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Mechanism of generation of reactive oxygen species with accumulation of copper in the liver of Long-Evans Cinnamon (LEC) rats and its relationship to the onset of acute hepatitis

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PC 12 cells, exposure to 50 mM KCl or 100 μM ATP resulted in simultaneous release of norsalsolinol and dopamine. The time courses of release of dopamine and norsalsolinol evoked by 50 mM KCl or 100 μM ATP coincided to each other. These releases were dependent on the concentrations of secretagogues. These findings suggest that norsalsolinol is taken up with dopamine into secretory vesicles via the vesicular catecholamine transporter. These findings may also be related to postural abnormality in Parkinson's disease.

Mechanism of generation of reactive oxygen species with accumulation of copper in the liver of Long-Evans Cinnamon (LEC) rats and its relationship to the onset of acute hepatitis

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Long-Evans Cinnamon (LEC) rats accumulate excess copper (Cu) in the liver in a manner similar to patients with Wilson's disease (WD), and they spontaneously develop acute hepatitis with severe jaundice at 3 ~ 5 months after birth. Reactive oxygen species (ROS) generated as a consequence of the accumulation of excess Cu are thought to be responsible for acute hepatitis in LEC rats. However, the mechanisms by which the excess Cu generates the ROS and induces hepatitis have not yet been revealed in this animal model. In this study, the author investigated the mechanisms of ROS generation accompanying Cu accumulation in the liver of LEC rats and their relationship to the onset of acute hepatitis.

1) The author investigated the mechanism of increased lipid peroxidation (LPO) in the liver using an in vitro incubation system. The levels of LPO in the liver S-9 from hepatic LEC rats were increased by incubating the liver S-9 in the presence of NADPH-generating system (NADPH-gs). This increase was inhibited by EDTA, butylated hydroxytoluene, and catalase (CAT), suggesting that the hydroxyl radicals (·OH) generated by the Fenton-type reaction between H₂O₂ and free Cu, are involved in this increase in LPO. H₂O₂ and ·OH are known to be generated one after another during Cu-catalyzed GSH oxidation. Electron spin resonance study revealed a marked increase in ·OH generation in the liver cytosol from hepatic LEC rats in the presence of excess free Cu.

2) In vivo ·OH production in plasma and liver of hepatic LEC rats was quantified by trapping ·OH with salicylic acid (SA) as 2,3-dihydroxybenzoic acid (2,3-DHBA). The ratios of 2,3-DHBA/SA were significantly higher in plasma and liver of hepatic LEC rats and acute Cu-overload Wistar rats than in those of Wistar rats and LEC rats showing...
no sign of hepatitis. Treatment with D-
mannitol (an · OH scavenger) to LEC rats
suppressed the increases in serum aspartate
aminotransferase activity and total bilirubin
concentration. D-mannitol also significantly
reduced hepatic mitochondrial LPO, a process
which is important in the pathogenesis of Cu-
induced hepatotoxicity. The author showed
the first in vivo evidence of accelerated · OH
generation in the livers of hepatic LEC rats,
and this increase in · OH generation may
play important roles in the development of
acute hepatitis.

3) α-Lipoic acid has ROS quenching and
metal chelating activities. DL-α-lipoic acid
(LA) was administered to LEC rats by gavage
at doses of 10, 30 and 100mg/kg five times per
week, for 4 weeks. LA prevented severe
jaundice in a dose-dependent manner. Anti-
oxidant system analyses in liver showed that
LA treatment significantly suppressed the in-
activations of CAT and glutathione peroxi-
dase, as well as the induction of heme
oxygenase-1. LA at the highest dose slightly
suppressed the accumulation of Cu in crude
mitochondrial fraction, but it had no effect on
the accumulation of Cu in cytosolic fraction.
While the increase in LPO in the microsomal
fraction was completely suppressed by LA at
the highest dose, the suppressive effect
against LPO in crude mitochondrial fractions
was slight. On the basis of these results, the
author concluded that LA has antioxidant ef-
facts at the molecular level against the devel-
opment of Cu-induced hepatitis in LEC rats.
Moreover, mitochondrial oxidative damage
might be important for the development of
acute hepatitis in LEC rats.

Nutritional status of sika deer (Cervus nippon yesoensis Heude)
in eastern Hokkaido, Japan

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Nutritional status of wild ungulate pro-
vides important information on population
status, because it affects winter survival, re-
productive rate, fetal growth, and body size.
Sika deer (Cervus nippon Temminck) in Ja-
pan were shown to have a wide range of
adaptability to their habitat. Few studies of
nutritional strategy, however, have investig-
gated sika deer. Hokkaido sika deer (C. n. ye-
soensis Heude) are widely distributed in east-
ern Hokkaido, which has the most severe win-
ter condition in Japan. The basic information
on nutritional ecology will help us to under-
stand the key factor of their life history, adap-
tation to the dynamism of their environment,
and their management.

This study was designed to understand
the characteristics of nutritional ecology of
Hokkaido sika deer seasonally, and to set up
the standard for nutritional assessment of the
population. For the fundamental study, qualita-
tive and quantitative analyses of food hab-
its and nutritional value of sika deer diets
were conducted. Second, to evaluate the nutri-
tional status of the population, seasonal
changes of fat indices were investigated and