複合薬物薬理学分野　Division of Medicinal Pharmacology

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◇研究目的

中枢神経系疾患の病態と発症機構に関する薬理学的研究を行うとともに，和漢薬をはじめ，複合成分からなる薬物の薬効に関する計量薬理学的評価，作用本体の追求および分子レベルでの作用機序の解明を目的とした研究を行っている。

◇研究概要

Ⅰ）　中枢神経系疾患の病態と発症機構に関する基礎研究

1) 心理的ストレスで起こる異常行動および薬物応答性変化の神経機構の解析および神経機能修飾因子の役割に関する研究
2) 病態モデルにおける神経伝達物質等の内在性因子や天然薬物成分の脳内動態に関する研究

Ⅱ）　複合薬物及びその成分の中枢作用に関する神経薬理学的研究

1) 脳血管性認知症モデルをはじめとする病態モデル系における和漢薬および和漢薬成分の抗認知症作用と神経保護作用の評価ならびに作用分子機構の解明
2) 神経保護薬をはじめ，新規リード化合物の開発をめざした伝統薬物・民族薬の薬理作用の探索と作用機序の解析
3) ツメガエル受容体遺伝子発現系を用いた神経伝達受容体の機能解析，薬物作用およびその作用機序に関する電気生理学的研究

Ⅲ）　遺伝子発現を指標とした薬物作用の解明と和漢薬作用に関する研究

1) 慢性脳虚血等のストレスにより発現する脳内遺伝子 vof のクローニングとその生理機能解析
2) 和漢薬および抗うつ薬を利用したうつ病態関連因子のクローニング，発現変化の作用解析，およびうつ病発病機序の分子的解明

◇原著論文

1)　Tohda M., Mingmalairak S., Murakami Y., and Matsumoto K.: Enhanced expression of BCL2/adenovirus EIB 19-kDa-interacting protein 3 mRNA, a candidate for intrinsic depression-related factor, and effects of imipramine in the frontal cortex of stressed mice. Biol. Pham. Bull. 33, 53-7; 2010.

Abstract: We previously reported that long-term treatment with some antidepressants at low concentrations upregulates BCL2/adenovirus E1B 19-kDa-interacting protein 3 (BNIP3) mRNA expression in NG108-15 cells without causing cell damage, suggesting that BNIP3 is a candidate of intrinsic depressive disorder-related factor(s). In this study, to clarify the physiologic functions of BNIP3, we investigated whether BNIP3 is actually related to the depressive condition in the brain using learned

helplessness (LH) mice, an animal model of depression. Based on the score of escape failure, an index of depression degree, stressed animals were divided into groups with LH and without depressive-like symptoms (i.e., non-depressed phenotype, non-LH). The score of escape failure of the LH group was decreased after 14 d of treatment with imipramine in a dose-dependent manner. BNIP3 mRNA expression was enhanced in both the LH and non-LH groups. Imipramine treatment at 5 and 20 mg/kg/d enhanced BNIP3 mRNA expression only in the LH group but not in non-LH group or non-stressed group. These results raise the possibility that BNIP3 acts as an antistress factor in the brain.

2) **Pham N.T., Tohda M., Tezuka Y., and Matsumoto K.: Influence of an adenosine deaminase inhibitor, erythro-9-(2-hydroxy-3-nonyl) adenine hydrochloride, on 5-HT2CR mRNA editing in primary cultured cortical cells. Biol. Pham. Bull. 33, 527-9; 2010.**

Abstract: Treatment of primary cultured cortical cells with erythro-9-(2-hydroxy-3-nonyl) adenine hydrochloride (EHNA), an inhibitor of adenosine deaminase (ADAR), for 6 d significantly and concentration-dependently reduced the editing efficacy at sites C and D but not at site A or B of 5-HT2CR mRNA. The treatment failed to affect the editing of ADAR-2 pre-mRNA and a subunit of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)-type glutamate receptor (GluR2) mRNA. These findings suggest that EHNA is useful for clarifying the functional roles of 5-HT2CR mRNA editing at sites C and D.

3) **Yamabe N., Kim H.Y., Kang K.S., Zhao Q., Matsumoto K., and Yokozawa T.: Effect of Chinese prescription Kangen-karyu on lipid metabolism in type 2 diabetic db/db mice. J Ethnopharmacol. 129, 299-305; 2010.**

Abstract: AIM OF THE STUDY: Chinese prescription Kangen-karyu is clinically used as a treatment for cardiovascular diseases, and we have reported the beneficial effects on chemically induced hyperlipidemic animal models. The present study was investigated to evaluate the hypolipidemic effect of Kangen-karyu in type 2 diabetic db/db mice which has not been explored yet. **MATERIALS AND METHODS:** Male db/db mice were divided into three groups, vehicle (control), Kangen-karyu 100, or 200 mg/kg body weight/day, and orally administered for 5 weeks every day. Age-matched non-diabetic m/m mice were used as a normal group. **RESULTS:** Serum triglyceride (TG) and total cholesterol levels in db/db mice were increased compared with those of m/m mice. However, the administration of Kangen-karyu reduced hyperlipidemia in db/db mice through a decline in the serum levels of TG and total cholesterol. The hepatic TG and total cholesterol levels of db/db mice were markedly higher than those of m/m mice, but these elevated lipid levels were significantly reduced by 200 mg/kg Kangen-karyu administration. Also, oil red O staining showed that the increased lipid deposition level in the liver of db/db control mice was improved by Kangen-karyu administration. The expression of sterol regulatory element-binding protein-1 in the liver of db/db mice was significantly down-regulated by the administration of Kangen-karyu at a dose of 200 mg/kg body weight. Kangen-karyu caused a slight elevation in the expression of peroxisome proliferator-activated receptor alpha in the liver of db/db mice. **CONCLUSIONS:** This study provides scientific evidence that Kangen-karyu improves hyperlipidemia and lipid deposition via the regulation of hepatic SREBP-1 expression in type 2 diabetic db/db mice.

4) **Mingmalairak S., Tohda M., Murakami Y., and Matsumoto K.: Possible involvement of signal transducers and activators of transcription 3 system on depression in the model mice brain. Biol Pharm Bull. 33, 636-40; 2010.**

Abstract: The anti-aging activities of persimmon oligomeric proanthocyanidins (POPs), reported to improve life span and behavioral characteristics associated with the aging process, were investigated using the senescence-accelerated mouse (SAM) P8, which is a good model for studies on aging-related behavioral changes as well as life span. We demonstrated that the administration of POPs extended the life span of SAMP8. In addition, POPs elevated Sirt1 expression, which is recognized as an essential factor for

life span extension in the brain. On the other hand, the administration of POPs did not induce stereotypical behaviors such as rearing, jumping, and hanging from the lid of a cage, whereas food restriction increased these frequencies without a significant change in motor function. The present study suggests a promising role of POPs as anti-aging agents to extend life span, although further studies elucidating their anti-aging mechanisms acting are needed.

5) **Zhao Q., Yokozawa T., Yamabe N., Tsuneyama K., Li X., and Matsumoto K.: Kangen-karyu improves memory deficit caused by aging through normalization of neuro-plasticity-related signaling system and VEGF system in the brain.**
J Ethnopharmacol. 131, 377-85; 2010.

Abstract: AIM OF THE STUDY: Kangen-karyu (KK) is a traditional Chinese prescription consisting of six different herbs. This study was conducted to investigate the anti-dementia effect of KK on aging-induced cognitive deficits and the underlying mechanism using senescence-accelerated mice prone (SAMP8). **MATERIALS AND METHODS:** Twenty-week old SAMP8 (older SAMP8) were used as an animal model of aging and age-matched senescence-resistant inbred strain (SAMR1) and 8-week-old SAMP8 (young SAMP8) were as controls. Older SAMP8 received daily administration of KK (100 mg/kg, p.o.) or water vehicle for 22 days. **RESULTS:** Compared to the controls, older SAMP8 exhibited cognitive deficits in the object recognition and object location tests; however, KK improved the deficits caused by aging. Moreover, the older SAMP8 treated with vehicle exhibited reduced anxiety-like behavior in the elevated plus-maze test compared to SAMR1, but KK had no effect on emotional disorder of older SAMP8. The levels of biochemical factors related to neuro-plasticity and learning and memory; i.e., phosphorylated forms of N-methyl-D-aspartate receptor 1, Ca^{2+}/calmodulin-dependent protein kinase II, and cyclic AMP-responsive element-binding protein, and brain-derived neurotrophic factor, were significantly decreased in older SAMP8 compared to those in the control animals. KK normalized the levels of these factors. Moreover, the mRNA and protein levels of vascular endothelial growth factor (VEGF) and its receptor type 2 in the cerebral cortices of older SAMP8 were down-regulated by aging, but these levels were reversed by KK. **CONCLUSIONS:** These findings suggest that normalization of neuro-plasticity-related neuronal signaling and VEGF systems in the brain may be of the mechanisms underlying the ameliorative effects of KK on the cognitive deficits in older SAMP8.

6) **Tohda M., Hang P.N.T., Kobayashi N., and Matsumoto K.: Serotonin 2C receptor (5-HT2CR) mRNA editing-induced down-regulation of 5-HT2CR function in Xenopus oocytes: the significance of site C editing. J Pharmacol Sci. 113, 362-7; 2010.**

Abstract: Serotonin 2C receptor (5-HT2CR) mRNA receives editing at 5 nucleotide positions (sites A-E) located in the sequence encoding the second intracellular loop of 5-HT2CR. 5-HT2CR mRNA without editing and with editing at sites AB, ABD, ABC, ABCD, and C are translated to 6 isoforms of 5-HT2CR: INI(non-edited), VNI(AB), VNV(ABD), VSI(ABC), VSV(ABCD), and ISI(C), respectively. In this study, we investigated electrophysiologically the ability of these isoforms to couple with the G protein/phospholipase C (PLC) system using Xenopus oocytes injected with edited 5-HT2CR RNAs and muscarinic M(1) receptor (M1R) RNA. The efficacy with which 5-HT stimulated each isoform was calculated by comparing 5-HT-induced current with 100 μM acetylcholine-induced M1R current. Stimulation with 5-HT of INI(non-edited), VNI(AB), VNV(ABD), VSI(ABC), VSV(ABCD), and ISI(C) expressed in Xenopus oocytes showed concentration-dependent responses with EC(50) values of 8.6, 17.2, 76,5, 22.0, 91.2, and 20.3 nM, respectively. No significant difference in the ability of 5-HT to induce currents among the oocytes expressing these isoforms was detected, but in the oocytes expressing VSI(ABC) or VSV(ABCD), 5-HT had a significantly reduced ability to induce currents. These results suggest that editing at site C together with sites A and B and/or D markedly reduces 5-HT2CR function by generating isoforms with reduced ability to activate PLC.

◇学会報告　(*: 特別講演，シンポジウム，ワークショップ等)

* 1) 東田道久：うつ病に立ち向かう和漢薬．平成21年度富山大学-富山県連携事業，初心者にもわかる和漢薬一日セミナー，2010, 1/30，富山.

* 2) 東田道久：補中益気湯によるうつ病関連分子の探索と作用機序解明．第83回日本薬理学会年会，2010, 3/16-18，大阪.

3) Zhao Q., Matsumoto K., Sakata K., and Yokozawa T.：Kangenkaryu, a herbal prescription, improves memory deficit in type 2 diabetic mice.　第 83 回日本薬理学会年会，2010, 3/16-18，大阪.

4) 東田道久，小林直史，小松かつ子，松本欣三：補中益気湯によるセロトニン 2C 受容体応答調節とその有効性成分解析．第 83 回日本薬理学会年会，2010, 3/16-18，大阪.

5) 林田未希，ミンマーライラックサリーン，村上孝寿，趙琦，東田道久，松本欣三：マウスの嗅球摘出により誘発される記憶障害に対する抑肝散の改善効果. 第 83 回日本薬理学会年会，2010, 3/16-18，大阪.

6) 堀仁美，村上孝壽，Zhao Q.，東田道久，松本欣三：一過性脳虚血誘発のラット海馬グルタミン酸遊離増加に対する黄連解毒湯の作用．第 83 回日本薬理学会年会，2010, 3/16-18，大阪.

7) 松本欣三，趙琦，山辺典子，横澤隆子：認知症改善薬としての漢薬「冠元顆粒」－病態から捉えた新たな有用性－．伝統医薬学シンポジウム，2010, 3/19，富山.

* 8) Matsumoto K.：Chotosan and Recognition Behavior. 第 16 回国際薬理学会，2010, 7/17-23，コペンハーゲン (デンマーク) (招待)

* 9) 東田道久：和漢薬はうつ病の救世主になりえるか．第 15 回和漢医薬学総合研究所夏期セミナー，2010, 8/23-25，富山.

10) 山邉典子，盧貞淑，朴鍇欽，姜奇成，趙琦，松本欣三，横澤隆子：糖尿病の脂質代謝異常における冠元顆粒の有用性．第 27 回和漢医薬学会，2010, 8/28-29，京都.

11) 趙琦，横澤隆子，宮田健，常山幸一，松本欣三：老化促進モデルマウス SAMP8 の学習記憶障害及び脳内 VEGF/PDGF 系障害に対する釣藤散の改善作用. 第 27 回和漢医薬学会，2010, 8/28-29，京都.

12) 東田道久，松本欣三：和漢処方によるBNIP-3 mRNA発現上昇と抗うつ作用との関連性に関する検討．第27回和漢医薬学会，2010, 8/28-29，京都.

13) 東田道久，松本欣三：ラット大脳皮質初代培養細胞の培養日数に伴う各種 mRNA 発現量変化とそれへの 5-HT2CR RNA editing の影響．第 61 回日本薬理学会北部会，2010, 9/10，札幌.

14) 趙琦，横澤隆子，宮田健，常山幸一，松本欣三：2 型糖尿病モデルマウスの認知・情動行動障害に対する漢方薬釣藤散の改善効果．第 61 回日本薬理学会北部会，2010, 9/10，札幌.

15) 大内啓史，松本欣三：隔離飼育ストレス負荷マウスの潜在学習・注意力障害及び ADHD 病態モデルとしての可能性．第 61 回日本薬理学会北部会，2010, 9/10，札幌.

* 16) Matsumoto K., Zhao Q., Yokozawa T., and Tsuneyama K.：Kangen-karyu, a traditional Chinese prescription: experimental insight into its utility as an anti-dementia drug. The 2nd China, Japan and Korea International Conference for TCM & The 7th Sino-Russia Biomedical Forum. 2010, 9/16-17，ハルピン (中国) (招待).

17) 朴鍇欽，盧貞淑，山邉典子，岡本拓也，趙琦，松本欣三，横澤隆子：冠元顆粒の腎における役割－2型糖尿病モデルを用いた検討－．第22回腎とフリーラジカル研究会，2010, 10/15，東京.

* 18) 松本欣三：駆瘀血薬を応用した認知症治療戦略とその基礎的EBM．第31回研究所特別セミナー．2010, 10/23，富山.

19) 山田麻利名，林田未希，柴原直利，松本欣三：嗅球摘出マウスの学習記憶障害に対する抑肝散の改善効果とその機序．日本薬学会北陸支部第122回例会，2010, 11/20，金沢.

20) Yamada M., Hayashida M., Shibahara N., Miyata T., and Matsumoto K.：Ameliorative effect of

yokukansan on learning and memory impariment in olfactory bulbectomized mice. The 9th JSPS-NRCT Joint Seminar. 2010.12/8-9, バンコック (タイ).

21) Ouchi H., and Matsumoto K.：Social isolation stress in mice as an epigentci model of attention deficit hyperactivity disorder: behavioral and pharmacological evidence. The 9th JSPS-NRCT Joint Seminar. 2010.12/8-9, バンコック (タイ).

22) Tohda M., Kanzaki M., and Sukma M.：γ-Mangostin as an antidepressant drug: evaluation by the *in vitro* assay systems highly responsive to antidepressant. The 9th JSPS-NRCT Joint Seminar. 2010.12/8-9, バンコック (タイ).

◇その他

1) 松本欣三，済木育夫：話題「JSPS(日本学術振興会)支援による拠点大学交流事業．ファルマシア．46, 770-774; 2010.
2) 東田道久：右脳思考のすすめ．ファルマシア．46, 976; 2010.
3) 東田道久：新たな付加価値の創造とそれをもたらす斬新な発想の重要性．ファルマシア．46, 1169; 2010.

◇共同研究

研究所内

1) 田中謙：生薬資源科学,「漢方薬の抗認知症効果を担う脳内メディエータに関する研究」, 2008, 4/1～
2) 横澤隆子：薬効解析部,「老化モデル動物および糖尿病モデル動物の認知情動行動障害を指標とした駆瘀血薬効果の解析」, 2008, 12/1～
3) 柴原直利：漢方診断学分野,「ストレス性障害に有用な和漢薬とその作用機序に関する研究」, 2009, 4/1～
4) 宮田健：「漢方薬の抗認知症効果を担う脳内メディエータに関する研究」, 2010, 4/1～

学内

1) 嶋田豊：富山大学大学院医学薬学研究部,「慢性脳虚血ラット脳における遺伝子発現に及ぼす釣藤散の作用に関する研究」, 2001, 4/1～
2) 常山幸一：富山大学大学院医学薬学研究部,「漢方薬の抗認知症効果を担う脳内メディエータに関する研究」, 2007, 4/1～

海外

1) Chulikhit Yaowared：タイ・コンケン大学薬学部,「クルクミンをはじめとする天然薬物の抗うつ作用と分子機構に関する研究」, 2010, 3-
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4) Pham Nguiet Thi Hang：ベトナム・国立天然薬物研究所,「ベトナム伝統薬物の抗認知症作用と作用機序に関する研究」, 2010, 10-
5) Sukma Monrudee：タイ・シラパコーン大学,「γ-mangostin の抗うつ作用に関する分子薬理学的研究」, 2007, 10-

◇研究費取得状況

1) 文部科学省科学研究費，基盤研究 B（代表：松本欣三）「漢方薬の抗認知症効果を担う脳内薬効メディエータに関する研究」310 万 (3/3 年目)
2) 文部科学省科学研究費，基盤研究 A（代表：東田道久）「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」650 万 (2/5 年目)

3) 学長裁量経費教育研究費「持続発展型国際交流と人材育成をめざした「拠点大学方式による学術交流事業」活用プログラム」（代表：松本欣三）100 万

4) 重点配分経費教育研究費 一般 Yawared Chulikhit（分担：松本欣三）22 万

5) 重点配分経費教育研究費 一般 Pham Nguiet Thi Hang（分担：松本欣三）37 万

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文部科学省国費留学生：Le Thi Xoan (ベトナム・国立天然薬物研究所, 2010, 10/6-)
外国人客員研究員：Dr. Chulikhit Yaowared (タイ・コンケン大学薬学部, 2010, 10/3-11/13)
Dr. Boonyarat Chantana (タイ・コンケン大学薬学部，2010, 10/3-11/28)
Dr. Pham Nguiet Thi Hang (ベトナム・国立天然薬物研究所, 2010, 10/6-12/28)