生 物 試 験 部 門

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◇研究目的

本部門では，和漢薬の新しい薬効評価法を確立するための基礎研究，和漢薬の中枢作用を定量的に評価し，その作用本体を追求する研究及びその作用機序を分子レベルで明らかにすることを目的としている。

◇研究概要

Ⅰ．和漢薬の新しい薬効評価法を確立するための基礎的研究

1）脳血管性痴呆病態モデル動物の確立とそれによる和漢薬および抗痴呆薬の薬効評価
2）情動ストレス反応の不安・うつ病態モデルとしての応用と和漢薬作用
3）新規リード化合物の開発をめざした各種民族薬の薬理作用の探索と作用機構の解析

Ⅱ．中枢作用薬の神経薬理学的研究

1）心理的ストレス反応に関わる神経機構，受容体機能修飾因子，分子機序の解析
2）神経伝達物質の脳内動態および代謝回転の解析と薬物作用

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）慢性脳虚血感受性の脳内遺伝子のクローニングとその機能解析
2）うつ病態関連脳内遺伝子の発現変化と抗うつ薬・和漢薬の作用解析

◇原　著

1) **Nguyen T.T.H., Matsumoto K. Kasai R., Yamasaki K. and Watanabe H.: *In vitro* antioxidant activity of Vietnamese Ginseng saponin and its components. Biol. Pharm. Bull., 21 : 978–981, 1998.**

Abstract : To elucidate the antioxidant action of Vietnamese ginseng saponin against free radial-mediated cellular damage, we examined the effect of Vietnamese ginseng saponin on lipid peroxidation in the mouse brain, liver, and liver microsomes by using two *in vitro* free radical generating systems (iron ferrous+ascorbic acid and iron ferrous+ hydrogen peroxide). Free radical-mediated lipid peroxidation was determined by measuring the endogenous and stimulated accumulation of thiobarbituric acid reactive substance (TBA-RS). Vietnamese ginseng saponin (0.05 - 0.5 mg/ml), as well as vitamin E, significantly inhibited the formation of TBA-RS in tissue homogenates. Panex ginseng saponin, at the same concentration range as Vietnamese ginseng saponin, also had inhibitory action on free radical-mediated lipid peroxidation. However, majonoside-R2, ginsenoside-Rgl and ginsenoside-Rb1, the main saponin components of Vietnamese ginseng saponin fraction, had no effect on lipid peroxidation. These results suggest that Vietnamese ginseng exerts a protective action against free radical-induced tissue injury and that this effect is attributable to minor components rather than the main saponin components tested.

2) **Li H.-B., Matsumoto K. and Watanabe H.: An α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonists and an *N*-methyl-D-aspartate (NMDA) channel blocker synergistically impair spatial memory in rats. Biol. Pharm. Bull., 21 : 1228–1230, 1998.**

Abstract : The interaction of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonist YM90K with the competitive *N*-methyl-D-aspartate (NMDA) antagonist CGS19755 or with the NMDA channel blocker MK801 on the spatial memory of rats was examined by the 4-arm-baited radial maze task. When administered alone, these drugs had no effect on the spatial memory. The combination of YM90K and MK801 synergistically disrupted working and reference memories, whereas the combination of YM90K and CGS19755 had no effect. These results indicate that the blockade of the AMPA receptor and NMDA channels produces a synergistic impairment of spatial memory and suggest that interaction between the AMPA and NMDA receptors plays a role in cognitive function.

3) **Leewanich P., Tohda M., Matsumoto K., Subhadhirasakul S., Takayama H. Aimi N. and Watanabe H.: A possible mechanism underlying corymine inhibition of glycine-induced Cl^- current in *Xenopus* oocytes. Eur. J. Pharmacol., 348 : 271–277, 1998.**

Abstract : We previously reported that corymine, an alkaloid extracted from the leaves of *Hunteria zeylanica* native to Thailand, inhibited glycine-induced chloride current using a receptor expression model of *Xenopus* oocytes. In this study, we investigated the mechanism

underlying the inhibitory action of this alkaloid on glycine current using the same model. Corymine inhibited glycine current in a noncompetitive fashion. Co-application with strychnine, a competitive glycine receptor antagonist, or 4,4'-diisothiocyanostilbene-2,2'-disulfonic acid (DIDS), a Cl^- channel blocker, corymine decreased the ED_{50} value of strychnine, but did not change that of DIDS. Moreover, the inhibitory effects of corymine and either strychnine or DIDS were additive. The desensitization phase of glycine current showed two exponentials and corymine preferentially inhibited the fast component, whereas strychnine affected both of them to the same extent and DIDS preferentially inhibited the slow component. When these drugs were applied repeatedly, the inhibitory effects of corymine and strychnine were not use-dependent and reversible, while the effect of DIDS was use-dependent and irreversible. The inhibitory effect of corymine on γ-aminobutyric acid (GABA) current was less potent than the effect on glycine current, while this alkaloid failed to affect acetylcholine and serotonin currents. These results demonstrate that corymine inhibits glycine-gated Cl^- channels by interacting with the site different from that of DIDS.

4) **Nanri M., Yamamoto J., Miyake H. and Watanabe H.: Protective effect of GTS-21, a novel nicotinic receptor agonist, on delayed neuronal death induced by ischemia in gerbils. Jpn J. Pharmacol., 76 : 23–29, 1998.**

Abstract : The neuroprotective effects of GTS-21 [3-(2,4-dimethoxybenzylidene)-anabaseine dihydrochloride] were studied and compared with those of nicotine, 9-amino-1,2,3,4-tetrahydroacridine hydrochloride hydrate (THA) and pentobarbital-Na (PB) using a cerebral ischemia model in Mongolian gerbils. The learning performance and memory retention were elucidated by a step-through passive avoidance task at 2 and 3 days after ischemia-reperfusion. In this task, the ischemia-operated gerbils showed impairment of learning performance and memory retention. Neuronal cell death in the hippocampal CA1 area was observed at 7 days after ischemia. When administered i.p. 30 min before ischemia, GTS-21 (5 mg/kg), (-)-nicotine (1.5 mg/kg), THA (5 mg/kg) and PB (50 mg/kg) significantly attenuated the impairment of passive avoidance performance and the neuronal cell death induced by the ischemia. When administered orally twice daily for 2 weeks prior to the ischemia, GTS-21 (10 mg/kg) significantly suppressed both amnesia and neuronal cell death, while (-)-nicotine (10 mg/kg) and THA (10 mg/kg) suppressed only the amnesia. These results suggest that GTS-21 exerts a protective activity on not only impairment of learning and memory but also delayed neuronal death and that the underlying mechanism of GTS-21 differs from that of nicotine or THA.

5) **Leewanich P., Tohda M., Matsumoto K., Subhadhirasakul S., Takayama H. Aimi N. and Watanabe H.: Inhibitory effects of corymine-related compounds on glycine receptors expressed in *Xenopus* oocytes. Jpn J. Pharmacol., 77 : 169–172, 1998.**

Abstract : We examined the effects of 4 corymine-related compounds on glycine-induced chloride current in *Xenopus* oocytes. Dihydrocorymine, *N*-demethyl-3-epi-dihydrocorymine

and deformylcorymine dose-dependently decreased the glycine current with IC_{50} values of 34, 37 and 55 μM, respectively. The effect of these compounds on the glycine current was more potent than that of pleiocarpamine (IC_{50}>1 mM). *N*-Demethyl-3-epi-dihydrocorymine and dihydrocorymine, at 100 μM, also decreased the γ-aminobutyric acid-induced current by 65% and 22%, respectively, whereas deformylcorymine and pleiocarpamine failed. The inhibitory action of deformylcorymine on the glycine current was noncompetitive. These results suggest that deformylcorymine is a novel specific noncompetitive glycine receptor antagonist . The structure-activity relationship of these compounds was discussed.

6) **Nanri M., Kasahara N. Yamamoto J., Miyake H. and Watanabe H.: A comparative study on the effects of nicotine and GTS-21, a new nicotinic agonist, on the locomotor activity and brain monoamine level. Jpn J. Pharmacol., 78 : 385–389, 1998.**

Abstract : Effects of GTS-21 [3-(2,4-dimethoxybenzylidene)-anabaseine dihydrochloridel, a selective nicotinic agonist, on locomotor activity and dopamine turnover were examined and compared to those of nicotine to test if GTS-21 exhibits side effects similar to those of nicotine. GTS-21 had no effect on locomotor activity in mice or dopamine turnover in rats. In contrast, nicotine produced a biphasic effect on locomotor activity. It also enhanced dopamine turnover rates in the striatum and cerebral cortex, suggesting the involvement of dopaminergic systems in the nicotine-induced changes in locomotor activity. GTS-21 exhibits fewer adverse effects, suggesting that it has therapeutic potential for cognitive disorders related to central cholinergic dysfunction.

7) **Peungvicha P., Thirawarapan S.S. and Watanabe H.: Possible mechanism of hypoglycemic effect of 4-hydroxybenzoic acid, a constituent of *Pandanus odorus* root. Jpn J. Pharmacol., 78 : 395–398, 1998.**

Abstract : We studied the hypoglycemic effect of 4-hydroxybenzoic acid, a constituent of the root of *Pandanus odorus* Ridl. (Pandanaceae, Thai name: Toei-hom), in streptozotocin-diabetic rats. Oral administration of 4-hydroxybenzoic acid caused a decrease in plasma glucose levels dose-dependently in the diabetic rat. The constituent did not affect serum insulin level and liver glycogen content in the diabetic model, but increased glucose consumption in normal and diabetic rat diaphragms. These results suggest that 4-hydroxybenzoic acid produces a hypoglycemic effect mediated by an increase in the peripheral glucose consumption.

8) **Nanri M., Miyake H., Murakami Y., Matsumoto K. and Watanabe H.: GTS-21, a nicotinic agonist, attenuates multiple infarctions and cognitive deficit caused by permanent occlusion of bilateral common carotid arteries in rats. Jpn J. Pharmacol., 78 : 463–469, 1998.**

Abstract : We examined the effects of GTS-21 [3-(2,4-dimethoxybenzylidene)-anabaseine dihydrochloride], a nicotinic agonist, on histopathological changes of the brain and radial

maze learning performance in rats with permanent occlusion of the bilateral common carotid arteries (2VO) and elucidated whether this compound has a protective effect against the neuronal degeneration and spatial cognitive deficit caused by chronic ischemia. Rats were administered GTS-21 (1 and 10 mg/kg, p.o.) or vehicle 24 hr and 30 min before the 2VO operation and then once daily for 2 months after the operation. The 2VO rats given vehicle had multiple infarctions in the cerebral cortex, hippocampus and striatum and rarefaction in the white matter at 2 months after the operation, although the number and distribution of infarctions varied among individual animals. In addition, the 2VO rats given vehicle showed a higher rate of errors in the acquisition trials of the 8-arm radial maze task than sham-operated controls. However, 2VO rats treated with GTS-21 (1 and 10 mg/kg, p.o.) showed significantly decreased neuropathological changes and less errors in the acquisition trials compared to the vehicle-treated 2VO rats. These results indicate that GTS-21 attenuates impairment of spatial cognitive deficit and progressive neuronal degeneration induced by 2VO and suggest that this compound is beneficial for the treatment of neurodegenerative diseases following chronic cerebral hypoperfusion.

9) **Tohda M. and Watanabe H.: Enhancement of 5-HT2C receptor mRNA expression by antidepressants possessing the receptor-blocking activity in the rat brain. Jpn J. Pharmacol., 78 : 515–517, 1998.**

Abstract : The effects of repeated oral administration of antidepressants on the serotonin 2C receptor subtype (5-HT2CR) mRNA level in the rat brain were examined. Imipramine (20 mg/kg, p.o.) enhanced the hybridization signal in a time (days)-dependent manner, reaching a maximum at day 4 and maintaining a high level until day 14. Desipramine and mianserin, which have 5-HT2CR antagonistic activity, also stimulated the mRNA expression to about same extents as imipramine, but nomifensine, which has no effect on 5-HT2CR, was ineffective. These results suggest that long-term treatment with antidepressants, which act as 5-HT2CR antagonists, stimulates 5-HT2CR mRNA expression.

10) **Peungvicha P., Thirawarapan S.S., Temsiririrkkul R., Watanabe H., Kumar-Prasain J. and Kadota S.: Hypoglycemic effect of the water extract of *Piper sarmentosum* in rats. J. Ethnopharmacol., 60 : 27–32, 1998.**

Abstract : The hypoglycemic effect of the water extract of the whole plant of *Piper sarmentosum* Roxb. (Piperaceae, Thai name: Chaplu) was examined in normal and streptozotocin-diabetic rats. In an oral glucose tolerance test, a single oral administration of the water extract at doses of 0.125 and 0.25 g/kg significantly lowered the plasma glucose level in the normal rats. A reference drug, glibenclamide, at a dose of 5 mg/kg (per os, p.o.) also showed a significant hypoglycemic effect in the normal rats. In contrast, a single oral administration of the water extract at these doses and glibenclamide did not significantly lower the plasma glucose level in the diabetic rats. However, the repeated oral administration of the water extract at a dose of 0.125 g/kg for 7 days produced a significant hypoglycemic

effect in the diabetic rats. Glibenclamide (5 mg/kg, p.o.) also caused significant hypoglycemia in the diabetic rats. These results demonstrated that the water extract of whole plant of *Piper sarmentosum* has a hypoglycemic effect in rats.

11) **Peungvicha P., Temsiririrkkul R., Kumar-Prasain J., Tezuka Y., Kadota S., Thirawarapan S.S. and Watanabe H.: 4-Hydroxybenzoic acid: a hypoglycemic constituent of aqueous extract of Pandanus odorus root. J. Ethnopharmacol., 62: 79–84, 1998.**

Abstract: Hypoglycemic activity-guided fraction led to the isolation of the known compound, 4-hydroxybenzoic acid, from *Pandanus odorus* Ridl. (Thai name: Toei-hom, Pandanaceae). This compound showed a hypoglycemic effect in normal rats after the oral administration of 5 mg/kg. Additionally, the compound increased serum insulin levels and liver glycogen content in normal rats.

12) **Thongpraditchote S., Matsumoto K., Tohda M., Takayama H., Aimi N., Sakai S. and Watanabe H.: Identification of opioid receptor subtypes in antinociceptive actions of supraspinally-administered mitragynine in mice. Life Sciences, 62: 1371–1378, 1998.**

Abstract: Mitragynine (MG), a major alkaloidal constituent extracted from the plant *Mitragyna speciosa* Korth, is known to exert an opioid-like activity. Our previous study showed the involvement of opioid systems in the antinociceptive activity of MG in the tail-pinch and hot-plate tests in mice. In the present study, to clarify the opioid receptor subtypes involved in the antinociceptive action of MG, we investigated the effects of selective antagonists for μ-, δ- and κ- opioid receptors on antinociception caused by the intracerebroventricular (i.c.v.) injection of MG in the tail-pinch and hot-plate tests in mice. The coadministration of a selective μ-opioid antagonist, cyprodime (1-10 μg, i.c.v.) and the pretreatment with a selective μ1-opioid antagonist naloxonazine (1-3 μg, i.c.v.) significantly antagonized the antinociceptive activities of MG (10 μg, i.c.v.) and morphine (MOR, 3 μg, i.c.v.) in the tail-pinch and hot-plate tests. Naltrindole (1-5 ng, i.c.v.), a selective δ-opioid antagonist, also blocked the effects of MG (10 μg, i.c.v.) without affecting MOR (3 μg, i.c.v.) antinociception. Nor-binaltorphimine, a selective κ-opioid antagonist, significantly attenuated MG (10 μg, i.c.v.) antinociception in the tail-pinch test but not in the hot-plate test at the dose (1 μg, i.c.v.) that antagonized the antinociceptive effects of the selective κ-opioid agonist U50,488H in both tests, while it had no effect on MOR antinociception in either tests. These results suggest that antinociception caused by i.c.v. MG is dominantly mediated by μ- and δ-opioid receptor subtypes, and that the selectivity of MG for the supraspinal opioid receptor subtypes differs from that of MOR in mice.

13) **Matsumoto K., Kohno S.-I., Ojima K. Tezuka Y., Kadota S. and Watanabe H.: Effects of methylenechloride-soluble fraction of Japanese angelica root extract,**

ligustilide and butylidenephthalide, on pentobarbital sleep in group-housed and socially isolated mice. Life Sciences, 62 : 2073–2082, 1998.

Abstract : We previously showed that the extract of Japanese angelica root (JAR-E) reversed the decrease in pentobarbital (PB) sleep induced by isolation stress and yohimbine and methoxarnine, stimulants of central noradrenergic systems, in mice. Here, we tested the effects of several fractions from JAR-E and ligustilide and butylidenephthalide, phthalide components of JAR-E, on PB sleep in isolated mice to elucidate the mechanism of the action of JAR-E. Methanol-soluble (Met-S) and -insoluble (Met-IS) fractions were obtained from JAR-E. Methylenechloride-soluble (MC-S) and -insoluble fractions (MC-IS) were prepared from Met-S. MC-S (11.4 - 76 mg/kg, p.o.) reversed the isolation stress-induced decrease in PB sleep, but neither Met-IS (0.8 - 2.4 g/kg, p.o.) nor MC-IS (0.7 - 2 g/kg, p.o.) had the same effect. The i.p. administration of MC-S exhibited a similar activity to that observed after the p.o. administration of the same fraction. Ligustilide (5-20 mg/kg, i.p.) and butylidenephthalide (10-30 mg/kg, i.p.) reversed PB sleep decrease in isolated mice. Both components (20 mg/kg, i.p.) attenuated the suppressive effects of yohimbine (30 nmol, i.c.v.), methoxamine (200 nmol, i.c.v.) and a benzodiazepine inverse agonist FG7142 (10 mg/kg, i.p.) on PB sleep in group-housed mice. These results suggest the contribution of ligustilide and butylidenephthalide to the effect of JAR-E on PB sleep in isolated mice, and implicate central noradrenergic and/or $GABA_A$ systems in the effects of these components.

14) **Nanri M., Miyake H., Murakami Y., Matsumoto K. and Watanabe H.: Chronic cerebral hypoperfusion-induced neuropathological changes in rats. Jpn J. Psychopharmacol., 18 : 181–188, 1998.**

Abstract : We investigated the time courses of histopathological changes in various brain regions following permanent occlusion of the bilateral common carotid arteries (2VO) in rats. 2VO rats exhibited rarefaction in the white matter, shrinkage of neurons in the cerebral cortex and hippocampus CA1-3 and dentate gyrus areas 1-3 days after the operation. These histological changes in the cortex and hippocampus were accompanied by a decrease in immunoreactivity for microtubule-associated protein 2 (MAP2), a marker protein of neuronal dendrites. Immunoreactivity for glial fibrillary acid protein (GFAP) was observed at 3-7 days after the 2VO operation. A marked increase in GFAP staining of the astrocytes in the cerebral cortex and hippocampus was found 30 days after ligation. Eight-arm radial maze performance was tested from 14 days to 60 days after the operation. The 2VO rats showed fewer initial correct responses than sham-operated control rats during a repeated training period. These findings suggested that the loss in dendritic MAP2 immunoreactivity and an increase in astroglial staining and/or rarefaction of the white matter may cause neuronal death, infarction and learning impairment under conditions of chronic hypoperfusion.

◇総　説

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16) Watanabe H. : Effects of Si-Wu-Tang, component herbs and their constituents on spatial cognitive deficits in the rat. The first meeting of international research program on traditional Chinese and natural medicine, 1998, 9, Hong Kong.

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2）山崎和男，笠井良次：広島大学医学部，グエン・トイ・ニャム：ベトナム薬用人参センター「ベトナム人参の薬理作用の研究」1994.4.1-1999.3.31

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◇研究費取得状況

1）文部省科学研究費，萌芽的研究（代表：渡辺裕司）「慢性脳虚血ラットの記憶障害に関与する内因性物質の分子生物学的研究」130万

2）特別研究員奨励費（代表：渡辺裕司）「エジプト薬用植物成分の中枢セロトニン神経賦活作用」120万

3）文部省科学研究費，基盤研究Ｂ（２）（代表：渡辺裕司）「新しい痴呆モデルラットに関する薬理学的研究」90万

4）文部省科学研究費，基盤研究Ｃ（２）（代表：松本欣三）「ニューロステロイド系を介したGABA-A 受容体機能制御と新規中枢作用薬への応用」310万

5）文部省科学研究費，奨励研究（A）（代表：東田道久）「内因性の学習障害誘発因子の単離同定とその生理機能・発現制御機構の解明」130万

6）平成10年度富山県受託研究費：和漢薬・バイオテクノロジー研究（第３年度），（分担：松本欣三）「和漢薬の生物活性に関する総合的研究―基盤から臨床まで―」（分担課題）老人性痴呆に有効な和漢薬，40万

7）平成10年度富山医科薬科大学教育研究学内特別経費（代表：東田道久）「学習障害に伴い発現変化する遺伝子の機能解析に関する研究」80万

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Dr. Chutamanee Suthisisang（日本学術振興会，Mahidol Univ., 1998.10–11）

国際教育協会留学生：Monthakantirat Orawan（Mahidol Univ., 1998.9–1999.2）

◇学位取得者

修士：

池野谷真美「両側総頚動脈永久結紮ラットの学習障害に対するコリンエステラーゼ阻害剤及びカルシウム拮抗薬の作用」

博士：

Leewanich Pathama

「Neuropharmacological studies on extracts of a Thai medicinal plant, *Hunteria zeylanica*, and its main component, corymine」

Thongpradichote Suchitra

「Neuropharmacological studies on Thai medicinal plants : *Pluchea indica* extract and mitragynine, an indole alkaloid extract from *Mitragyna speciosa*」