

総説

## 神経障害性疼痛に対する牛車腎気丸の分子薬理機序の解明 — 脊髄活性化ミクログリア由来の TNF- $\alpha$ を抑制して痛みを軽減する

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**要旨：**高齢者は、神経障害性疼痛の発生率が高く、鎮痛薬の副作用の問題から治療手段が限られるため、慢性疼痛に移行しやすい。漢方薬の牛車腎気丸 (GJG) は、古来より痛みを含めた高齢者の諸症状に使われてきたが、その鎮痛機序は十分に解明されていない。今回、我々は、絞扼性神経損傷 (CCI) モデルマウスを用いて、GJG の鎮痛効果の分子薬理機序を解明することを目的とした。痛み行動テストでは、GJG は早期より CCI 群の疼痛閾値の低下を有意に改善した。免疫組織化学染色およびウエスタンブロット法による組織学的検討では、GJG は、CCI 群における脊髄の Iba1 および TNF- $\alpha$  の発現が増加、これらの共発現を有意に抑制した。TNF- $\alpha$  の髄腔内投与が、GJG の鎮痛効果に及ぼす影響を検討した。TNF- $\alpha$  投与と GJG の鎮痛効果との間には負の相乗効果があった。以上の結果より、GJG はミクログリア由来の TNF- $\alpha$  の発現を抑制して神経障害性疼痛を軽減させることが明らかになった。今後は、GJG は神経炎症応答による神経障害性疼痛の治療に有用な薬剤となる可能性が示唆された。

**索引用語：**牛車腎気丸, TNF- $\alpha$ , ミクログリア, 絞扼性神経損傷 (CCI) モデル, 漢方薬

### PAIN AND KAMPO MEDICINE Vol.28 (2018)

Goshajinkigan (GJG) attenuated allodynia via suppression of the TNF- $\alpha$  derived from microglia in chronic constriction injury model mice  
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**Abstract:** Elderly patients in general indicate a higher incidence of chronic and neuropathic pain (NP) conditions. Goshajinkigan (GJG), a traditional Japanese medicine, has been used for meralgia and numbness in elderly patients. However, the exact mechanism of GJG is unclear. This study aimed to investigate the molecular mechanism of the analgesic effect of GJG in a chronic constriction injury (CCI) model. GJG significantly reduced allodynia and hyperalgesia from the early phase. Immunohistochemistry (IHC) and western blot analysis showed that GJG suppressed the number of Iba1 and TNF- $\alpha$  in the ipsilateral dorsal horn. Double IHC staining indicated that TNF- $\alpha$  was expressed in Iba1-positive cells in CCI mice. GJG significantly decreased the number of TNF- $\alpha$ /Iba1 double positive cells. To confirm the relationship between GJG and TNF- $\alpha$  in pain alleviation, we intrathecally injected (i.t.) TNF- $\alpha$  into the GJG treated CCI mice. Lt.TNF- $\alpha$  opposed the anti-allodynic effect of GJG in the cold-plate test. A synergistic interaction between GJG and TNF- $\alpha$  in increasing neuropathic pain was observed. We clearly demonstrated that GJG attenuated hyperalgesia and allodynia in CCI mice via suppression of the TNF- $\alpha$  derived from microglia. GJG is thus a promising drug for the treatment of neuropathic pain induced by neuro-inflammation.

**Key words:** Goshajinkigan (GJG), TNF- $\alpha$ , microglia, chronic constriction injury (CCI) model, Kampo medicine

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