INCREASE IN TRANSFORMING GROWTH FACTOR-BETA IN THE BRAIN DURING INFECTION IS RELATED TO FEVER, NOT DEPRESSION OF SPONTANEOUS MOTOR ACTIVITY

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Background- When viral infection occurs, this information is transmitted to the brain, and symptoms such as fever and tiredness are induced. One of the causes of these symptoms is the secretion of proinflammatory cytokines in blood and the brain. Transforming growth factor-beta (TGF-beta), a pleiotropic cytokine, regulates cell proliferation, differentiation and apoptosis, and plays a key role in development and tissue homeostasis. Generally, TGF-beta is known as an anti-inflammatory cytokine because it suppresses microglial activation and B-lymphocyte functions. However, the role of TGF-beta in infectious diseases remains unclear, therefore we investigated the relationship between TGF-beta in the brain and the physiological response against viral infection.

Procedure- We used eight-week-old male Sprague-Dawley rats and viral mimic, polyinosinic:polycytidylic acid (poly I:C) to make an experimental infection model. After intraperitoneal administration of poly I:C to rats, we collected the cerebrospinal fluid for the measurement of brain TGF-beta level. Second, we administered TGF-beta to the brain of intact rats and measured their body temperature.

Results- Intraperitoneal administration of poly I:C significantly elevated body temperature and decreased spontaneous motor activity of the rats. Poly I:C increased TGF-beta concentration in the cerebrospinal fluid. Pretreatment of an anti-TGF-β antibody partially inhibited fever induced by poly I:C; however, this treatment did not affect the decrease in spontaneous motor activity. Intracisternal administration of TGF-β raised the body temperature. Pretreatment with cyclooxygenase-2 (COX-2) selective inhibitor significantly suppressed TGF-beta-induced fever. COX-2 is known as one of the rate-limiting enzymes of the PGE2 synthesis pathway, suggesting that fever induced by TGF-beta is COX-2 and PGE2 dependent. TGF-beta increased PGE2 levels in cerebrospinal fluid and increased the expression of COX-2 in the endothelial cells of brain blood vessels.

Conclusion- Theses results raise the possibility that TGF-beta may increase in the brain during infectious disease and may be partially related to fever. In addition, these results clearly indicate the pro-inflammatory aspect of this pluripotent cytokine and present a novel mechanism for the pro-inflammatory actions of TGF-beta in the brain.