（様式３号）

学 位 論 文 の 要 旨

氏名 MEHER MIRZA MIENUR

〔題名〕

Neurochemical Characterization of Huntingtin-Associated Protein 1 and Choline Acetyltransferase in the Adult Mouse Forebrain.

(成体マウス前脳におけるハンチンチン関連タンパク質１とコリンアセチルトランスフェラーゼの神経化学的特徴　)

〔要旨〕

Huntingtin-associated protein-1 (HAP1) is a neuro-cytoplasmic protein and is involved in both intracellular trafficking and neuroprotection. The neuronal marker Choline acetyltransferase (ChAT) is an enzyme used to recognize the cholinergic neurons; that neuron influences attention, learning, motor control, and emotional responses. Despite their apparent importance to neurodegenerative disorders, little is known about the distribution and the neurochemical heterogeneity throughout the mouse forebrain. This study implemented Western blotting and immunohistochemistry in adult mice to map HAP1 and ChAT immunoreactive (ir) neurons throughout the BFCN, which included the brain area of the medial septum (MS), vertical and horizontal limbs of the diagonal band of Broca (VDB, HDB), and substantia innominata basal part (SIB). Furthermore, research was conducted across the caudate putamen (CPu) and habenula. Neuropeptides (CGRP, CCK), calcium-binding proteins (calbindin, calretinin, parvalbumin), and other markers, including neuronal nitric oxide synthase (nNOS) and Substance P (SP), were employed to assess co-expression as an indicator of neurochemical heterogeneity.

High regionalized HAP1 expression was found in BFCN, with the highest densities found in MS and VDB and medium to high expression in HDB and SIB. In contrast, HAP1 was sparsely distributed over the CPu. There were numerous ChAT-ir neurons in the CPu and across the BFCN, but ChAT neurons in CPu consistently did not co-express with HAP1. The highest co-expression of ChAT and HAP1 was observed in MS and VDB, indicating an enriched association in the forebrain cholinergic populations.

There was intensive co-expression of CGRP and CCK with ChAT neurons in the basal forebrain, particularly in the HDB and CPu. Calretinin had more selective co-expression in the VDB, SIB, and CPu, whereas calbindin was widely distributed and had significant co-localization with ChAT-ir neurons in both the VDB and HDB. However, parvalbumin neurons were not co-localized with ChAT. Furthermore, HAP1 showed selective and region-specific co-expression patterns. HAP1 was found to moderately co-localize with the CGRP and CCK in the MS, VDB, and HDB but didn't co-express with parvalbumin in the studied brain regions.

In the habenula, the majority of ChAT-positive neurons were found in the medial habenula (MHb), which lacked expression of HAP1. Conversely, HAP1 was only expressed in the lateral habenula (LHb); specifically, it was enriched in the central and paracentral subnuclei of LHb. In LHb, HAP1 showed the highest co-expression with CGRP and CCK neurons, whereas HAP1 had few overlaps with nNOS neurons and a moderate co-expression with calbindin and calretinin. Though the co-localization of HAP1 with parvalbumin and SP neurons was absent. However, the selective expression of CCK and CGRP by ChAT neurons in the MHb revealed unique peptidergic pathways that are mediated by cholinergic nuclei.

These results show neurochemical distinctions between cholinergic and HAP1-expressing neurons. The selective HAP1-ChAT interaction in MS and VDB but not in striatal cholinergic neurons suggests a spatially diverse inherent protective potential of the HAP1 and ChAT. The regionalized and heterogenous immunohistochemical relationships between HAP1, ChAT, neuropeptides, and calcium-binding proteins indicate selective synaptic regulatory and protective effects against neurodegenerative stress. Our results provide a neurochemical foundation for future functional and mechanistic research on HAP1 and ChAT, especially in the context of different neurological diseases.

作成要領

１．要旨は、８００字以内で、１枚でまとめること。

２．題名が欧文の場合は、和訳を（）書きで記載すること。

学位論文審査の結果の要旨

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学位論文題目名

Neurochemical Characterization of Huntingtin-Associated Protein 1 and Choline Acetyltransferase in the Adult Mouse Forebrain.
(成獣マウス前脳におけるハンチンチン関連タンパク質1とコリンアセチルトランスフェラーゼの神経化学的特徴)

学位論文の関連論文題目名

Immunohistochemical relationships of huntingtin-associated protein 1 with choline acetyltransferase in the forebrain cholinergic nuclei of adult mice.
(成獣マウスの前脳コリン作動性神経核におけるハンチンチン関連タンパク質HAP1 とコリンアセチルトランスフェラーゼの免疫組織化学的関係について)

掲載雑誌

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【論文審査の要旨】Abstract of the Thesis

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【学位論文の総評】

申請された論文は、免疫組織化学的手法を用いて、成獣マウス前脳におけるハンチンチン関連 1 (HAP1) 発現の不均一性 (heterogeneity) を明らかにするとともに、神経マーカーであるコリンアセチルトランスフェラーゼ、各種神経ペプチド、カルシウム結合タンパク質、神経型一酸化窒素合成酵素、サブスタンスＰなど、神経細胞で発現する他の分子との共発現について詳細に検討したものである。

これらの精緻な解析は、HAP1 の神経保護作用をはじめとする機能解明に向けた重要な基盤となるものであり、学術的価値は高い。関連論文は国際ジャーナルに掲載されており、保健学専攻博士後期課程の学位論文（博士論文）として十分に値すると評価できる。

以上より、本審査委員会は MEHER MIRZA MIENUR 氏が博士後期課程の学位論文審査に合格したと判断する。