民族薬物研究センター　Research Center for Ethnomedicine

薬効解析部　　Division of Biofunctional Evaluation

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◇研究目的

民族薬物研究センター薬効解析部は，民族薬物の薬効解析に関する研究を推進するために設置された。特に，アルツハイマー病，脊髄損傷，注意欠陥多動性障害といった難治性神経変性疾患をターゲットとして研究を行っている。これらの疾患制御に関わる生体の分子メカニズムを解明するとともに，神経回路網が破綻した後からでもこれら疾患における神経機能を正常に回復させる根本的治療戦略としての“神経回路網再構築薬”の開発を目指す。

薬効解析部ではこれまでに，神経変性疾患からの回復に最も必要とされる要因に対して，ある種の伝統薬物が切れ味鋭い作用を示すという実験事実をもとに，画期的な効力を示す薬物の発見と，それらの作用分子の解析による神経回路網再構築の鍵を握る分子を進めている。このように，伝統薬物と神経科学を融合させ，創薬と病態解析へ展開させる独創的で有益なアプローチとして「伝統薬物-based 創薬」を提案し実践している。

◇研究概要

1) 中枢神経における神経ネットワーク再構築を制御する分子機序の包括的解明
2) 伝統薬物-based 創薬による，アルツハイマー病および脊髄損傷に対する根本的治療薬の研究

◇著書

1) 東田千尋：アルツハイマー病に有効な漢方処方：帰脾湯．漢方薬・生薬薬剤師講座テキスト　財団法人　日本薬剤師研修センター. 4, 81-94, 2010.

◇原著論文

1) Bai Y., Tohda C., Zhu S., Hattori M., Komatsu K.: Active components from Siberian ginseng (*Eleutherococcus senticosus*) for protection of amyloid β(25-35)-induced neuritic atrophy in cultured rat cortical neurons. J. Nat. Med. 65: 417-423, 2011.

Abstract: Not only neuronal death but also neuritic atrophy and synaptic loss underlie the pathogenesis of Alzheimer's disease as direct causes of the memory deficit. Extracts of Siberian ginseng (the rhizome of *Eleutherococcus senticosus*) were shown to have protective effects on the regeneration of neurites and the reconstruction of synapses in rat cultured cortical neurons damaged by amyloid β (Aβ)(25-35), and eleutheroside B was one of the active constituents. In this study, a comprehensive evaluation of constituents was conducted to explore active components from Siberian ginseng which can protect against neuritic atrophy induced by Aβ(25-35) in cultured rat cortical neurons. The ethyl acetate, n-butanol and water fractions from the methanol extract of Siberian ginseng showed protective effects against Aβ-induced neuritic atrophy. Twelve compounds were isolated from the active fractions and identified. Among them, eleutheroside B, eleutheroside E and isofraxidin showed obvious protective effects against Aβ(25-35)-induced atrophies of axons and dendrites at 1 and 10 μM.

2) Joyashiki E., Matsuya Y., Tohda C.: Sominone improves memory impairments and increases

axonal density in Alzheimer's disease model mice, 5XFAD. Int. J. Neurosci. 121:.181-190, 2011.

Abstract: Previously we showed that steroidal sapogenin, sominone improved memory after a single i.p. injection into normal mice. However, it had not been reported that sominone could recover memory deficits in a severe Alzheimer's disease (AD) model animal. Therefore, we aimed to investigate that sominone improved memory impairments in the 5XFAD mouse, model for AD. In the current study, we used sominone that we had synthesized. 5XFAD mice were given 10 μmol/kg sominone intraperitoneally for 9 days. In addition to object recognition memory, axonal density, amyloid plaque number, and activated microglia in the brain were evaluated. Sominone treatment significantly improved object recognition memory compared with vehicle control treatment. Sominone treatment significantly enhanced axonal densities in the frontal cortex and parietal cortex but had no effects on amyloid plaque number and activated microglia. In cultured cortical neurons, the axonal length was significantly reduced by Aβ(1-42) treatment. However, that was markedly recovered 5 days after the treatment with 1 μM sominone. Neuronal loss was not observed in the cortex and hippocampus of 5XFAD mice at 6-8 months of age. These results suggest that memory deficits in AD may be improved by sominone independently of reducing amyloid plaques and neuroinflammation.

3) **Tohda C., Nakada R., Urano T., Okonogi A., Kuboyama T.: Kamikihi-to (KKT) Rescues Axonal and Synaptic Degeneration Associated with Memory Impairment in a Mouse Model of Alzheimer's Disease, 5XFAD. Int. J. Neurosci. 121: 641-648, 2011.**

Abstract: Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder. Current agents for AD are employed for symptomatic therapy and insufficient to cure. We consider that this is quite necessary for AD treatment and have investigated axon/synapse formation-promoting activity. The aim of this study is to investigate the effects of Kamikihi-to [KKT; traditional Japanese (Kampo) medicine] on memory deficits in an AD model, 5XFAD. KKT (200 mg/kg, p.o.) was administered for 15 days to 5XFAD mice. Object recognition memory was tested in vehicle-treated wild-type and 5XFAD mice and KKT-treated 5XFAD mice. KKT-treated 5XFAD mice showed significant improvement of object recognition memory. KKT treatment significantly reduced the number of amyloid plaques in the frontal cortex and hippocampus. Only inside of amyloid plaques were abnormal structures such as bulb-like axons and swollen presynaptic boutons observed. These degenerated axons and presynaptic terminals were significantly reduced by KKT treatment in the frontal cortex. In primary cortical neurons, KKT treatment significantly increased axon length when applied after Aβ(25-35)-induced axonal atrophy had progressed. In conclusion, KKT improved object recognition memory deficit in an AD model 5XFAD mice. Restoration of degenerated axons and synapses may be associated with the memory recovery by KKT.

◇総説

1) **Tohda C., Kuboyama T.: Current and future therapeutic strategies for functional repair of spinal cord injury. Pharmacol. Ther. 132: 57-71, 2011.**

Abstract: Spinal cord injury (SCI) causes serious, chronic dysfunction which is difficult to treat. Disability, including long-lasting motor and sensory dysfunction, typically results from damage to the descending and ascending spinal tracts and interneurons and, secondarily, to the neuronal degeneration that occurs proximal and distal to the spinal insult. Numerous strategies are being implemented to protect neurons from damage, to enhance axon growth and to foster cell proliferation. Described in this report are recent clinical trials aimed at testing strategies to restore locomotion after SCI. While laboratory animal studies have indicated that it may be possible to minimize neuronal damage resulting from spinal cord injury, little progress has been made in reducing or reversing the events associated with the chronic phase of this condition. The strategy aiming to inhibit single molecule sometimes shows controversial results. In SCI, a lot of players participate in motor and sensory dysfunctions. Therefore, sufficient functional recovery may be achieved by regulating multiple targets. Regrowth of tracts connecting the brain and

spinal cord, and axonal sprouting of propriospinal interneurons are fundamentally important for neuronal network working. In addition, remyelination, protection of neuronal death, inhibition of inflammation, and upregulation of beneficial influence of astrocytes are also quite crucial to supporting the axonal refining. Combination of several strategies might be useful as a practical therapy. Several compounds such as a Sema3A inhibitor, estrogen, withanoside IV and their relating compounds or other neurotrophic factor-mimicking agents may be candidates for useful SCI therapeutic drugs since those have multi-effects on damaged spinal cord.

2) **Tohda C.: Potential of traditional medicine-derived compounds as therapeutic drugs for Alzheimer's diseases. Basics of Evidences-Based Herbal Medicine. Research Signpost/Transworld Research Network. Kerala, India. 89-104, (2010).**

Abstract: While acetylcholine esterase inhibitors are primarily used in the treatment of Alzheimer's disease, they only delay the progression of dementia rather than actually restore brain function. Recovery of brain function after injury requires the reconstruction of neuronal networks, including neurite regeneration and synapse reformation. Several candidates (synthesized compounds, natural medicine-derived compounds, physiologically activity substances, antibodies, etc.) for anti-Alzheimer's disease have been studied in experimental models in vitro and in vivo. This review focuses on traditional medicine-derived compounds isolated from Ashwagandha, Ginseng Radix, Astragali Radix, Siberian Ginseng, Salviae Miltiorhizae Radix and Aurantii Nobilis Pericarpium, and shows their effects on amyloid β-induced neurite atrophy, cell death or memory deficits. The therapeutic potency of a variety of structures, such as saponins, sapogenins, flavonoids, iridoids, and phenylpropanoids, has been indicated in several experimental models.

◇学会報告　（*：特別講演，シンポジウム，ワークショップ等）

1) Teshigawara K., Nagata A., Kuboyama T., Tohda C.：1-Deoxy-nor-sominone (Denosomin) promotes the neurite outgrowth via astrocyte-mediated signaling in the spinal cord. 第 84 回日本薬理学会年会，2011，3，22-24，横浜.
2) 柴原直利，東田千尋，Zhu Shu，櫻井宏明，数馬恒平，山本武，小泉桂一，紺野勝弘，門脇真，小松かつ子：「伝統医薬データベース」の構築，第 28 回和漢医薬学会学術大会，2011, 8，27-28，富山.
3) Wang X., Kuboyama T., Miyanaga S., Kazuma K., Konno K., Satake M., Tohda C.： Searching for natural medicines that improve spinal cord injury，第 28 回和漢医薬学会学術大会，2011，8，27-28，富山.
4) 中田理恵，東田千尋：アルツハイマー病モデルマウスの記憶障害と軸索変性を改善する加味帰脾湯の作用，第 28 回和漢医薬学会学術大会，2011，8，27-28，富山.
5) 勅使川原匡，久保山友晴，松谷裕二，東田千尋：新規化合物 1-deoxy-nor-sominone (Denosomin)によるアストロサイトを介した脊髄損傷の改善作用. 第 54 回日本神経化学会大会，2011，9，26-28，加賀.
6) 執行美智子，長田愛子，勅使川原匡，久保山友晴，松谷裕二，東田千尋：脊髄損傷の運動機能回復に関与する Denosomin の軸索伸展作用．第 54 回日本神経化学会大会，2011，9，26-28，加賀.
7) 久保山友晴，Jerry Silver，東田千尋，上口裕之：コンドロイチン硫酸プロテオグリカンによる軸索再生阻害のシグナル伝達機構．第 54 回日本神経化学会大会，2011，9，26-28，加賀.
8) 中田理恵，久保山友晴，東田千尋：アルツハイマー病モデルマウスの記憶障害と軸索変性に対する加味帰脾湯の改善作用．第 54 回日本神経化学会大会，2011，9，26-28，加賀.

招待講演

＊ 1) Tohda C.: The study of natural medicine for exploring key pathways of neuroregeneration. The 11th Southeast Asian Western Pacific Regional Meeting of Pharmacologists, 2011, 3, 22-24, Yokohama.

＊ 2) Komatsu K., Zhu S., Tohda C.: Genetic, chemical and pharmacological diversity of Ginseng drugs. The 6th CCTNM-KSP-JSP Joint Symposium on Pharmacognosy. 2011, 10, 20-22, Shenyang, China.

◇その他

その他の講演

1) 東田千尋：神経変性疾患を知る・克服する．第 54 回日本神経化学会大会　神経化学の若手研究者育成セミナー　2011，9，26-28，加賀．

2) 久保山友晴：コンドロイチン硫酸プロテオグリカンによる軸索再生阻害のシグナル伝達機構．「軸索再生」連絡会議，2011，11，29-30，和光．

3) 東田千尋：漢方方剤とアルツハイマー病．富山漢方会　2011，12，21，富山．

受賞

1) 中田理恵：第 28 回和漢医薬学会学術大会 優秀発表賞．「アルツハイマー病モデルマウスの記憶障害と軸索変性を改善する加味帰脾湯の作用．」2011，8，27-28，富山．

新聞・雑誌

1) 「医療最前線第 5 部　飛躍　明日への処方箋　科学の力で見直される漢方」産経新聞，2011，3，3．

2) 加味帰脾湯が AD の記憶障害を改善　Medical Tribune　No.44(43)，p29，2011，10，27．

◇共同研究

1) 小松かつ子：富山大学，「神経変性疾患に有効な伝統薬物分子の探索とその治療戦略」

2) 松谷裕二：富山大学，「withanolide 類の研究」「新規化合物の神経保護作用の研究」

3) クラシエ製薬：加味帰脾湯の抗アルツハイマー病作用

4) 上口裕之：理化学研究所，「軸索再生不全の機序を解明するための研究」

5) 梅嵜雅人：富山大学，「生薬成分の薬効機構の解明」

6) 紺野勝弘：富山大学，「富山県産和漢薬から開発する脊髄損傷改善薬に関する研究」

7) 豊岡尚樹，森寿，水口峰之：富山大学，「構造活性相関に基づく神経変性疾患新規分子標的治療薬の開発拠点形成」

8) 上山健彦：神戸大学バイオシグナル研究センター，「各種ノックアウトマウスを用いた脊髄損傷におけるアストロサイトの機能解析」

9) 後藤幸織：McgGill University, Department of psychiatry, Canada，「Diosgenin の記憶改善作用に関する研究」

◇研究費取得状況

1) 文部科学省研究費補助金，基盤研究 C（代表：東田千尋）「慢性期脊髄損傷の回復を目指す研究－多能的新規化合物デノソミンの作用機序－」

2) 文部科学省研究費補助金，若手研究 B（代表：久保山友晴）「細胞接着斑形成に着目した神経軸索再生法開発のための基礎研究」

3) 文部科学省研究費補助金，若手研究 B（代表：勅使川原匡）「脊髄損傷の運動機能障害に対するデノソミンの薬理作用と神経回路網の構築機序の解析」
4) 文部科学省研究費補助金，基盤研究 A（連携：東田千尋）「うつ病のすべてがわかる和漢薬：発病機序の分子的解明から新規抗うつ薬開発まで」
5) 文部科学省研究費補助金，基盤研究 B 海外（分担：東田千尋）「サステイナブル伝統薬を志向した薬用資源植物の多様性の解析」
6) 文部科学省研究費補助金，基盤研究 C（連携：東田千尋）「2, 3-ベンゾジアゼピン類の高効率合成法の開発と中枢神経系疾患治療薬開発への展開」
7) 文部科学省知的クラスター創成事業（Ⅱ）広域化プログラム（分担：東田千尋）「天然薬物の遺伝子解析等に基づく標準化」
8) 厚生労働科学研究事業（分担：東田千尋）「漢方薬に使用される薬用植物の総合情報データベース構築のための基盤整備に関する研究班」
9) 富山県「和漢薬・バイオテクノロジー研究」（代表：東田千尋）「富山県産和漢薬から開発する脊髄損傷改善薬に関する研究」
10) 富山大学学長裁量経費（戦略的経費）（分担：東田千尋）「構造活性相関に基づく神経変性疾患新規分子標的治療薬の開発拠点形成（SR 阻害薬開発をモデルケースとして）
11) 文部科学省研究費補助金，新学術領域研究（連携：久保山友晴）「統合的神経機能の制御を標的とした糖鎖の作動原理解明」

◇研究室在籍者

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