Crosstalk between Brain and liver

Role of autonomic nervous systems in liver pathophysiology

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Neural interaction between brain and liver

<sympathetic nerve – system>
• Locus ceruleus – periphery

<Parasympathetic (vagus) nerve – system >
• Periphery – solitary tract nuclei (Afferent)
• Drosal motor nuclei – periphery (Efferent)
1. Role of sympathetic nerve in fulminant hepatitis (Fas-induced).

2. Role of parasympathetic (vagus) nerve in fulminant hepatitis (Fas-induced).

3. Role of autonomic nervous system in cancer regulation.
1. Role of sympathetic nerve in fulminant hepatitis (Fas-induced).

2. Role of parasympathetic (vagus) nerve in fulminant hepatitis (Fas-induced).

3. Role of autonomic nervous system in cancer regulation.
What is anti-Fas antibody?

Lethal effect of the anti-Fas antibody in mice.

The Fas protein is expressed in a cell surface and mediates apoptosis. Apoptosis is the process of programmed cell death, and it was reported that injection of anti-Fas antibody causes fulminant hepatitis. According to histological analysis of the liver, treatment with an anti-Fas antibody caused massive hemorrhaging, congestion, and parenchymal collapse.
Is hepatic sympathetic nerve involved in Fas-induced hepatitis?

Male B6 mice

SympX: hepatic sympathectomy
Jo-2: anti-Fas antibody

Exp: Protocol

- Survival
- NE level (Liver)
- Histological analysis
- Caspase-3 activity
Results 1

Hepatic sympathetic nerve denervation **aggravated** Fas-induced fulminant hepatitis.

Results 2

Hepatic sympathetic nerve denervation 
aggravated Fas-induced hepatocellular apoptosis.
The neurotransmitter of sympathetic nerve, liver NE level didn’t increase in the sympathectomized mice.
We checked whether or not NE influence SympX-triggered aggravation.

**Exp: Protocol**

- **Male B6 mice**
- **SympX**: hepatic sympatectomy (Phenol + microsurgery)
- **Jo-2**: anti-Fas antibody

**Diagram**:
- **8W**
- **D7**
- **- 0.5h**
- **Survival**

**Protocol**:
- **NE (i.p.)**
  - 0.5 µg/g
  - 5.0 µg/g
- **Jo-2 (i.v.)**
  - 0.35 µg/g
Results

NE supplementation reversed sympathectomy induced exacerbation of mortality.
Hepatic sympathetic nerve plays a protective role in Fas-induced fulminant hepatitis.
1. Role of sympathetic nerve in fulminant hepatitis (Fas-induced).

2. Role of parasympathetic (vagus) nerve in fulminant hepatitis (Fas-induced).

3. Role of autonomic nervous system in cancer regulation.
Selective hepatic vagus nerve denervation
Is hepatic vagus nerve involved in Fas-induced hepatitis?

**Exp: Protocol**

- Male B6 mice
- VagoX: hepatic vagotomy
- Jo-2: anti-Fas antibody
- Jo-2 0.25 mg/kg
  - 0.35 mg/kg i.v.
- D7

- Survival
- Histological analysis
- Caspase-3 activity
Hepatic vagus nerve denervation aggravated Fas-induced fulminant hepatitis.
Hepatic vagus nerve denervation aggravated hepatocellular apoptosis.
Dose nicotine or PNU-282987 supplementation reverse vagotomyp-induced exacerbation of hepatitis?

8W: Male B6 mice

VagoX: hepatic vagotomy
Jo-2: anti-Fas antibody

Nicotine PNU-282987 (i.p.)
Jo-2 (i.v.) 0.25 μg/g

- 0.5h
D7

• Survival
• Caspase-3 activity

Brain
Liver

Exp: Protocol
Nicotine supplementation reversed vagotomy induced exacerbation of mortality.
Parasympathetic nerve & liver inflammation

PNU-282987 (α7 nicotinic acetylcholine agonist) supplementation reversed vagotomy induced exacerbation of mortality.

Is macrophage involved in vagotony-induced exacerbation of hepatitis?

- **Exp: Protocol**
- Male B6 mice
  - VagoX: hepatic vagotomy
  - Jo-2: anti-Fas antibody
  - lipoCl2MDP 50μl/mouse (i.v.)
  - Jo-2 (i.v.) 0.25 μg/g
- Survival
- Caspase-3 activity
Results

Macrophage plays a critical role in vagotomy-induced exacerbation of hepatitis.

Summary 2

Hepatic vagus nerve plays a protective role in Fas-induced fulminant hepatitis.

Hepatic vagus nerve works via α7 nicotinic acetylcholine receptors on Kupffer cell.
1. Role of sympathetic nerve in fulminant hepatitis (Fas-induced).

2. Role of parasympathetic (vagus) nerve in fulminant hepatitis (Fas-induced).

3. Role of autonomic nervous system in cancer regulation.
Autonomic nervous system & cancer regulation

Protective Role of the Hepatic Vagus Nerve against Liver Metastasis in Mice.


Liver / Body Weight (%)

Sham
HVX

Capsaicine treatment (chemical vagus nerve denervation)

hepatic vagus nerve denervation
Autonomic nervous system & cancer regulation

The vagotomy-induced exacerbation of liver metastasis was attenuated by supplementary norepinephrine or phenylephrine, a selective α1-adrenoceptor agonist.
Summary 3

The hepatic vagus nerve and sympathetic nerve are cooperatively regulates liver cancer metastasis.
Stress & cancer regulation (clinical study)

Inhibition of emotional needs and emotional wellbeing predict disease progression of chronic hepatitis C patients: an 8-year prospective study.


<Methods>

Two hundred and forty Japanese CHC patients (mean age 62.4 years) were assessed for behavioral patterns (Stress Inventory), QOL (Functional Assessment of Chronic Illness Therapy-Spiritual), and known prognostic factors at baseline then followed for a maximum of 8 years for disease progression, defined as either the first diagnosis of hepatocellular carcinoma (HCC) or hepatitis-related death.
Results: Forty-nine events occurred during the study period (46 newly diagnosed HCC cases, three hepatitis-related deaths).
- Behavioral patterns associated with inhibition of emotional needs (hazard ratio (HR): 1.35; 95 % confidence interval (CI): 1.02–1.77; p = 0.036)
- QOL, representing emotional wellbeing (HR 0.60; 95 % CI 0.37–0.98; p = 0.041)
were each associated with the risk of disease progression.

Conclusion: Psychosocial factors such as behavioral patterns relevant to the inhibition of emotional needs and emotional wellbeing independently affect the clinical course of patients with CHC.
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