

Metabolic Roles of Endocannabinoid System in Alcoholic Fatty Liver

정 원 일

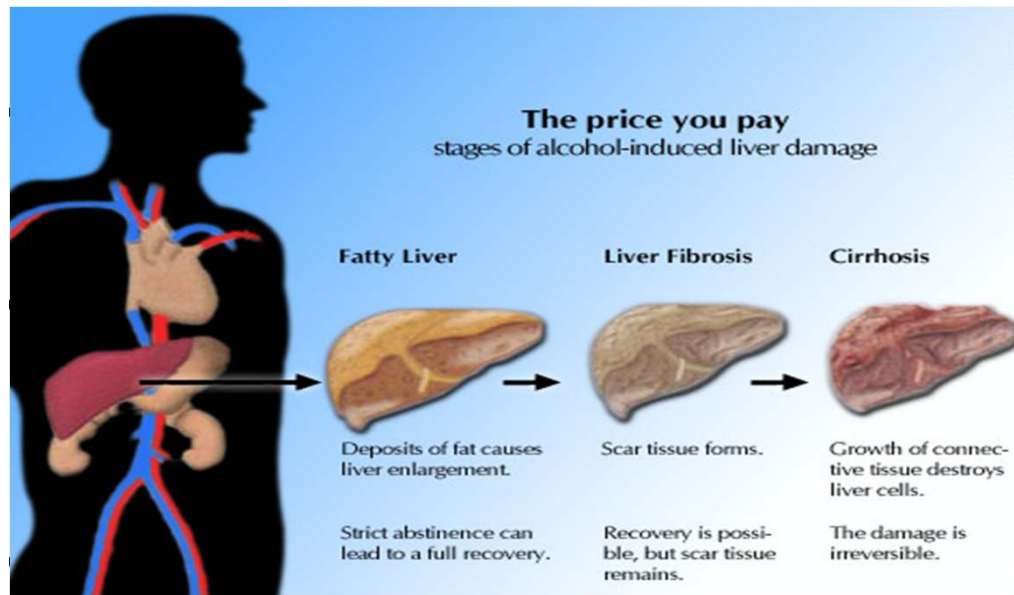
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❖ Alcoholic Liver Disease



of liver diseases in many

diseases include hepatic fibrosis, cirrhosis, and

attributed to **enhanced**

hepatic lipogenesis and **decreased fatty acid oxidation** in liver

- **Obesity** is also frequently associated with **fatty liver** and subsequent development of cirrhosis, and **high-fat diets** in rodents induce obesity, hepatic lipogenesis and steatosis

❖ Endocannabinoid and steatosis



Cannabis
(Marihuana)

- Endogenous cannabinoids (**endocannabinoids**) are lipid mediators that interact with cannabinoid receptors to produce effects similar to those of marihuana.
- To date, two types of main endocannabinoids and receptors (CBs) have been identified respectively; **Anandamide** and 2-arachidonoylglycerol (**2-AG**), **CB1** receptor (brain, liver, peripheral tissues) and **CB2** receptor (immune and hematopoietic cells)
- Endocannabinoids and **CB1 receptors** have been recently identified in the mouse fatty liver, where their expression is increased in response to a **high fat diet**.

Research article  Related Commentary, page 1130

Endocannabinoid activation at hepatic CB₁ receptors stimulates fatty acid synthesis and contributes to diet-induced obesity

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2005, JCI

- Mice deficient in CB1 receptors are **resistant** to high-fat-diet-induced **obesity and steatosis**, and in wild-type mice, both of these diet-induced effects are **reversed by** chronic treatment with a **CB1 receptor antagonist**
- The **hepatic steatosis** of genetically obese Zucker rats is also **reversed by CB1 antagonist** treatment and in wild-type mice, **CB1 blockade attenuates** the increase in **hepatic lipogenesis** induced by either a **high-fat diet** or treatment with a **cannabinoid agonist**



Research article

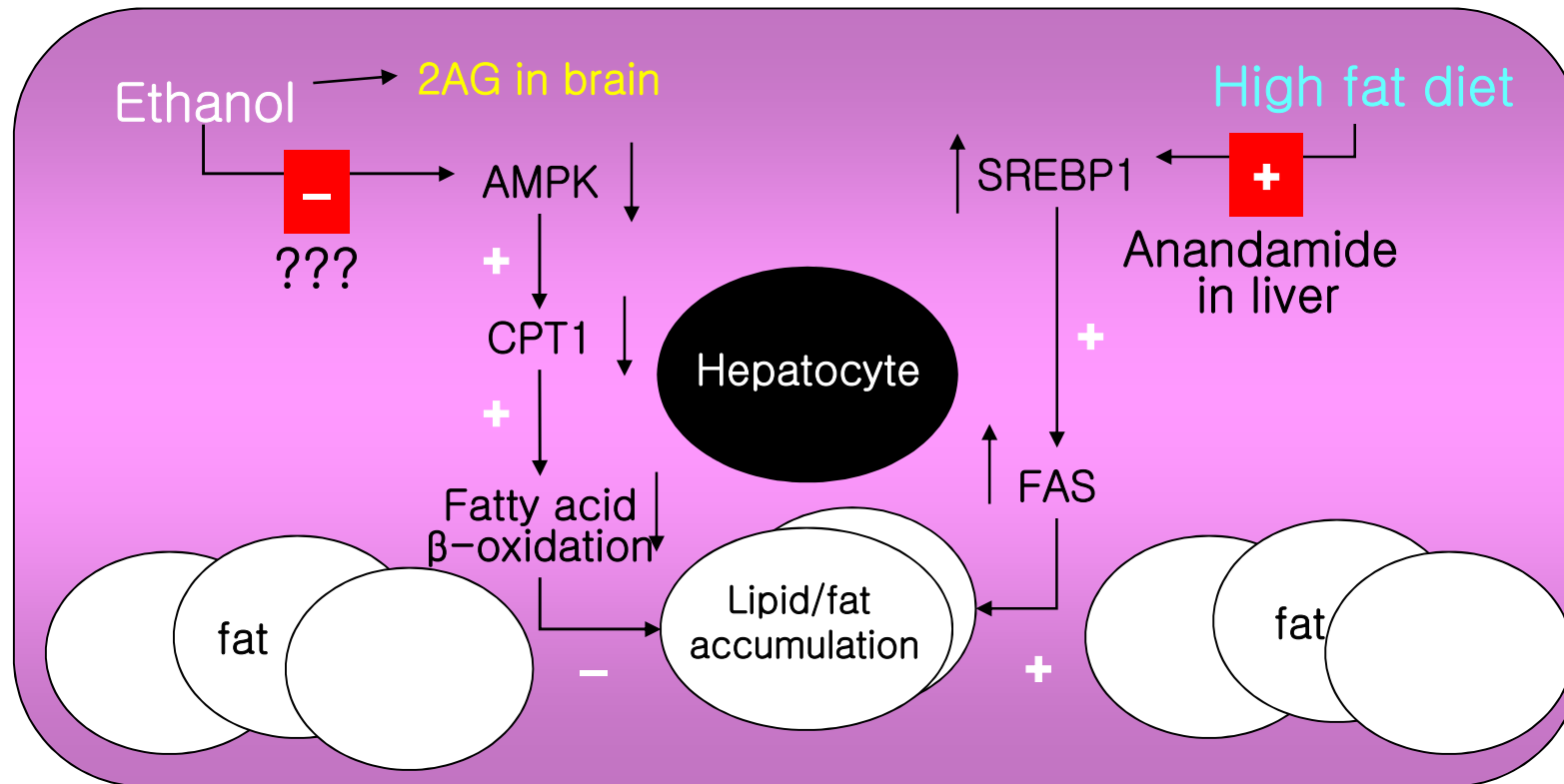


Hepatic CB₁ receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice

Douglas Osei-Hyiaman,¹ Jie Liu,¹ Liang Zhou,¹ Grzegorz Godlewski,¹ Judith Harvey-White,¹ Won-il Jeong,¹ Sándor Bátkai,¹ Giovanni Marsicano,² Beat Lutz,³ Christoph Buettner,⁴ and George Kunos¹

2008, JCI

- Hepatic CB1^{-/-} mice had **less steatosis, hyperglycemia**, dyslipidemia, **insulin** and leptin **resistance** than wild-type mice
- These findings implicated **endocannabinoids acting at hepatic CB1 receptors in diet-induced obesity, steatosis and insulin resistance**, although the possible role of CB1 receptors at extrahepatic sites, such as the central nervous system and/or adipose tissue, could not be excluded

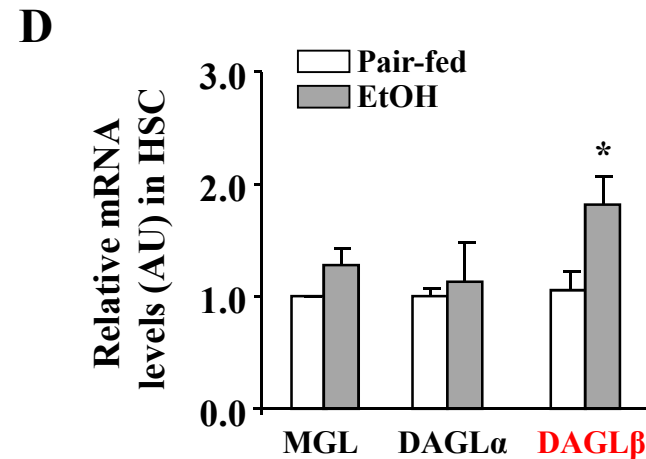
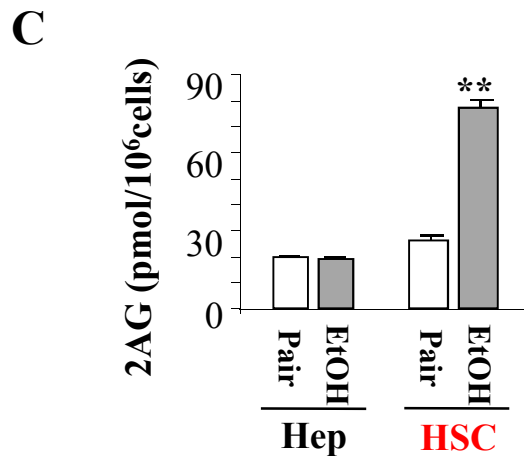
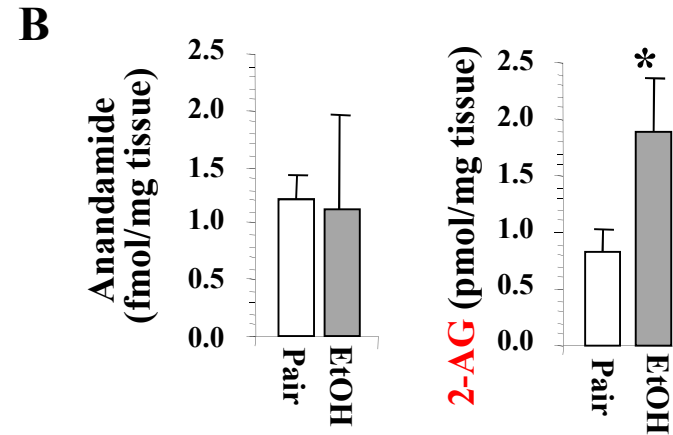
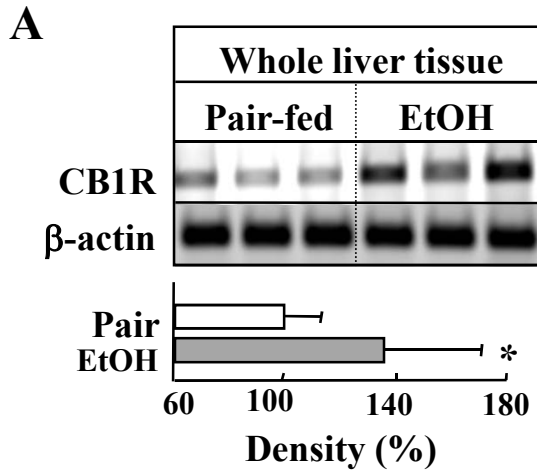


AMPK; AMP-activated protein kinase, **CPT1**; Carnitine palmitoyltransferase I,
SREBP1; Sterol response element-binding protein 1, **FAS**; fatty acid synthase

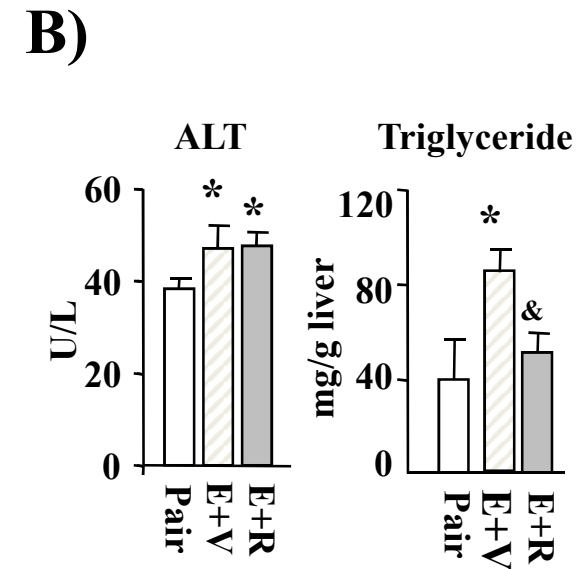
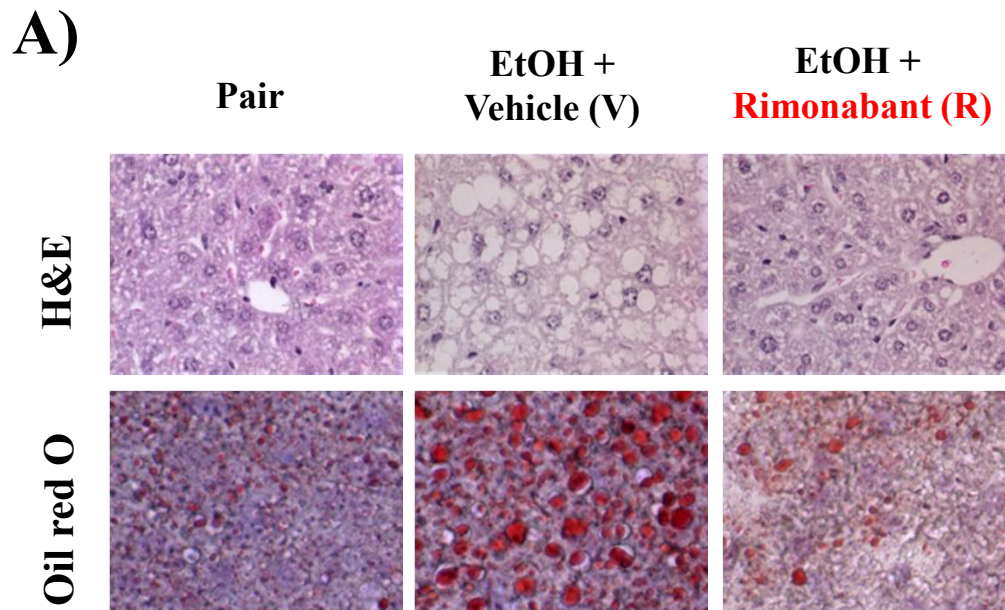
- Similar to high fat diet, **chronic ethanol exposure** can increase endocannabinoid levels, **at least in the brain**, suggesting that **endocannabinoids may also be involved in ethanol-induced fatty liver**.



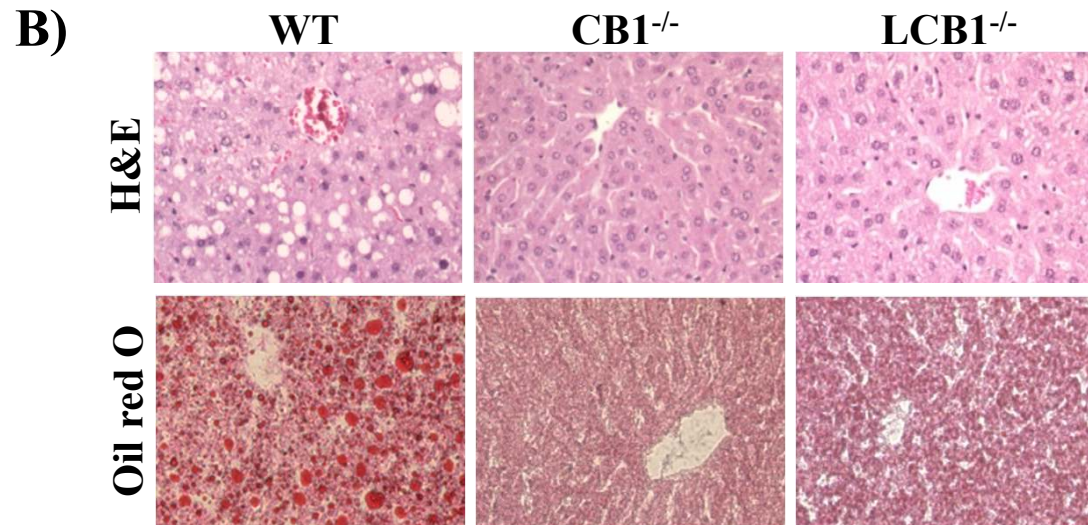
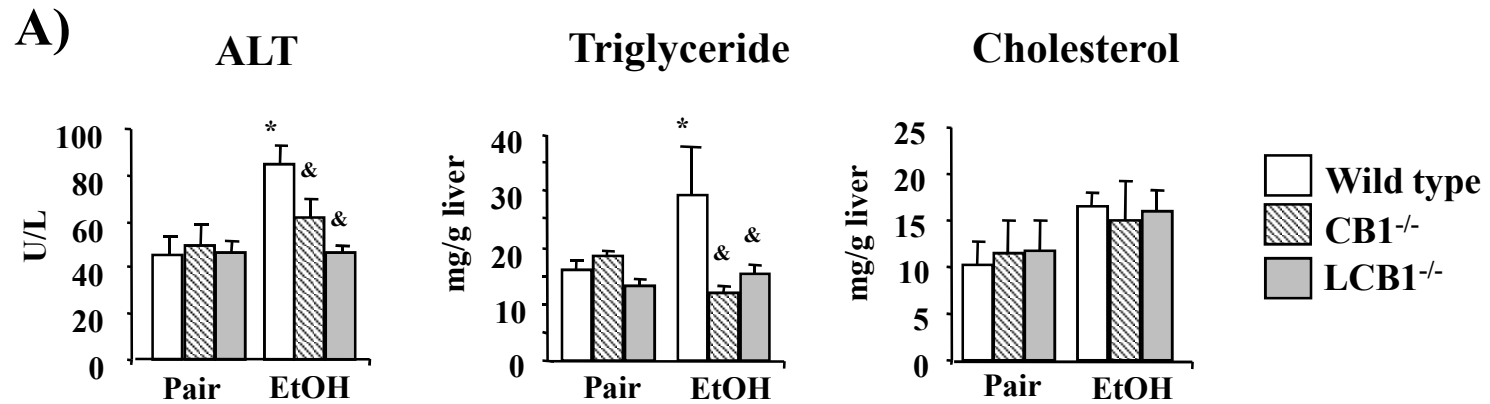
- We tested this hypothesis using a mouse model of alcoholic fatty liver
- Through the use of **wild-type mice** as well as **mice with either global or hepatocyte-specific genetic ablation of CB1 receptors**, we were able to provide a definitive answer as to the cellular target of endocannabinoids
- Our findings also revealed that a specific endocannabinoid, **2-AG**, generated in a unique cellular source, **the hepatic stellate cell**, is the most likely mediator involved



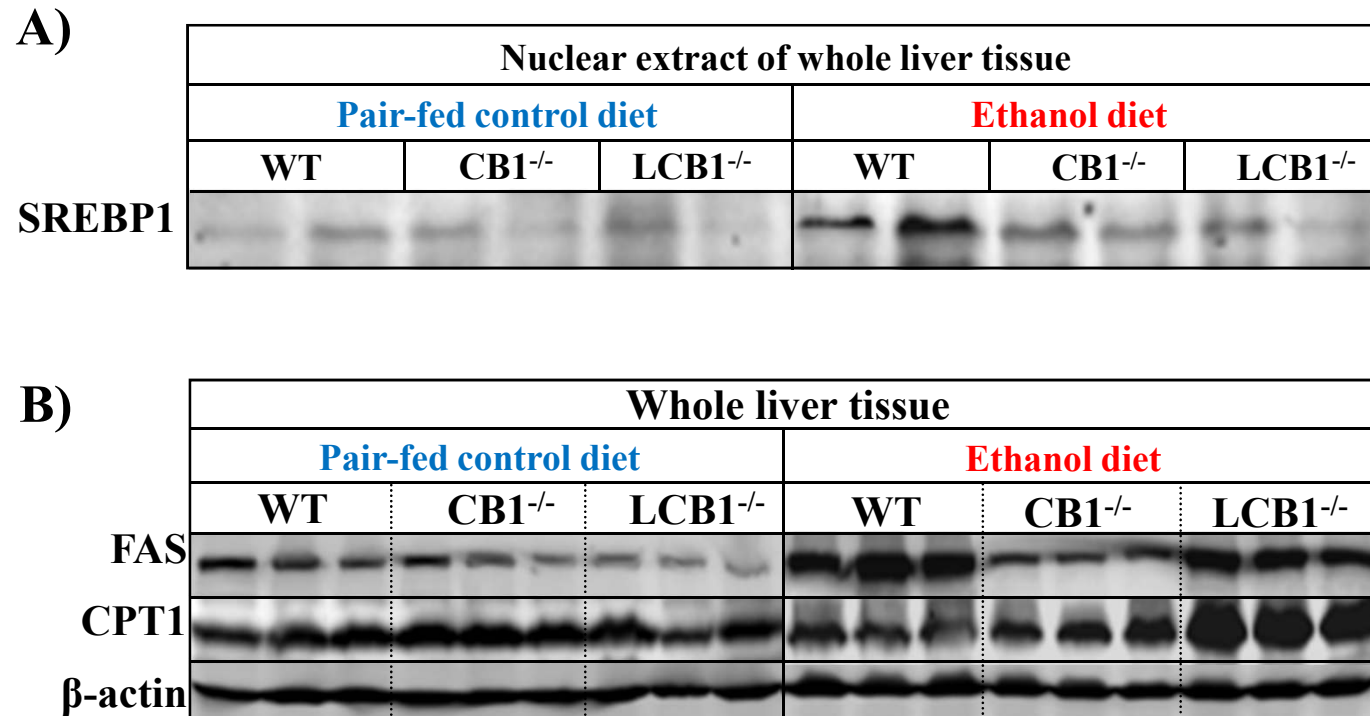
Chronic alcohol drinking induces CB1 receptor expression and endocannabinoid levels in the liver



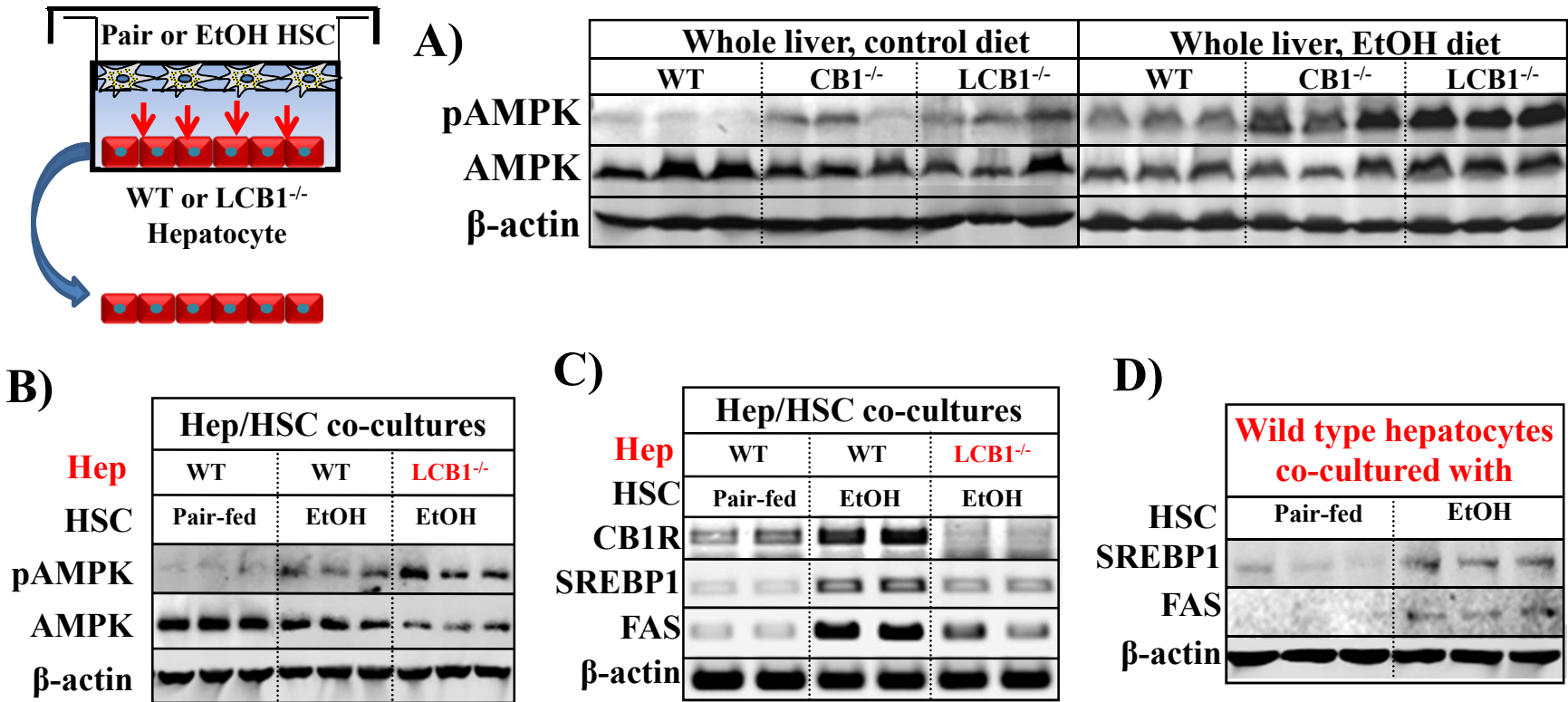
Hepatic steatosis is reduced by treatment of Rimonabant, CB1 receptor blocker



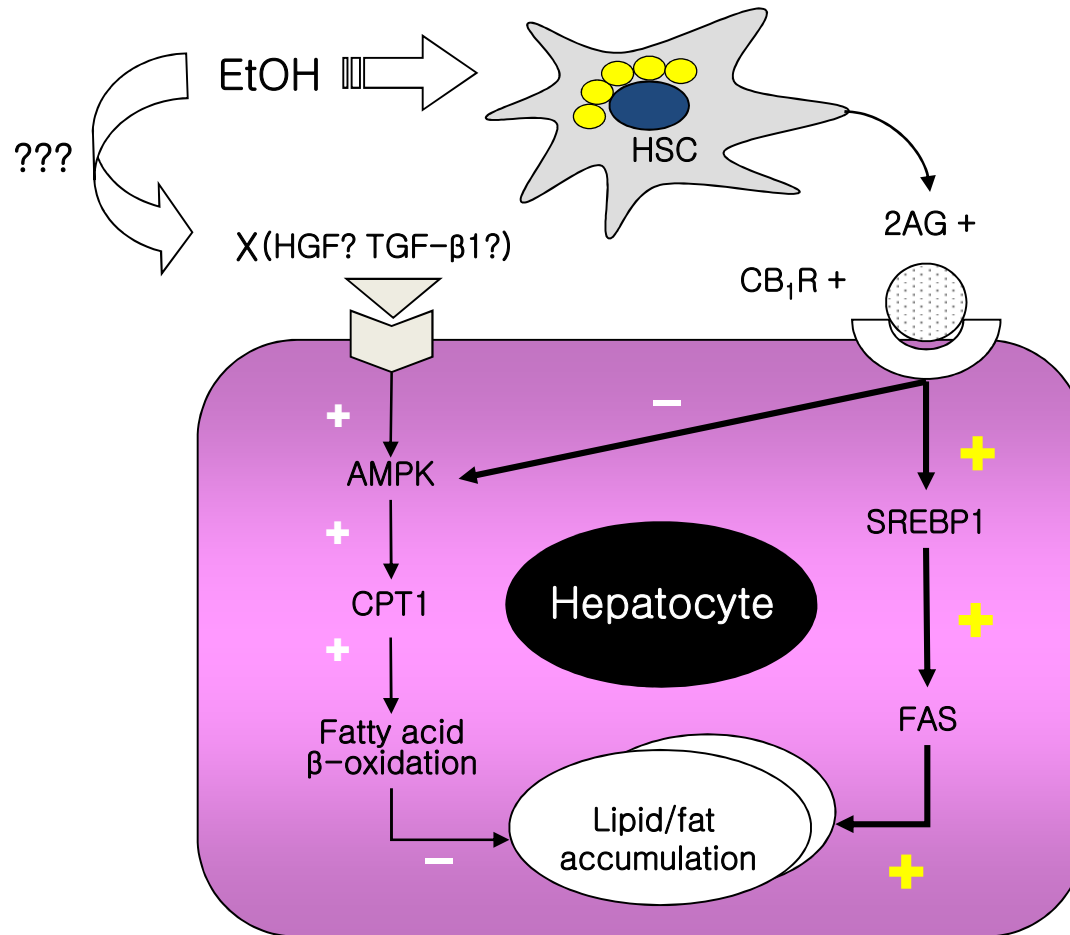
Mice with global or hepatocyte-specific knockout of CB1 receptors are resistant to ethanol-induced steatosis



Ethanol Upregulates Hepatic Lipogenic Gene Expression and Inhibits Fatty Acid Oxidation via Activation of Hepatic CB1 Receptors



Increased hepatic AMPK phosphorylation in the absence of CB1 receptors in ethanol-treated mice

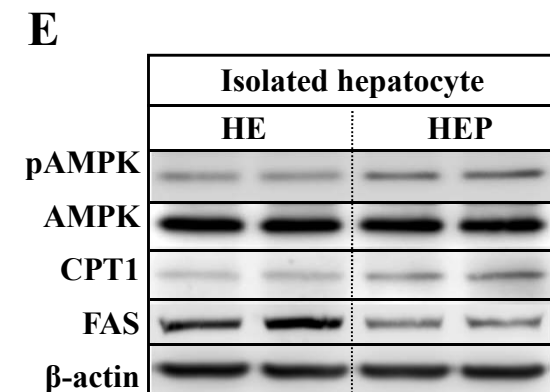
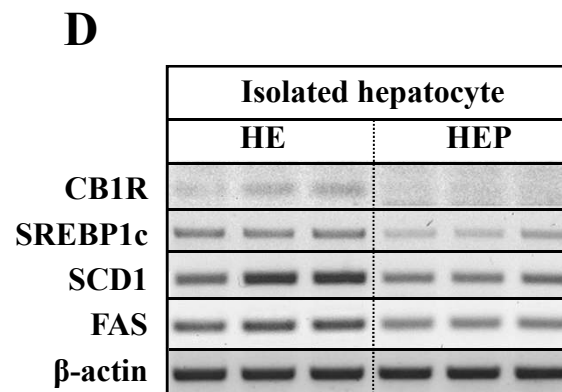
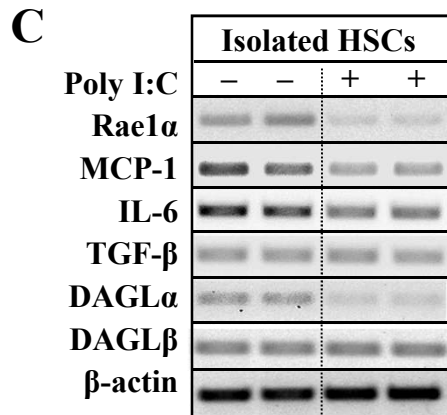
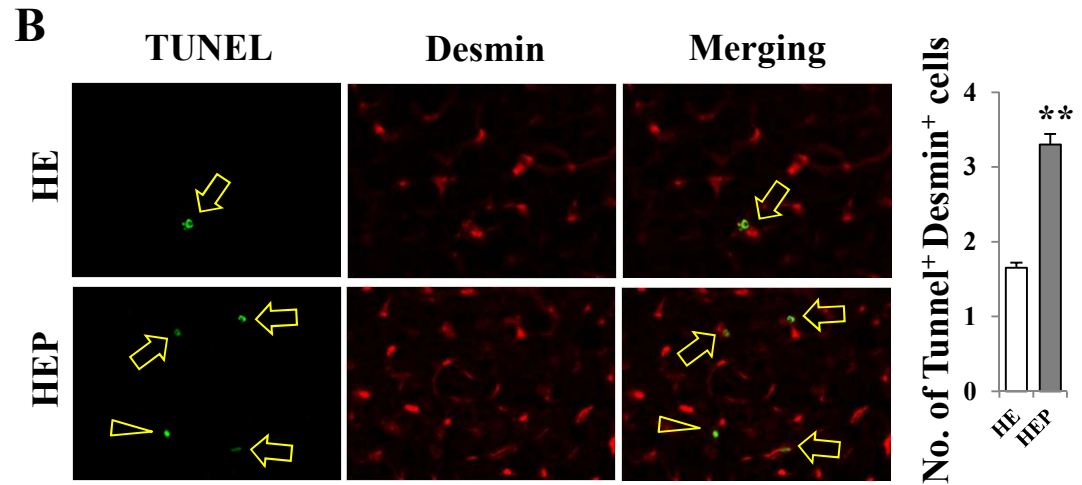
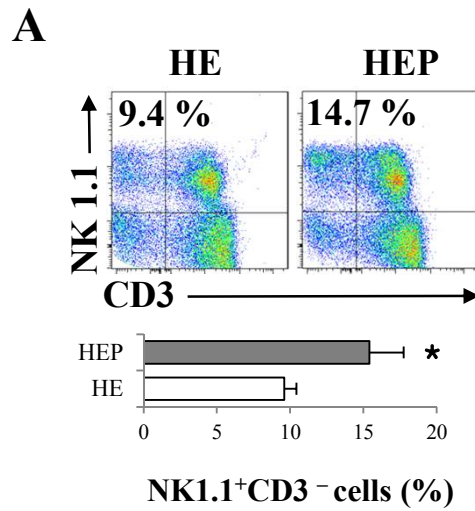


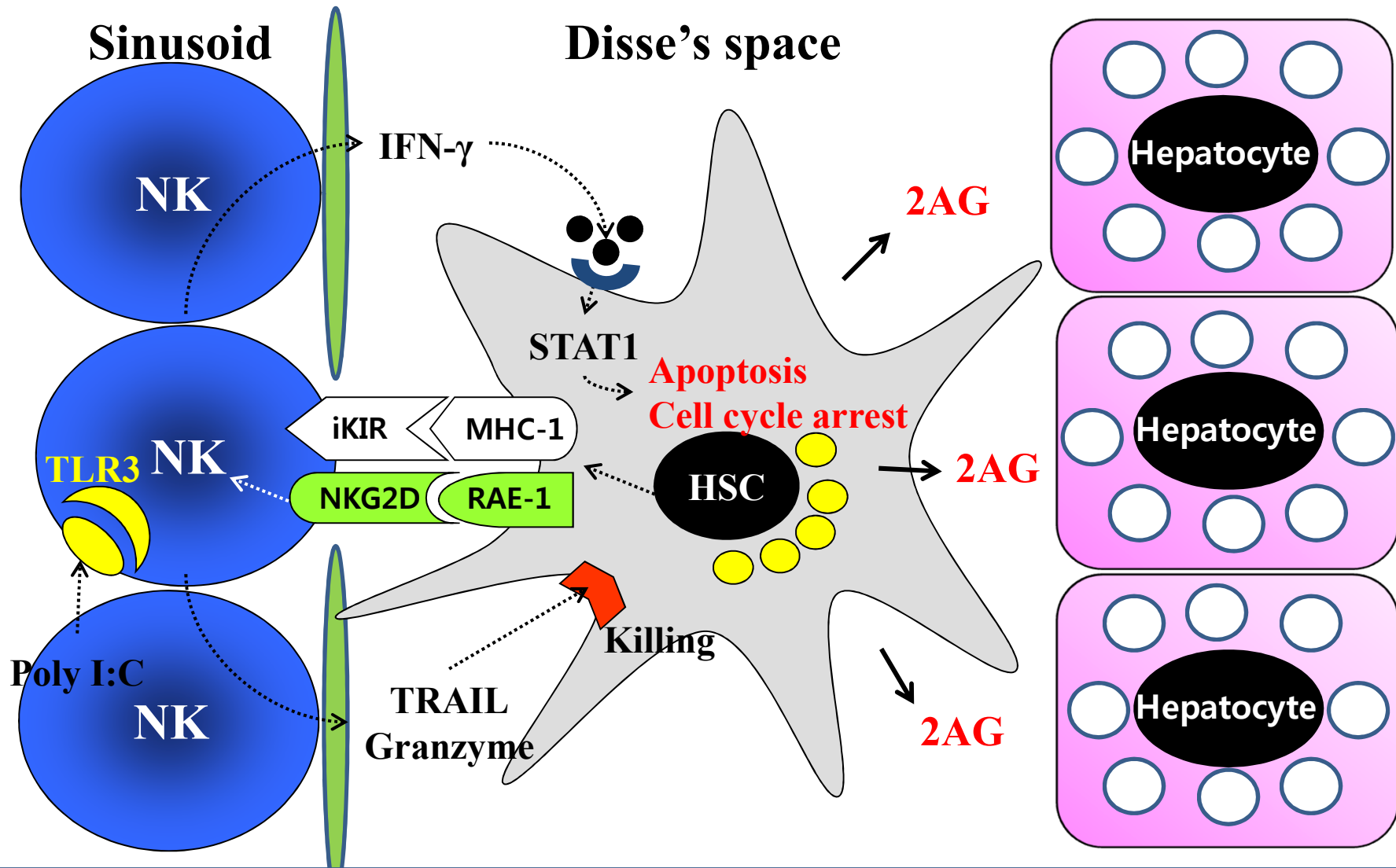
Scheme of paracrine regulation of hepatic lipogenesis via hepatic stellate cell-derived endocannabinoids acting on CB1 receptors in hepatocytes

STAT1 Inhibits Liver Fibrosis in Mice by Inhibiting Stellate Cell Proliferation and Stimulating NK Cell Cytotoxicity

2006 Hepatology

Won-Il Jeong, Ogyi Park, Svetlana Radaeva, and Bin Gao





Immunotherapy of alcohol-mediated hepatic fatty liver (steatosis) via NK cell killing against HSCs

Thanks for Your Attention !

❖ Lab Member



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