IJAE

Italian Journal of Anatomy and Embryology

Official Organ of the Italian Society
of Anatomy and Histology

78° Congresso
della Società Italiana di Anatomia e Istologia
Ravenna, 18-20 settembre 2025

78TH Meeting
of the Italian Society of Anatomy and Histology
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Vol. 129
N. 1
2025
Supplement
ISSN 1122-6714

FIRENZE
UNIVERSITY
PRESS

IJAE
Italian Journal of Anatomy and Embryology
Official Organ of the Italian Society of Anatomy and Histology

Founded by Giulio Chiarugi in 1901

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Firenze University Press
via Cittadella, 7
I-50144 Firenze, Italy
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Available online at
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Therapeutic Potential of a novel GPR120 Agonist (GprA) in Experimental Bile Duct Ligation- Associated Hepatic Fibrosis

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Free fatty acids (FFAs) may exert a direct protective role in inflammation and metabolism through their interaction with a subset of G protein-coupled receptors known as free fatty acid receptors (FFARs), including FFAR4 (GPR120) (1). Administration of FFAs has been reported to improve various liver diseases, including cholestatic conditions, which are characterized by impaired bile flow due to hepatocyte and cholangiocyte dysfunction (2). Building on this evidence, we investigated the effects of a GPR120 agonist (GprA) on liver fibrosis using a surgically induced cholestasis model via bile duct ligation (BDL). In this study, animals were administered with GprA orally at a dose of 60 mg/kg daily for three weeks. The effects of GprA were compared to those of obeticholic acid (OCA, 30 mg/kg daily), an approved treatment for primary biliary cirrhosis (3). GprA was well tolerated, resulting in a significant 40% improvement in survival compared to the untreated BDL group. Although GprA did not significantly affect inflammatory markers, including interleukins -1α, -1β, - 4, -5, -10, and -6, it effectively reduced the expression of key pro-fibrotic markers such as collagen types I and III, connective tissue growth factor (CTGF), and vimentin. Additionally, GprA modulated enzymes involved in extracellular matrix remodeling, including several matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), leading to a marked attenuation of the fibrogenic process. Moreover, GprA significantly decreased the expression of critical fibrogenesis-related proteins, including alpha-smooth muscle actin (α-SMA), a marker of hepatic stellate cell activation responsible for extracellular matrix deposition, and cytokeratin 19, indicative of cholangiocyte proliferation. Unexpectedly, OCA treatment was entirely ineffective in this experimental model, with treated animals exhibiting approximately 90% mortality. In conclusion, GprA demonstrates promising efficacy in mitigating fibrosis and cirrhosis severity in the BDL mouse model. Further investigations in additional experimental models of liver fibrosis are warranted and may pave the way for the development of effective therapeutic agents for various currently unresolved liver diseases.

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Keywords: Fibrosis, liver, free fatty acids.