Crosstalk between Brain and liver

Role of autonomic nervous systems in liver pathophysiology

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September 19, 2018
Ulaanbaatar, Mongolia

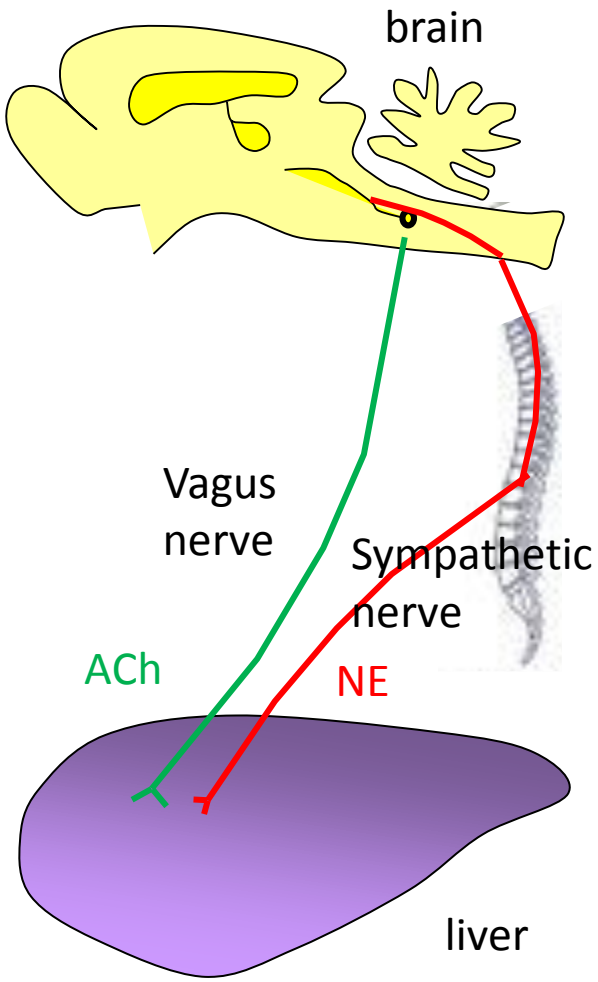
Neural interaction between brain and liver

<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.

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3. Role of autonomic nervous system in cancer regulation.

What is anti-Fas antibody?

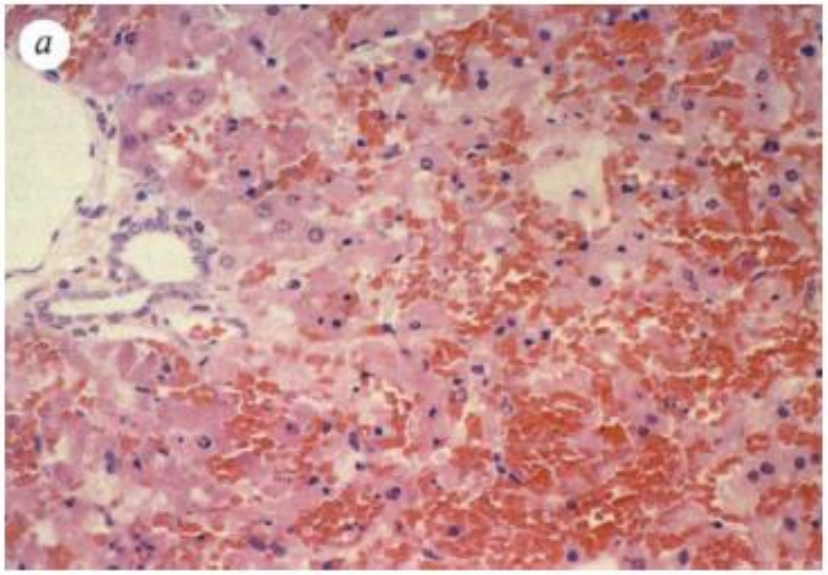
Lethal effect of the anti-Fas antibody in mice.

Ogasawara J, Watanabe-Fukunaga R, Adachi M, Matsuzawa A, Kasugai T, Kitamura Y, Itoh N, Suda T, Nagata S.
Nature. 1993;364(6440):806-9.

The Fas protein is expressed in a cell surface and mediates apoptosis.

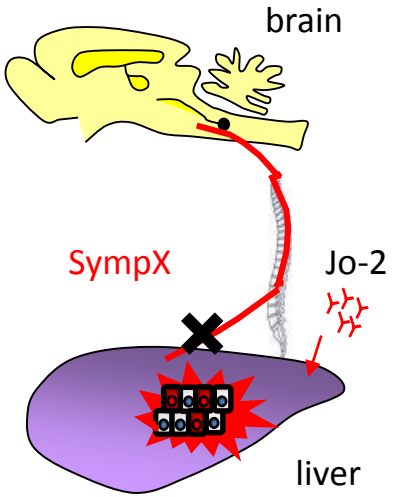
Apoptosis is the process of programmed cell death, and it was reported that injection anti-Fas antibody causes fulminant hepatitis.

According to histological analysis of the liver, treatment with an anti-Fas antibody caused massive hemorrhaging, congestion, and parenchymal collapse.



Exp: Protocol

Is hepatic sympathetic nerve involved in Fas-induced hepatitis?



Male
B6 mice

SympX

Jo-2 0.25 μg/g
0.35 μg/g i.v.

D7

8W

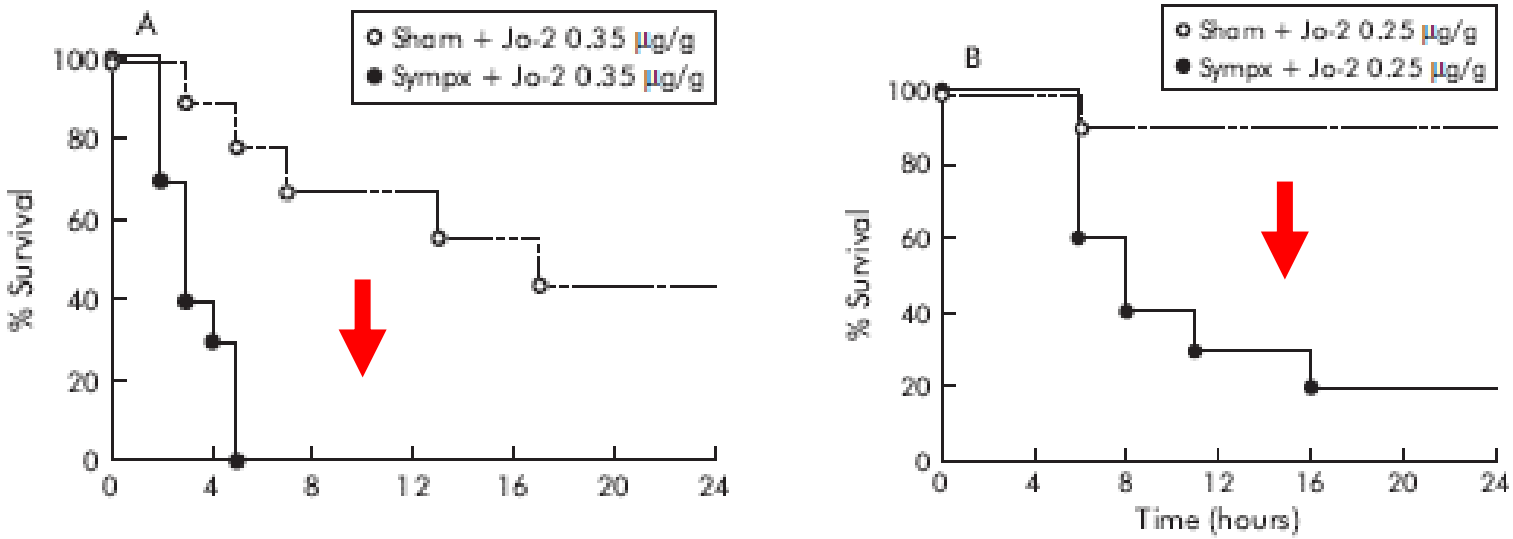
- Survival
- NE level (Liver)
- Histrogical analysis
- caspase-3 activity

SympX: hepatic sympathectomy

Jo-2: anti-Fas antibody

Results 1

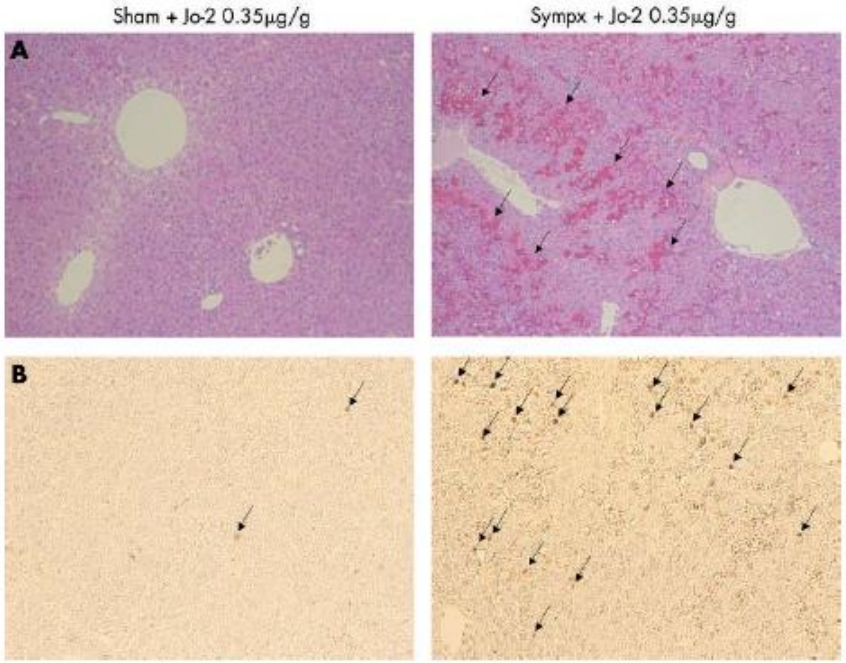
Hepatic sympathetic nerve denervation aggravated Fas-induced fulminant hepatitis.

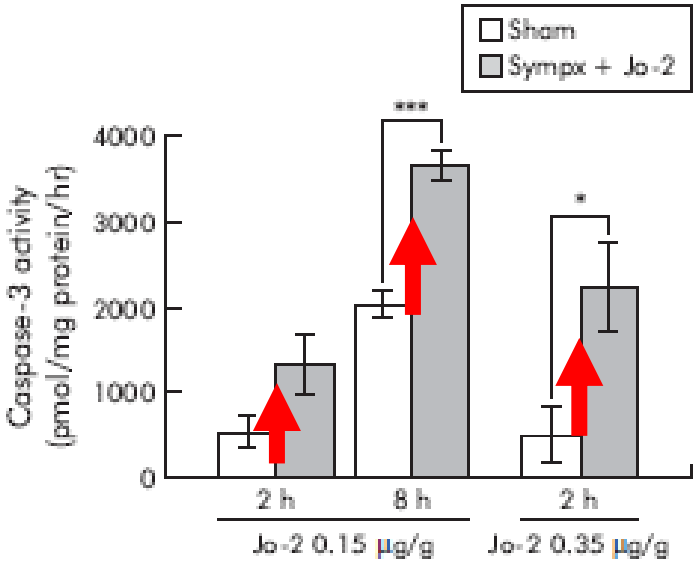


Chida Y, et al. Gut 2005;54:994–1002

Results 2

Hepatic sympathetic nerve denervation aggravated Fas-induced hepatocellular apoptosis.



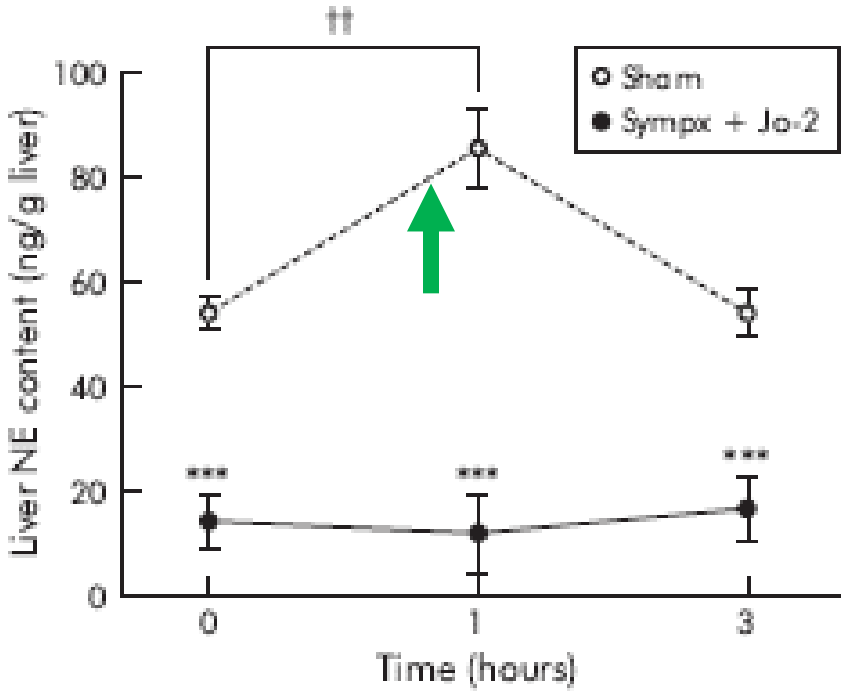


Chida Y, et al. Gut 2005;54:994–1002

Results 3

The neurotransmitter of sympathetic nerve, liver NE level

didn't increase in the sympathectomized mice.



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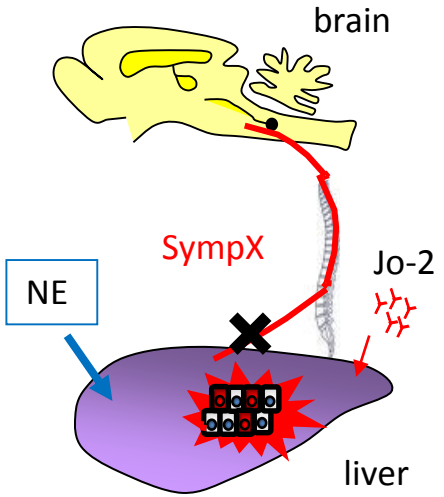
Exp: Protocol

We checked whether or not
NE influence
SympX-triggered aggravation.



Male
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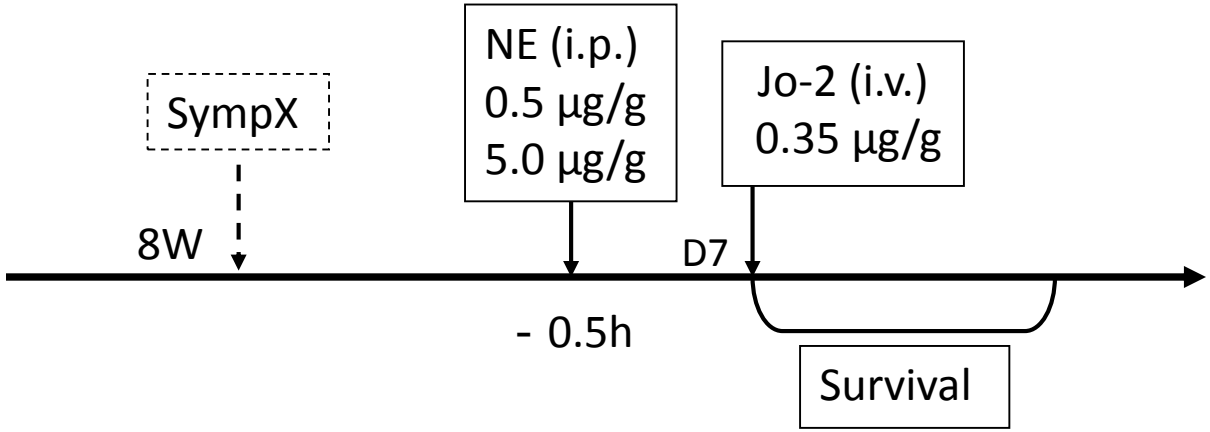
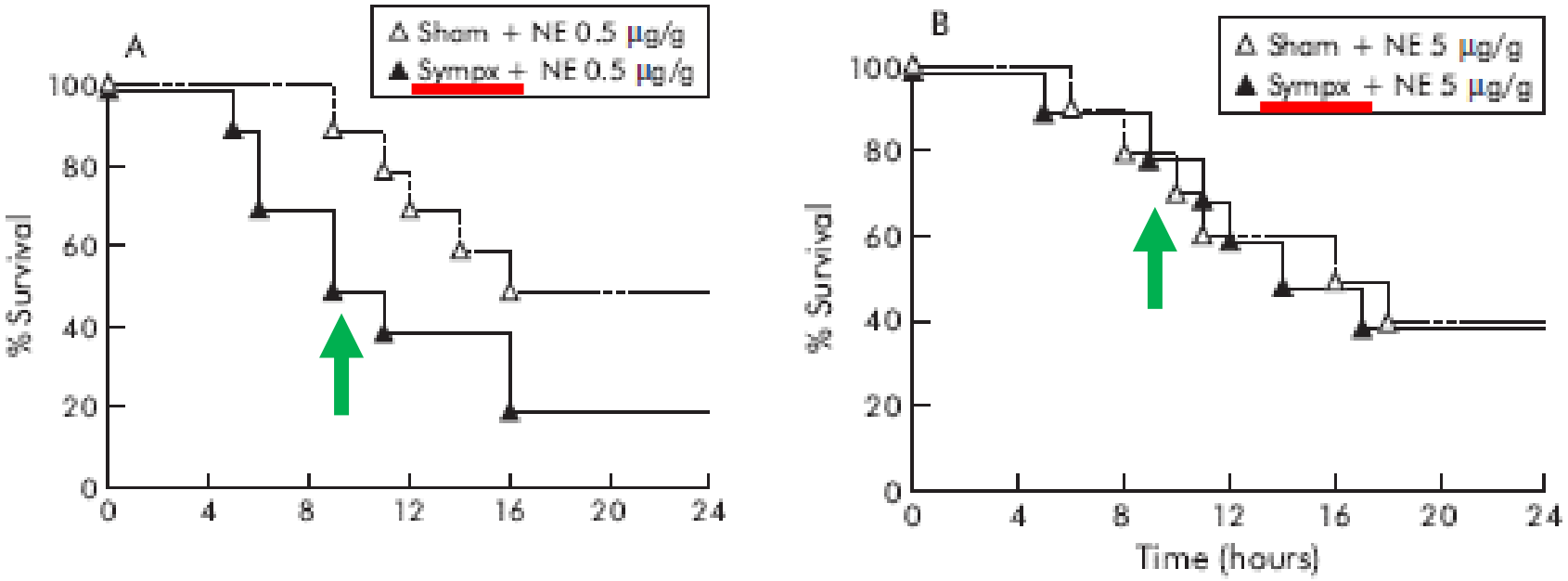


SympX: hepatic sympatectomy (Phenol + microsurgery)

Jo-2: anti-Fas antibody

Results

NE supplementation reversed sympathectomy induced exacerbation of mortality.



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Summary 1

Hepatic sympathetic nerve

prays a protective role in

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1. Role of sympathetic nerve in fulminant hepatitis (Fas-induced).

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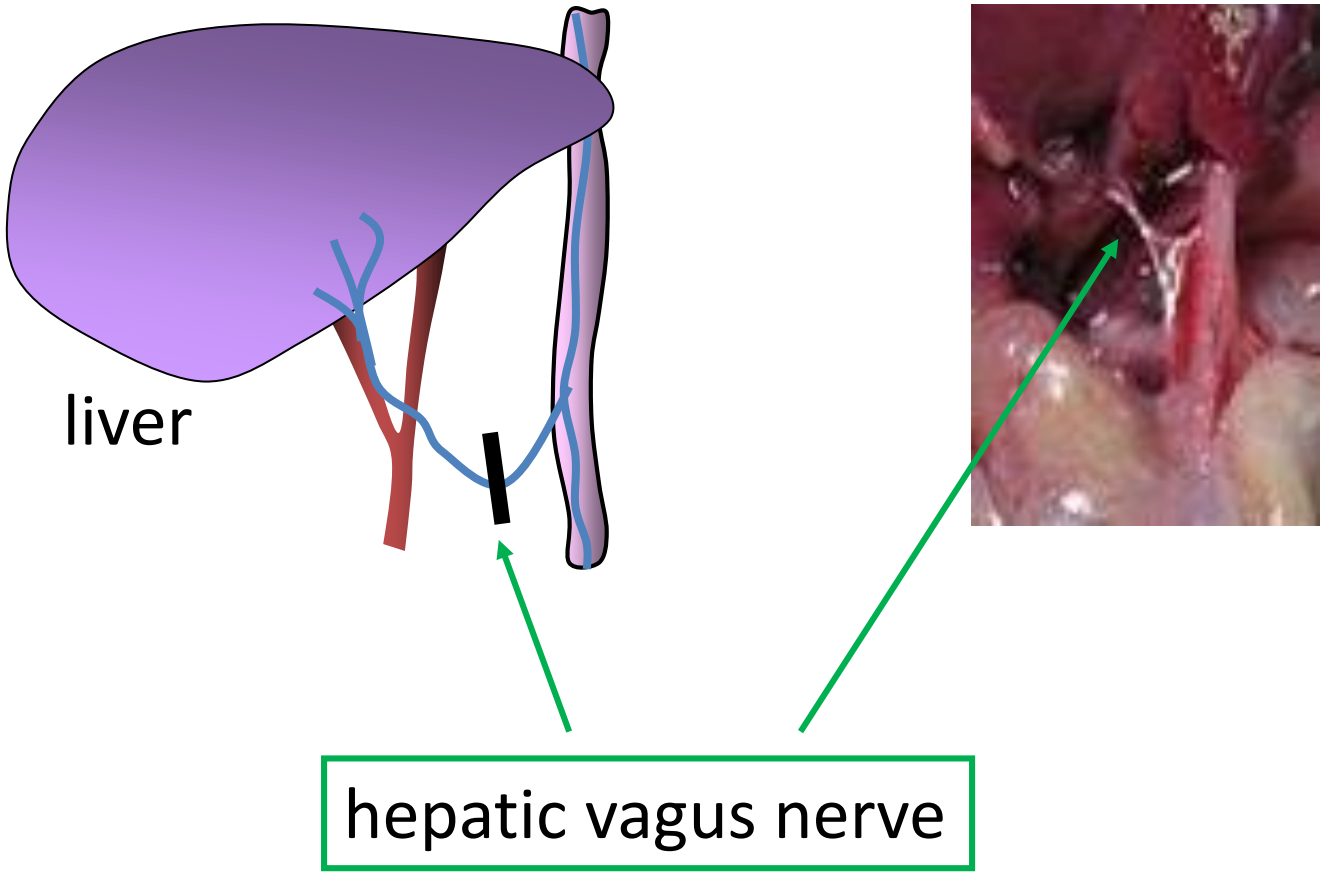
Selective hepatic vagus nerve denervation



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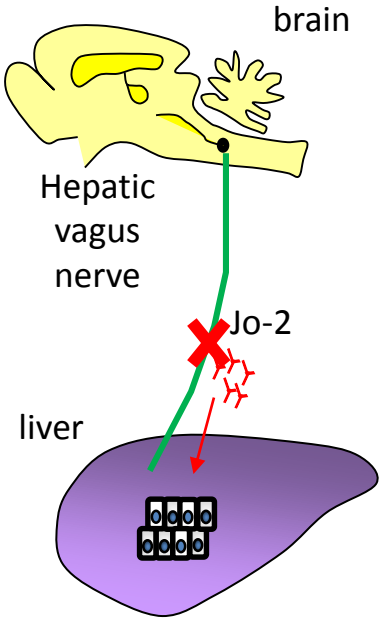
Is hepatic vagus nerve involved in Fas-induced hepatitis?



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VagoX

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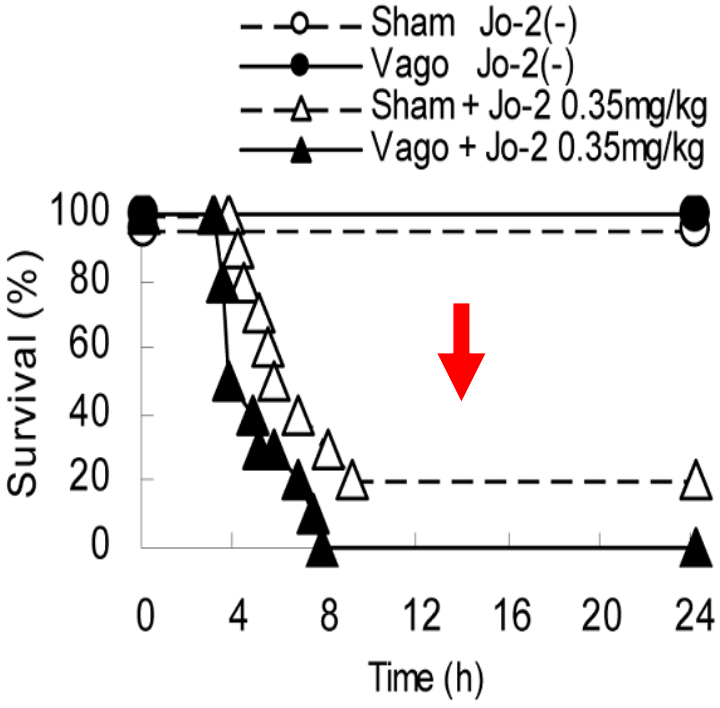
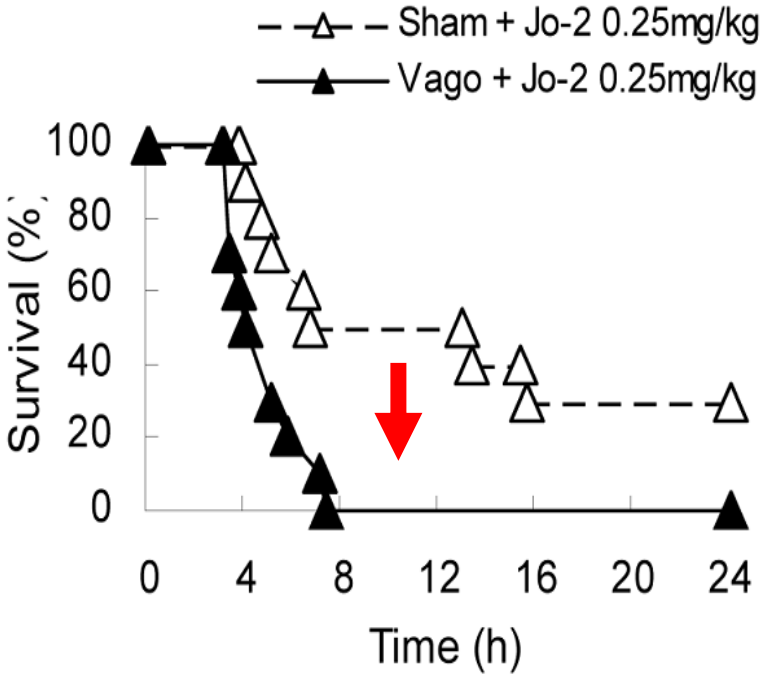
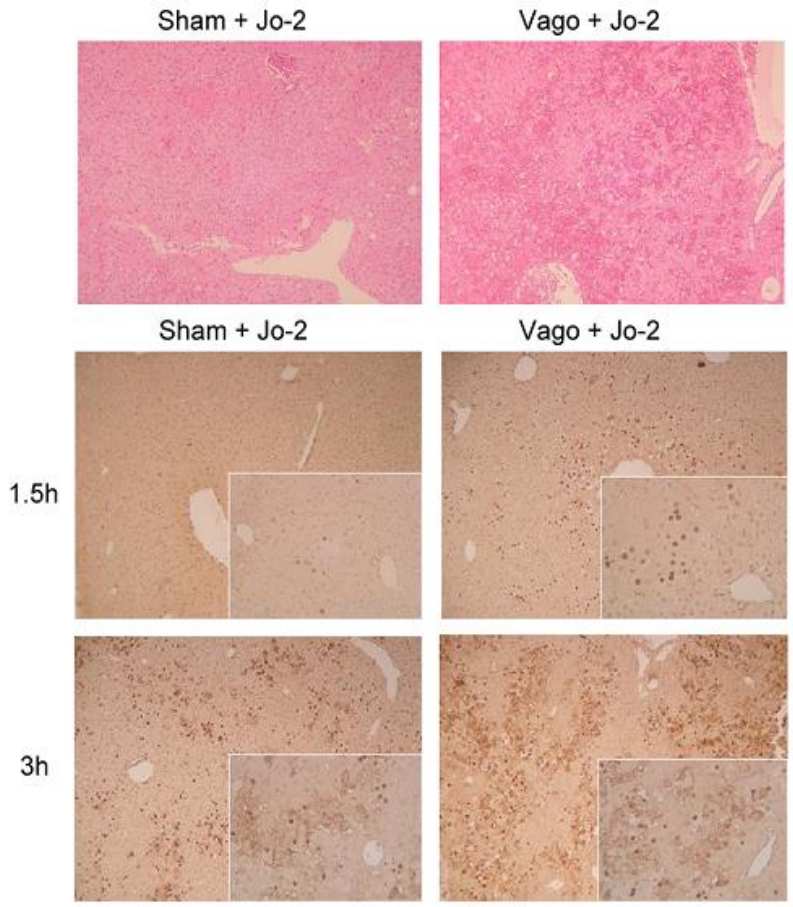


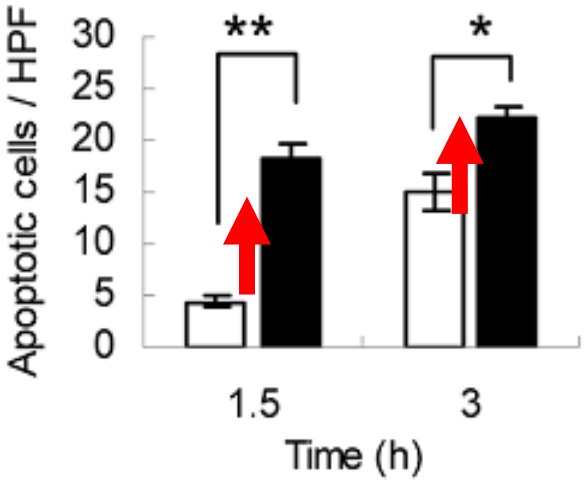


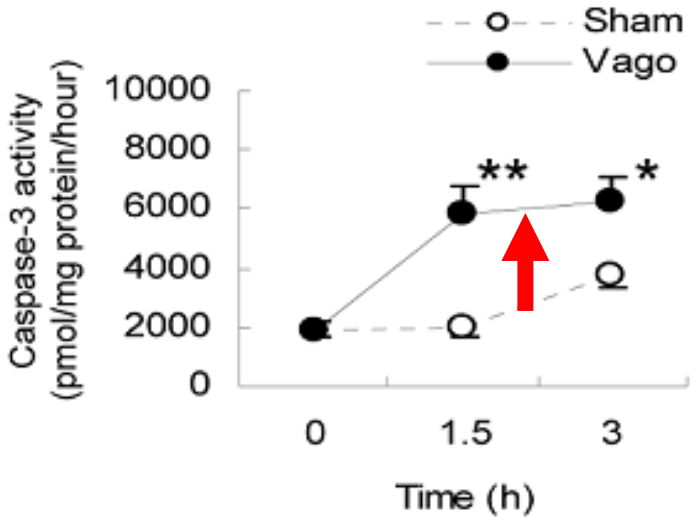
Hiramoto T, et al. GASTROENTEROLOGY 2008;134:2122–2131

Results 2

Hepatic vagus nerve denervation aggravated hepatocellular apoptosis.







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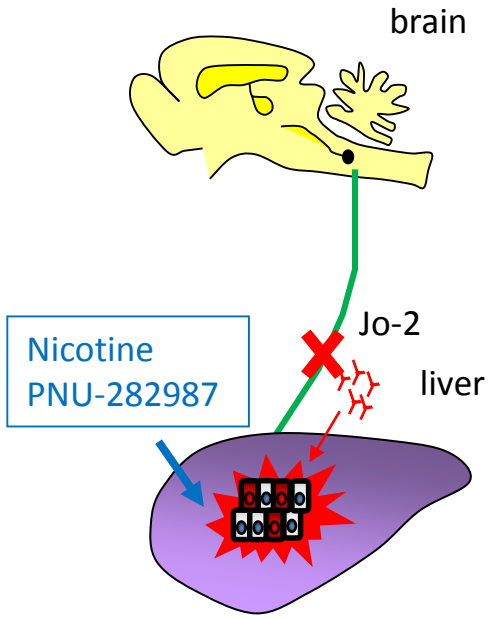
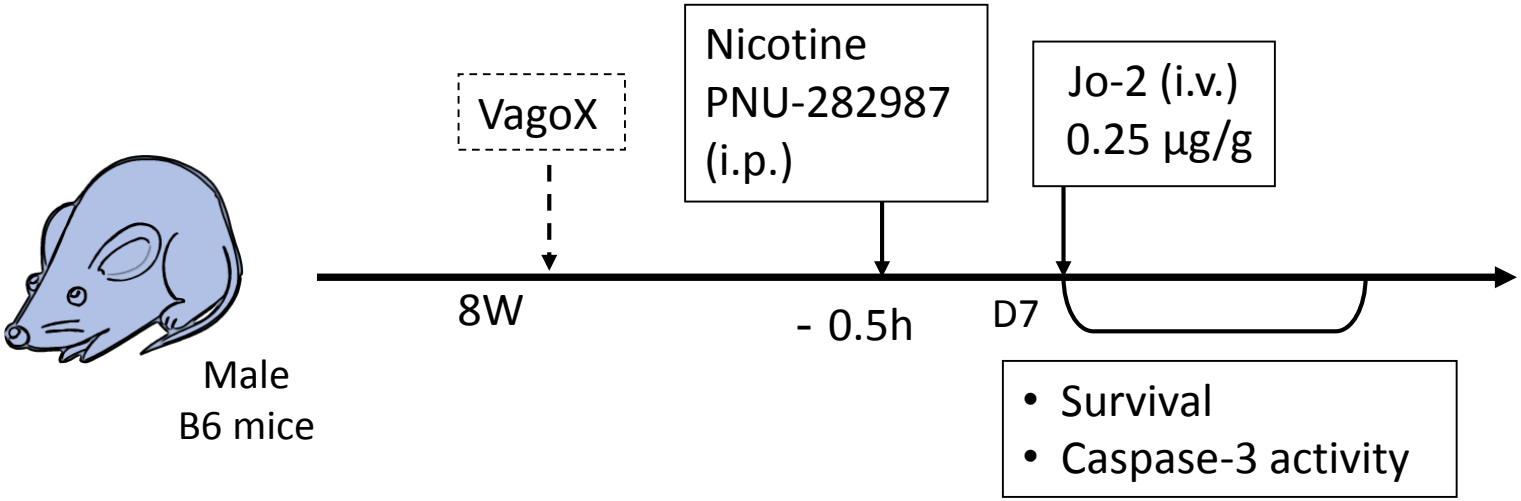
Exp: Protocol

Dose nicotine or PNU-282987 supplementation reverse vagotomy-induced exacerbation of hepatitis?



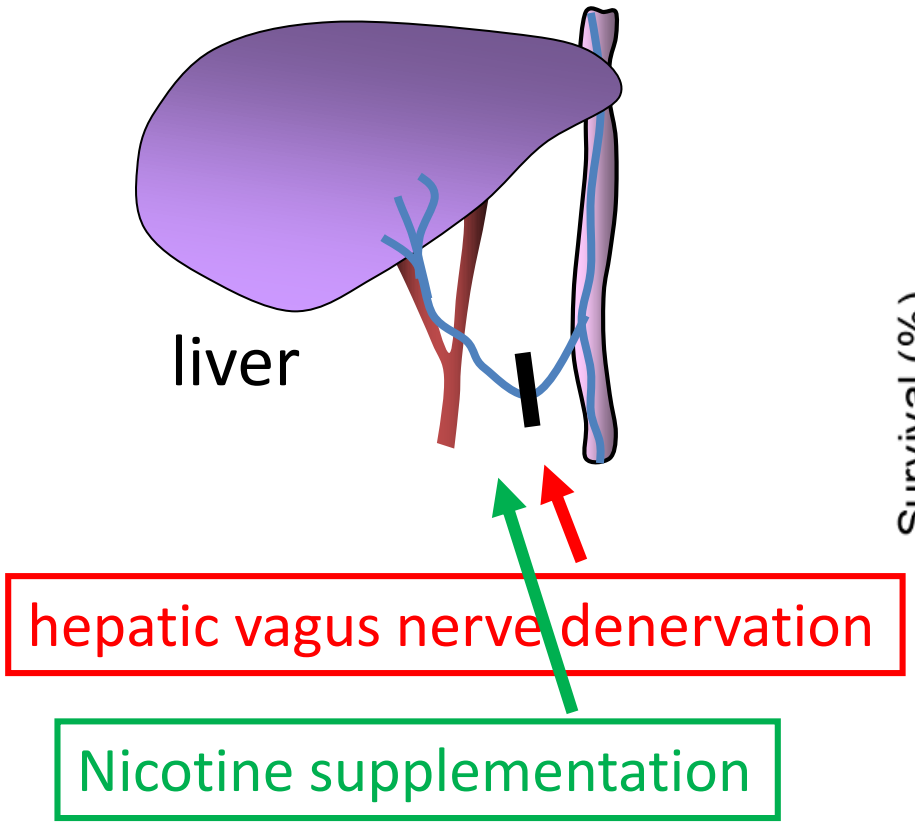


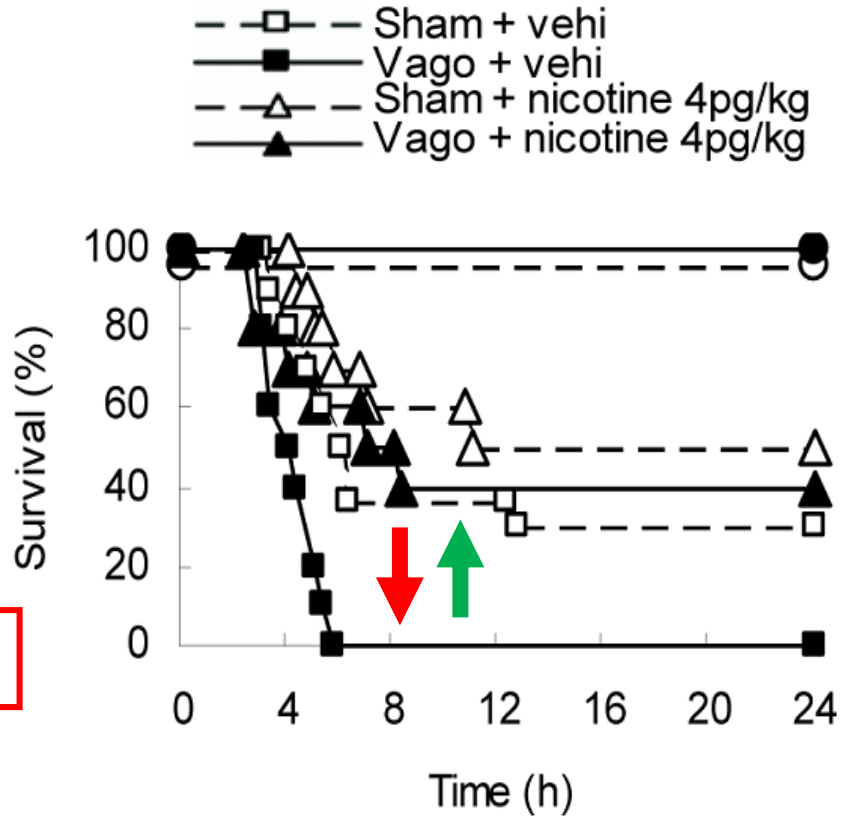
VagoX: hepatic vagotomy

Jo-2: anti-Fas antibody

Parasympathetic nerve & liver inflammation

Nicotine supplementation reversed vagotomy induced exacerbation of mortality.

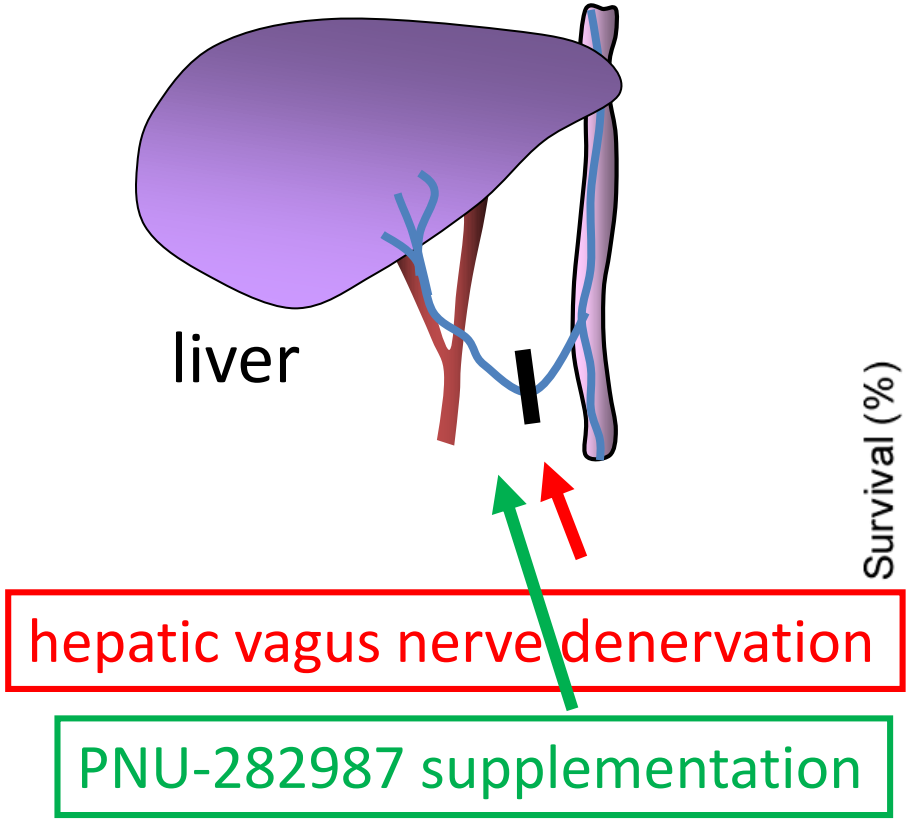


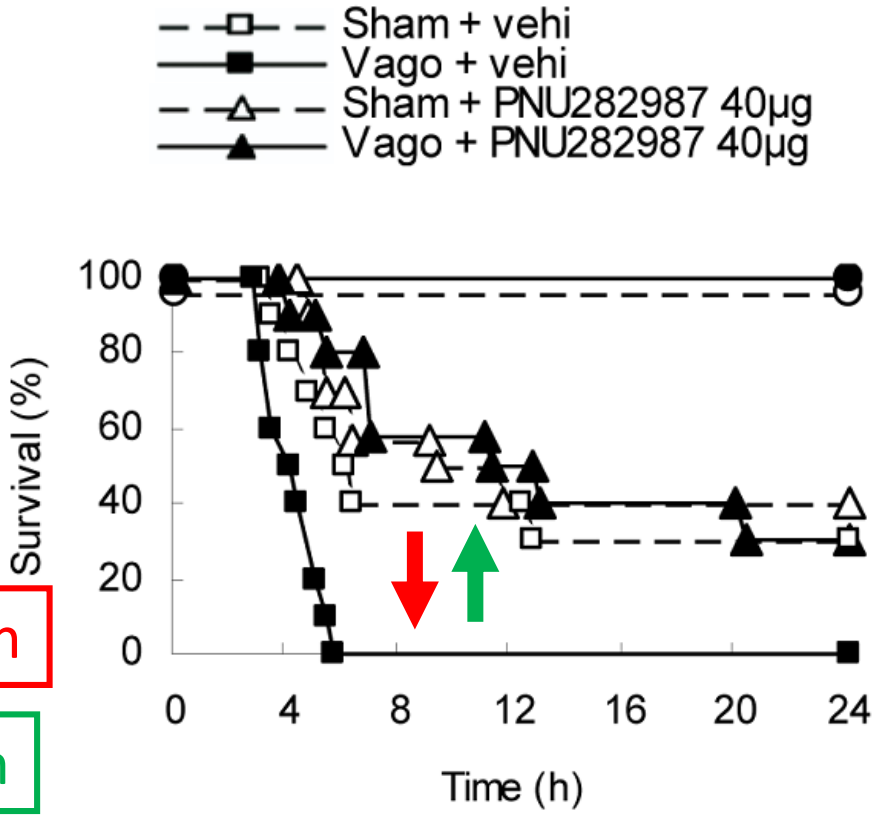


Hiramoto T, et al. GASTROENTEROLOGY 2008;134:2122–2131

Parasympathetic nerve & liver inflammation

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





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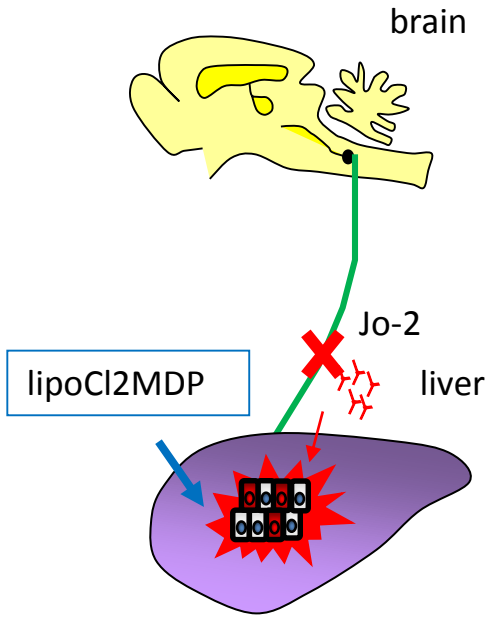
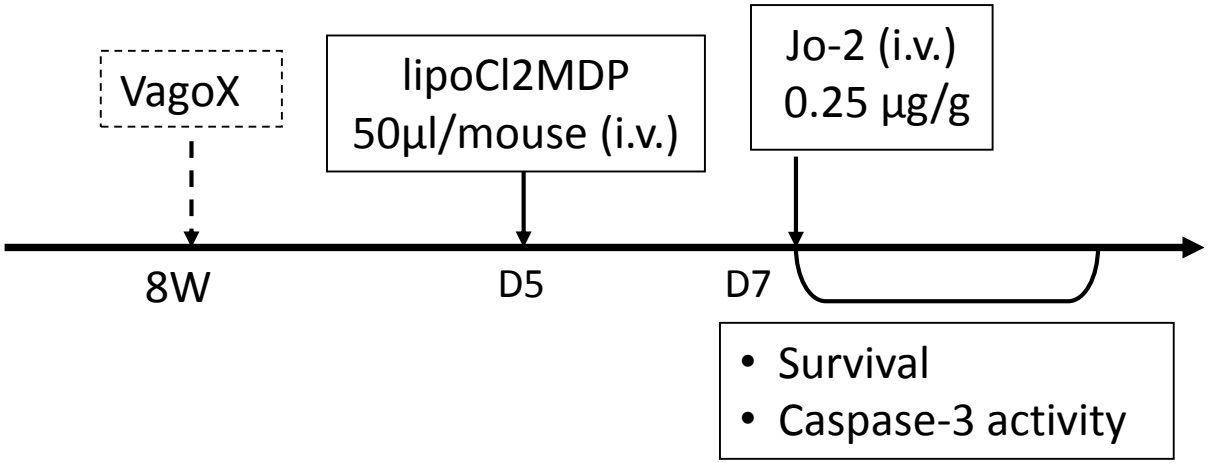
Exp: Protocol

Is macrophage involved in vagotomy-induced exacerbation of hepatitis?



Male
B6 mice

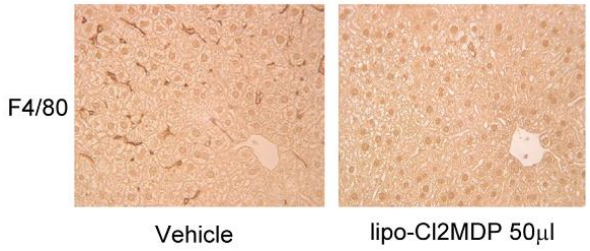


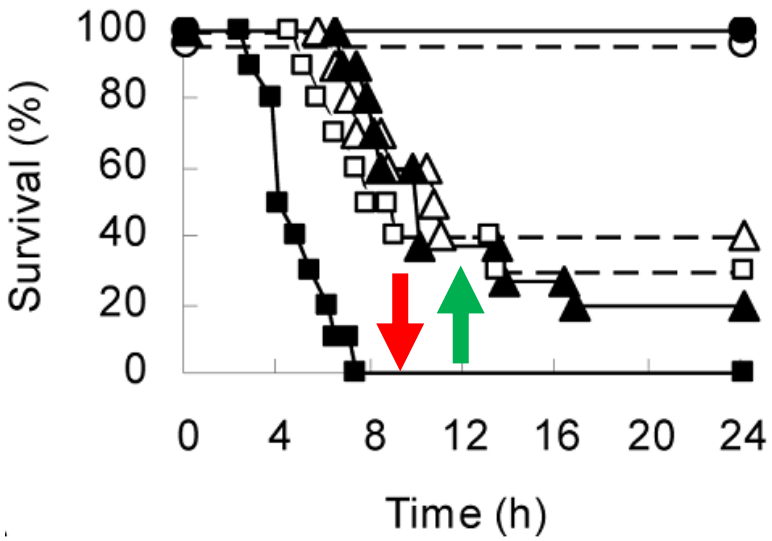
VagoX: hepatic vagotomy

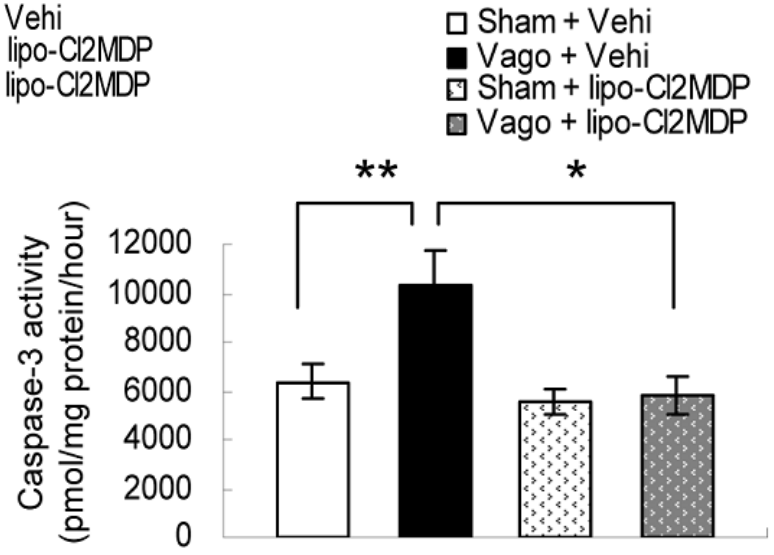
Jo-2: anti-Fas antibody

Results

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







Hiramoto T, et al. GASTROENTEROLOGY 2008;134:2122–2131

Summary 2

Hepatic vagus nerve
prays 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).

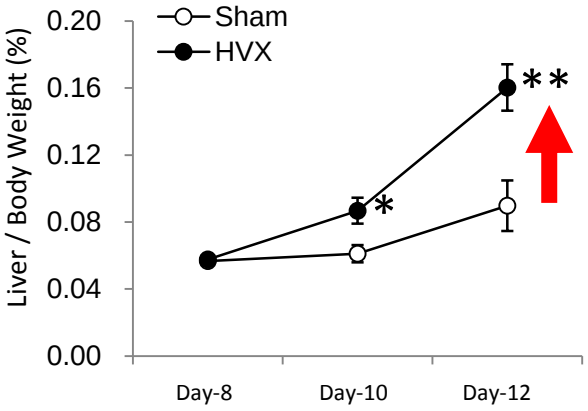
3. Role of autonomic nervous system in cancer regulation.

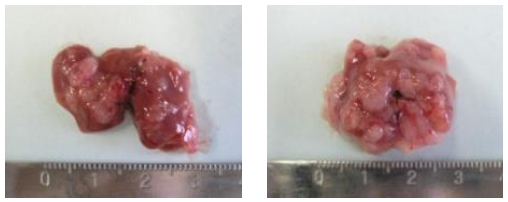
Autonomic nervous system & cancer regulation

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

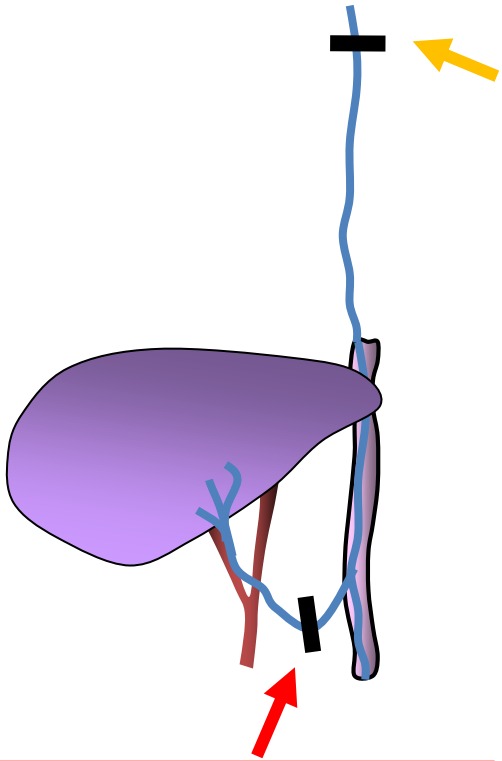
Hiramoto T, Yoshihara K, Asano Y, Sudo N.

Neuroimmunomodulation. 2017;24:341-347



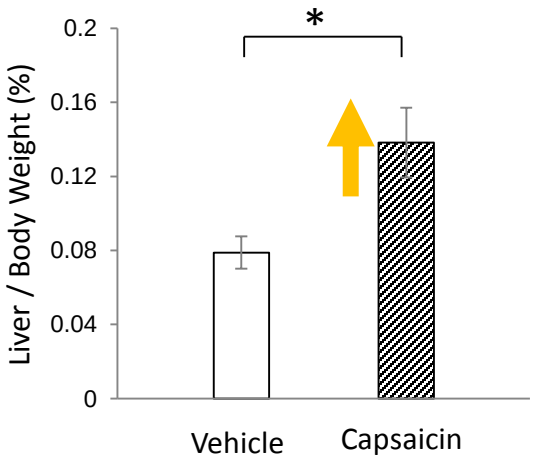


Sham HVX

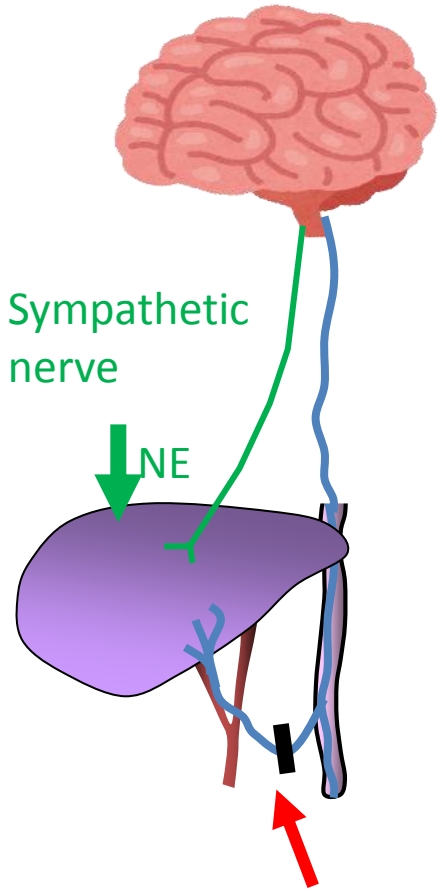


Capsaicine treatment (chemical vagus nerve denervationv)

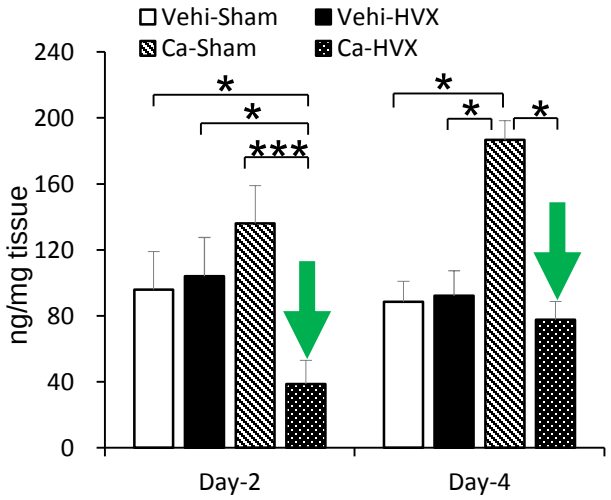
hepatic vagus nerve denervationv

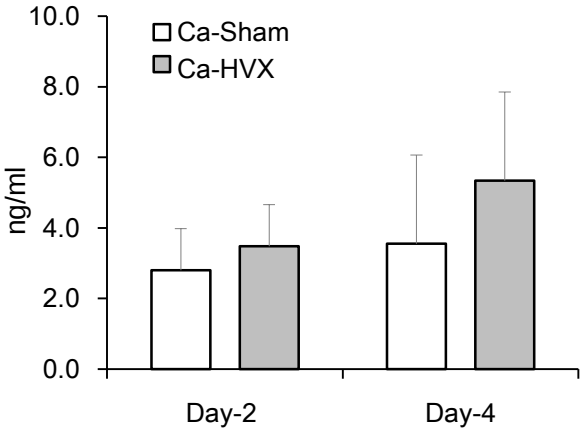


Autonomic nervous system & cancer regulation

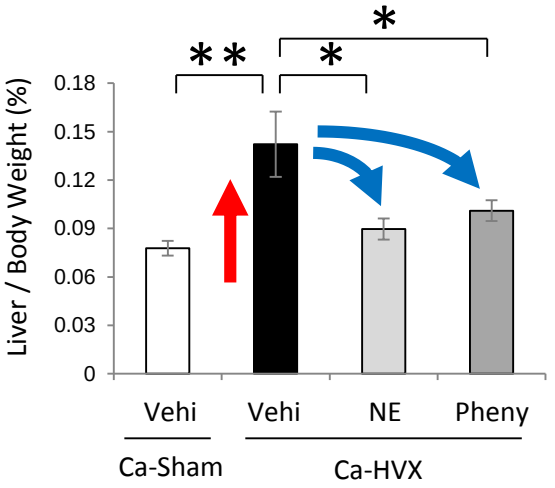


hepatic vagus nerve denervationv





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.

Sawamoto R, Nagano J, Kajiwara E, Sonoda J, Hiramoto T, Sudo N.
Biopsychosoc Med. 2016 Jul 29;10:24.

<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.

Stress & cancer regulation (clinical study)

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.

Acknowledgements

Department of Psychosomatic Medicine,
Graduate School of Medical Sciences,
Kyushu University, Fukuoka, Japan