of injurious process leading over a lifetime to development amyloid plaques.
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Data are taken from:

- Brain Res., 649: 323-328, 1994
- NeuroReport 7: 1261-1265, 1996
- NeuroReport 10: 3615-3619, 1999