

(様式3号)

学 位 論 文 の 要 旨

氏名 Tarif Abu Md Mamun

〔題名〕

Immunohistochemical phenotypes of huntingtin-associated protein 1 in the enteric nervous system of adult mouse

(成獣マウスの腸管神経系における HAP1 の免疫組織化学的発現形態)

〔要旨〕

Huntingtin-associated protein 1 (HAP1) is a neural huntingtin interactor and being considered as a core molecule of stigmoid body (STB). Brain or spinal cord regions with abundant STB/HAP1 expression are usually spared from neurodegeneration, whereas the regions with little STB/HAP1 expression are always neurodegenerative targets. The enteric nervous system (ENS) can act as a potential portal for pathogenesis of neurodegenerative disorders. To date, the expression of HAP1 and its neurochemical characterization have never been examined there. In the current study, we determined the expression and immunohistochemical phenotypes of HAP1 in ENS of adult rodents using Western blotting and light/fluorescence microscopy. HAP1 immunoreactivity was strongly expressed in both myenteric and submucosal plexuses of ENS. STBs were observed in the cytoplasm of most of the HAP1-immunoreactive (ir) cells in ENS. In myenteric plexus, a large number of calretinin, calbindin, NOS, VIP, ChAT, SP, somatostatin, and TH-ir neurons showed HAP1 immunoreactivity. In contrast, most of the CGRP-ir neurons were devoid of HAP1-immunoreactivity. In submucosal plexus, almost all the cholinergic secretomotor neurons containing ChAT/ CGRP/ somatostatin/ calretinin, non-cholinergic secretomotor neurons containing VIP/TH/calretinin and vasodilator neurons containing VIP/calretinin express HAP1. Our current study is the first to clarify that HAP1 is highly expressed in excitatory motor neurons, inhibitory motor neurons, and interneurons but almost absent in sensory neurons in myenteric plexus. While, HAP1 is expressed in all neuronal subgroups of Meissner's plexuses. These suggest that due to lack of putative STB/HAP1 protectivity, the sensory neurons (Dogiel type II) might be more vulnerable to neurodegeneration than STB/HAP1-expressing Dogiel type I neurons in myenteric plexus and secretomotor/vasodilator neurons in Meissner's plexuses. Our current results may reflect the involvement of HAP1 in modulation of excitatory and inhibitory motor neuron functions in myenteric plexus and the secretomotor and vasodilator functions of submucosal neurons. It will be of great interest to elucidate the physiological or pathological roles of HAP1 in ENS. Our current results might lay a basic foundation for future studies that seek to clarify the physiological/pathological effects of STB/HAP1 in the ENS.

作成要領

1. 要旨は、800字以内で、1枚でまとめること。
2. 題名は、和訳を括弧書きで記載すること。

## 学位論文審査の結果の要旨

令和 4 年 8 月 10 日

報告番号	甲 第 <b>1653</b> 号	氏 名	Tarif Abu Md Mamun
論文審査担当者	主査教授	美津島 大	
	副査教授	高見 太郎	
	副査教授	篠 田 晃	
学位論文題目名 (題目名が英文の場合、行を変えて和訳を括弧書きで記載する。)			
Immunohistochemical phenotypes of huntingtin-associated protein 1 in the enteric nervous system of adult mouse (成獣マウスの腸管神経系における HAP1 の免疫組織化学的発現形態)			
学位論文の関連論文題目名 (題目名が英文の場合、行を変えて和訳を括弧書きで記載する。)			
Immunohistochemical expression and neurochemical phenotypes of huntingtin-associated protein 1 in the myenteric plexus of mouse gastrointestinal tract. (マウス消化管筋層神経叢における HAP1 の免疫組織化学的発現と神経化学的フェノタイプ)			
掲載雑誌名 <i>Cell and Tissue Research</i> 第 386 巻 第 3 号 P. 533 ~ 558 ( 2021 年 12 月 ○掲載・掲載予定)			
著者 (全員を記載) Tarif AMM, Islam MN, Jahan MR, Yanai A, Nozaki K, Masumoto KH, Shinoda K			
(論文審査の要旨)			
<p>In this study, the applicant examined the detailed expression and immunohistochemical phenotypes of huntingtin-associated protein 1 (HAP1) in the enteric nervous system (ENS) of adult mice using Western blotting and immunohistochemistry. HAP1 immunoreactivity was strongly expressed in both myenteric and submucosal plexuses of ENS. Stigmoid body (STB) was observed in the cytoplasm of most of the HAP1-immunoreactive (ir) cells in ENS. The STB/HAP1-ir cells exhibited attributes of neurons but not of glial or Cajal cells in ENS. In myenteric plexus, a large number of calretinin, calbindin, NOS, VIP, ChAT, SP, somatostatin, and TH-ir neurons showed HAP1 immunoreactivity. In contrast, most of the CGRP-ir neurons were devoid of HAP1-immunoreactivity. The applicant also showed that almost all the cholinergic secretomotor neurons containing ChAT/ CGRP/ somatostatin/ calretinin, non-cholinergic secretomotor neurons containing VIP/TH/calretinin and vasodilator neurons containing VIP/calretinin express HAP1 in the submucosal plexus.</p> <p>Taken together, this study is the first to clarify that HAP1 is highly expressed in excitatory motor neurons, inhibitory motor neurons, and interneurons but almost absent in sensory neurons in myenteric plexus. While, HAP1 is expressed in secretomotor and vasodilator neurons but not in putative sensory neurons of Meissner's plexuses. These suggest that due to lack of putative STB/HAP1 protectivity, the sensory neurons (Dogiel type II) might be more vulnerable to neurodegeneration than STB/HAP1-expressing Dogiel type I neurons in myenteric plexus and secretomotor/vasodilator neurons in Meissner's plexuses. These results may reflect the involvement of HAP1 in modulation of excitatory and inhibitory motor neuron functions in myenteric plexus and the secretomotor and vasodilator functions of submucosal neurons. It will be of great interest to elucidate the physiological or pathological roles of HAP1 in ENS. The current results might lay a basic foundation for future studies that seek to clarify the physiological/pathological effects of STB/HAP1 in the ENS.</p>			