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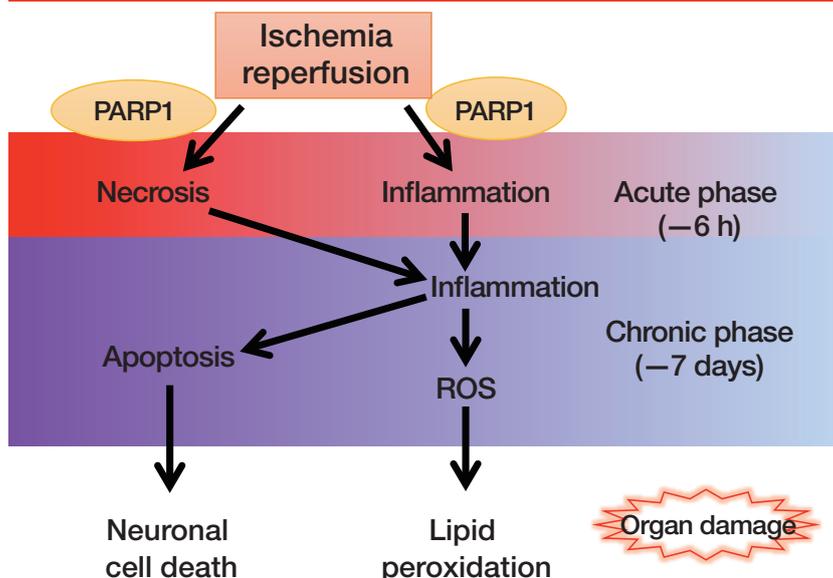
Purpose of Research

Various organs may be damaged when blood flow resumes after the treatment of cerebral and myocardial infarctions. In ischemia/reperfusion injuries, excessive activation of the poly (ADP-ribose) polymerase 1 (PARP1) molecule, which acts as a repair enzyme for healthy DNA, induces tissue damage. Therefore, there is demand for the development of a PARP1 inhibitor. However, conventional therapeutic agents for ischemia/reperfusion injury cause side effects due to their mechanism of action, and effective medication has yet to be developed. Our laboratory is developing a new drug with a novel mechanism for the treatment of ischemia/reperfusion injury.

Summary of Research

Ischemia/reperfusion injury is organ damage caused by the resumption of blood flow during the treatment of and/or recovery period after the treatment of ischemic diseases, which include cerebral infarction and myocardial infarction, and transient ischemia due to organ transplantation. This injury results from tissue damage by free radicals and inflammatory cytokines, which are caused by an excess of reactive oxygen species produced in the presence of fresh blood after ischemia. Cell death accompanied by the excessive activation of PARP1 is a known cause of this. Therefore, PARP1 inhibitors are considered to be effective drugs for ischemia reperfusion injury. So far, many PARP1 inhibitors have been clinically evaluated. However, most of those have side effects on organs other than the one targeted, due to their competitive inhibitory mechanism. The candidate PARP1 inhibitor found in this study has a novel mechanism which degrades the PARP1 protein. This compound is expected to become a drug for ischemia/reperfusion injury treatment, which acts with different molecular mechanism.

Cerebral Ischemia Reperfusion Injury (Acute phase to chronic phase)



Comparison with Conventional or Competitive Technologies

Almost all available PARP1 inhibitors are NAD⁺ mimetics, i.e. aimed at binding to the catalytic domain of PARP1 and competition with NAD⁺. The candidate PARP1 inhibitor found in this study has a novel mechanism which degrades the PARP1 protein in both p53 protein and proteasome-dependent manners. This compound is expected to become a drug for ischemia/reperfusion injury treatment with few side effects, because it is potentially effective at low concentrations.

Expected Applications

- A drug for ischemia/reperfusion injury
- An anticancer agent, particularly breast cancer with BRCA mutations

Future Developments

A detailed analysis of the PARP1 degradation mechanism in collaboration with interested companies.

- Intellectual Property: Japanese Patent No. 5954839
- Sample: Available

