

炎症性疼痛ラットの腰髄後角における TNF- α 誘導性 ASK1-JNK1 経路の活性化

用皆 正文

理学療法・作業療法学領域（理学療法学分野）

（指導教員：米 和徳 教授）

本研究の目的は、持続性の炎症性疼痛による腰髄後角内 Tumor necrosis factor- α (TNF- α) 誘導性 Apoptosis signal-regulating kinase 1 (ASK1) - c-Jun N-terminal kinase 1 (JNK1) 経路と、反応性アストロサイト内発現について評価することである。実験動物は、雄性 Wistar 系統ラット 9 週齢を使用した。Complete Freund's Adjuvant (完全フロイントアジュバント；CFA) を右側後肢足底に注入し、注入 7 日後と 17 日後、28 日後に各 5 匹を屠殺し、3 匹には何ら処置を加えず対照群とした。屠殺後、組織を摘出し、形態学的、免疫組織学的、生化学的観察を行った。

対照群と比較して、腰髄両側後角内の TNF- α 、phospho ASK1 (pASK1) と phospho JNK1 (pJNK1) の陽性領域割合が CFA 注入 7 日後に有意に増加した。pASK1、pJNK1 が腰髄両側後角内の反応性アストロサイト、神経細胞、オリゴデンドロサイトに発現していた。TNF- α と pASK1 の陽性領域割合、pASK1 と pJNK1 の陽性領域割合、pJNK1 と GFAP の陽性領域割合、GFAP の陽性領域割合と疼痛反応閾値が有意に相関した。

以上の結果より、持続性の炎症性疼痛により TNF- α 誘導性 ASK1-JNK1 経路が腰髄後角内にて活性化され、アロディニアに関与している可能性が示唆された。

キーワード：炎症性疼痛、Complete Freund's Adjuvant、TNF- α 誘導性 ASK1-JNK1 経路、反応性アストロサイト、アロディニア

Abstract

The activation of TNF- α induced ASK1-JNK1 signal pathway in the lumbar spinal cord dorsal horn in inflammatory rat model

Masafumi Youkai

Division of Physical Therapy and Occupational Therapy

(Section of Physical Therapy)

(Thesis Advisor ; Prof. Kazunori Yone)

The purpose of this study is to clarify immunohistochemically the role of the tumor necrosis factor- α (TNF- α) induced apoptosis signal-regulating kinase 1 (ASK1) - c-Jun N-terminal kinase 1 (JNK1) signal pathway and to identify the activation of the signal pathway in reactive astrocytes in the rat spinal cord dorsal horn in a model of persistent inflammatory pain induced by unilateral intraplantar complete Freund's adjuvant (CFA). Eighteen rats were randomly divided four groups as follows, CFA uninjected group rats, CFA injected seven days group rats, CFA injected seventeen days group rats and CFA injected twenty-eight days group rats. Three CFA uninjected group rats were sacrificed at the age of 9 weeks. CFA injected seven days group, seventeen days group rats and twenty-eight days group rats were sacrificed at seven day, seventeen day and twenty eight day each other after CFA injection from the age of 9 weeks. After the sacrifice, spinal cords were removed and served for histological, immunohistological and biochemical examination.

Compared to the control (untreated) group, the percentage of TNF- α , phospo ASK1 (pASK1) and phospo JNK1 (pJNK1) -positive area in the bilateral lumbar spinal dorsal horn increased significantly on seven days group after CFA injection. pASK1 and pJNK1 were expressed in astrocytes, neurons and oligodendrocytes in the bilateral lumbar spinal dorsal horn. The percentage of TNF- α -positive area and pASK1-positive area, pASK1-positive area and pJNK1-positive area, pJNK1-positive area and GFAP-positive area, GFAP-positive area in the bilateral lumbar spinal dorsal horn and pain reaction threshold were significantly correlative.

In conclusion, it suggested that the TNF- α induced ASK1-JNK1 signal pathway by persistent inflammatory pain is activated in the bilateral lumbar spinal dorsal horn, and its signal pathway may involve in allodynia.

Key word : Inflammatory pain, Complete Freund's adjuvant, TNF- α induced ASK1-JNK1 signal pathway, Reactive astrocytes, Allodynia