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学位の種類	博士（医学）
学位記番号	博士甲第７９６号
学位授与の要件	学位規則第４条第１項
学位授与年月日	平成３０年　３月　９日
学位論文題目	Age-related changes in the metabolic profiles of rat hippocampus, medial prefrontal cortex and striatum （ラット海馬、内側前頭前皮質および線条体における代謝プロファイルの加齢変化）
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別紙様式３（課程博士・論文博士共用）

論　文　内　容　要　旨

※整理番号	803	（ふりがな） 氏　　名	リナ ワティ ビンティ ドゥラーニ Lina Wati Binti Durani
学位論文題目	Age-related changes in the metabolic profiles of rat hippocampus, medial prefrontal cortex and striatum (ラット海馬、内側前頭前皮質および線条体における代謝プロファイルの加齢変化)		

Background:

Brain aging is a progressive and complex multifactorial process manifested by physiological and cognitive deterioration ultimately leading to death. It is a major risk factor for neurodegenerative diseases. Age-related aberrations are highly confined to specific regions. We have recently shown that age-dependent regional brain atrophy and lateral ventricle expansion may be linked with impaired cognitive and locomotor functions. However, metabolic profile transformation in different brain regions during aging is unknown. In order to find out mechanisms underlying age-related cognitive impairments we, therefore, examined regional metabolomic perturbations in the hippocampus, medial prefrontal cortex (mPFC), and striatum of middle-aged (MA) and late-aged (LA) rats using ultrahigh-performance liquid chromatography (UHPLC) coupled with high-resolution accurate mass (HRAM)-orbitrap tandem mass spectrometry (MS/MS).

Purpose:

To examine regional metabolomic perturbations in the hippocampus, medial prefrontal cortex (mPFC), and striatum of middle-aged (MA) and late-aged (LA) rats.

Method:

We studied the age-related changes in the metabolic profile on the specific brain region. The rats were divided into four age groups: 14 (n=14), 18 (n=13), 23 (n=7), and 27 (n=10) months. Behavioral evaluations and MRI measurements were performed as in our previous study. As shown in the previous study, behavioral tests showed a big difference between middle-aged (14 and 18 months) and late-aged (23 and 27 months) rats. Therefore, they were divided into two groups (middle- and late-aged) and metabolic changes in the hippocampus, mPFC and striatum were analyzed in four brains in each group.

（備考）１．論文内容要旨は、研究の目的・方法・結果・考察・結論の順に記載し、２千字程度でタイプ等を用いて印字すること。

２．※印の欄には記入しないこと。

別紙様式３の２（課程博士・論文博士共用）

（続紙）

Samples were extracted using the water-methanol-chloroform method. Methanol phase was lyophilized and used for the current analysis. Chromatography was performed on an UltiMate 3000 Rapid Separation LC system coupled to a Thermo Scientific Q Exactive HF Orbitrap mass spectrometry. Chromatographic separations were performed using a reversed-phase column with positive and negative electrospray ionization modes. Data were subjected to multivariate statistical analysis. Features were then identified by entering the mass-to-charge ratio in the online databases and followed by pathway analysis.

Result and discussion:

Our results suggested that not all metabolites displayed significant changes consistently throughout the brain regions. Metabolic alterations are related to brain functions in each region. OPLS-DA score plots displayed a distinct separation between MA and LA groups, indicating their different metabolic profiles. While S-plot can highlight the significant changes. Pathway analysis revealed that improved GSH metabolism in the hippocampus of LA rats, suggesting a protective mechanism against oxidative stress. While mPFC was in the oxidized state showed by the reduced GSH function. Altered taurine and hypotaurine metabolism in the hippocampus likely contributes to the age-related cognitive dysfunction. Sphingolipids metabolites were altered in the hippocampus and mPFC. These alterations implied a defect in the sphingomyelin metabolism and cellular membrane function. Purine metabolism deregulation occurred in the striatum which may reflect striatal neurons dysfunction. The mPFC region dysregulation with dopamine reduction was observed. This region receives dopaminergic inputs from the substantia nigra as a meso-cortical dopaminergic pathway. The pathway is implicated in some emotional changes and cognitive deficits.

Conclusion:

In conclusion, we indicate multiple metabolic pathways perturbed during aging. The metabolic changes were different between brain regions. High impact-value pathways were glutathione metabolism, taurine and hypotaurine metabolism, and sphingolipid metabolism in the hippocampus; glutathione metabolism, tyrosine metabolism, and sphingolipid metabolism in the mPFC; and purine metabolism in the striatum. The metabolic changes may reflect functional changes, including cognitive impairments with aging.

別紙様式８（課程博士・論文博士共用）

学位論文審査の結果の要旨

整理番号	803	氏　名	Lina Wati Binti Durani
論文審査委員			

（学位論文審査の結果の要旨）※明朝体１１ポイント、６００字以内で作成のこと

本論文では、超高性能液体クロマトグラフィー、高分解能精密質量/オービトラップタンデム質量分析法を用い、生後 14、18、23、27 か月のラットの海馬、内側前頭前皮質、線条体における代謝プロファイルの加齢に伴う変化について検討を行い、以下の点を明らかにした。

１）同研究グループからの先行論文において、行動テスト解析の結果が middle-aged 群（生後 14、18 か月）と late-aged 群（生後 23、27 か月）の間で差異が認められており、代謝プロファイル解析においてもこの 2 群間での比較を行った。
２）2 群間において、海馬、内側前頭前皮質、線条体における代謝産物につき、それぞれ 38 物質（増加 36、減少 2）、29 物質（増加 14、減少 15）、14 物質（増加 8、減少 6）の変化が見られた。
３）Late-aged 群において、海馬での glutathione 代謝の改善と内側前頭前皮質での低下、海馬における taurine/hypotaurine 代謝変化、海馬と内側前頭前皮質での sphingolipid 代謝の変化、線条体での purine 代謝の変化、内側前頭前皮質での dopamine 減少が認められた。
４）加齢に伴うこれらの代謝変化は部位により均一ではなく、各部位の脳機能の変化を反映していることが推測された。

本論文は、ラットの海馬、内側前頭前皮質、線条体における代謝プロファイルの加齢に伴う変化について新たな知見を与えたものであり、また最終試験として論文内容に関連した試問を実施したところ合格とされたので、博士（医学）の学位論文に値するものと認められた。

（総字数　579 字）

（平成 30 年 1 月 30 日）