

原 著

## 糖尿病病態において増強する牛車腎気丸の抗侵害受容作用機序 ——ダイノルフィンと一酸化窒素の関与——

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要旨：糖尿病動物で増強する牛車腎気丸の抗侵害受容作用は、ダイノルフィンの遊離と一酸化窒素の産生増加に基づくことが示唆された。糖尿病病態では脊髄内 $\kappa$ オピオイド受容体を介する抗侵害受容機構が亢進し、一酸化窒素の末梢性抗侵害受容作用も増強することが明らかになった。牛車腎気丸は末梢血行障害改善作用も併せ持っており、糖尿病患者の自覚症状軽減を図る上で理に適った漢方薬と考えられた。

索引用語：牛車腎気丸，抗侵害受容作用，ダイノルフィン，一酸化窒素，糖尿病

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#### Antinociceptive mechanisms of Gosha-jinki-gan in streptozotocin-induced diabetic animals

##### —— Roles of dynorphin and nitric oxide ——

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**Abstract** : The antinociceptive effect of Gosha-jinki-gan and its mechanism of action were examined in streptozotocin-induced diabetic mice and rats. Gosha-jinki-gan (0.1-1.0 g/kg, p.o.) administered to diabetic mice, which had lower nociceptive threshold values than non-diabetic mice, exhibited more potent antinociceptive activity than in non-diabetic mice, as determined by the tail-pressure test. The antinociceptive effect of Gosha-jinki-gan (0.3 g/kg, p.o.) in diabetic mice was inhibited by administration of either anti-dynorphin A (1-13) antiserum (5  $\mu$ g, i.t.) or nornalorphimine (10 mg/kg, s.c.), a  $\kappa$ -opioid receptor antagonist. The antinociceptive activity of Gosha-jinki-gan (0.3 g/kg, p.o.) was eliminated by a combination of anti-dynorphin antiserum (5  $\mu$ g, i.t.) and N<sup>G</sup>-nitro-L-arginine methyl ester (L-NAME; 5 mg/kg, i.p.), a nitric oxide synthase inhibitor. When L-NAME (10  $\mu$ g) or methylene blue (500  $\mu$ g) was topically administered to the intraplantar of the hind paw, the region used for the paw-pressure test, the antinociceptive activity of Gosha-jinki-gan (0.3 g/kg, p.o.) in diabetic rats was decreased. These results suggested that the increased antinociceptive effect of Gosha-jinki-gan on diabetic animals resulted from the stimulation of spinal  $\kappa$ -opioid receptors via dynorphin release and the peripheral action of increasing levels of nitric oxide. Gosha-jinki-gan was considered useful for treating painful diabetic neuropathy.

**Key words** : Gosha-jinki-gan, antinociceptive effect, dynorphin, nitric oxide, diabetic animals

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