的効果で多標的にアラキドン酸代謝酵素を抑制しプロスタグランジンＥ２を特異的に抑制する可能性が示唆され、癌に伴う炎症や痛みを大建中湯が抑制できる可能性が示唆できた。

Ｆ．研究発表

1. 論文発表

1. Kono T, Takeda H, Shimada M, Kase Y, Uezono Y. Novel therapeutics for adverse effects of antitumor therapy: the promise of multicomponent, traditional Japanese herbal remedies. Carcinog & Mutagen [Epub ahead of print] doi.org/10.4172/2157-2518.S8-007 Feb 25, 2014
2. Kono T, Kaneko A, Matsumoto C, Miyagi C, Ohbuchi K, Mizuhara Y, Miyano K, Uezono Y. Multitargeted Effects of Hangeshashinto for Treatment of Chemotherapy- Induced Oral Mucositis on Inducible Prostaglandin E2 Production in Human Oral Keratinocytes. Integr Cancer Ther. [Epub ahead of print] 2014
3. Shimada M, Morine Y, Nagano H, Hatano E, Kaiho T, Miyazaki M, Kono T, Kamiyama T, Morita S, Sakamoto J, Kusano M, Saji S, Kanematsu T, Kitajima M. Effect of TU-100, a traditional Japanese medicine, administered after Hepatic Resection in Patients with Liver Cancer: a multi-center, randomized, double-blind, placebo-controlled phase II trial (JFMC40-1001) Int J Clin Oncol. DOI 10.1007/s10147-014-0678-2 2014
4. Ueno N, Hasebe T, Kaneko A, Yamamoto M, Fujiya M, Kohgo Y, Kono T, Wang CZ, Yuan CS, Bissonnette M, Chang EB, Musch MW. TU-100 (daikenchuto) and ginger ameliorate anti-CD3 antibody induced T cell-mediated murine enteritis: microbe-independent effects involving Akt and NF-κB suppression PloS ONE [Epub ahead of print] 2014
5. Mizuno K, Kono T, Suzuki Y, Miyagi C, Omiya Y, Miyano K, Kase Y, Uezono Y. Goshajinkigan, a traditional Japanese medicine, prevents oxaliplatin-induced acute peripheral neuropathy by suppressing functional alteration of TRP channels in rat. J Pharmacol Sci. [Epub ahead of print] 2014
6. Aoyama T, Nishikawa K, Takiguchi N, Tanabe K, Imano M, Fukushima R, Sakamoto J, Oba MS, Morita S, Kono T, Tsuburaya A. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (hangeshashinto) for gastric cancer chemotherapy-induced oral mucositis. Cancer Chemother Pharmacol. [Epub ahead of print] 2014 Mar 21.
7. Watanabe K, Karasaki H, Mizukami Y, Kawamoto T, Kono T, Imai K, Einama T, Taniguchi M, Kohgo Y, Furukawa H. Cyst infection of intraductal papillary mucinous neoplasms of the pancreas: management of a rare complication: report of 2 cases. Pancreas. 43(3):478-81, 2014
8. Kono T, Kaneko A, Omiya Y, Ohbuchi K, Ohno N, Yamamoto M. Epithelial transient receptor potential ankyrin 1 (TRPA1)-dependent adrenomedullin up-regulates blood flow in rat small intestine Am J Physiol Gastrointest Liver Physiol. 304: 428-36, 2013

9. Kono T, Hata T, Morita S, Munemoto Y, Matsui T, Kojima H, Takemoto H, Fukunaga M, Nagata N, Shimada M, Sakamoto J, Mishima H Goshajinkigan Oxaliplatin Neurotoxicity Evaluation (GONE): a phase 2, multicenter, randomized, double-blind, placebo-controlled trial of goshajinkigan to prevent oxaliplatin-induced neuropathy Cancer Chemo Pharm 72(6), 1283-1290, 2013
10. Kono T, Kaneko A, Matsumoto C, Miyagi C, Ohbuchi K, Mizuhara Y, Miyano K, Uezono Y. Multitargeted effects of hangeshashinto for treatment of chemotherapy-induced oral mucositis on inducible PGE2 production in human oral keratinocytes. 2013 Integr Cancer Ther.doi:10.1177/1534735413520035
11. Munekage M, Ichikawa K, Kitagawa H, Uehara H, Watanabe J, Kono T, Hanazaki K. Population Pharmacokinetic Analysis of Daikenchuto, a Traditional Japanese Medicine (Kampo) in Japanese and US Health Volunteers. Drug Metab Dispos. 41: 1256-1263, 2013
12. Kaneko A, Kono T, Miura N, Tsuchiya N, Yamamoto M. Preventive effect of TU-100 on a type-2 model of colitis in mice: Possible involvement of enhancing adrenomedullin in intestinal epithelial cells. Gastroenterol Res Pract. 2013 doi:10.1155/2013/384057.
13. Sakatani A., Fujiya M, Ito T, Inaba Y, Ueno N, Kashima S, Tominaga M, Moriichi K, Okamoto K, Tanabe H, Ikuta K, Ohtake T, Kono T, Furukawa H, Ashida T, Kohgo Y. Infliximab extends the duration until the first surgery in patients with Crohn's disease. 2013 BioMed Res Int2013;2013:879491. doi: 10.1155/2013/879491. Epub 2013 Nov 26.
14. 河野　透、武田　宏司、上園保仁、島田光生　消化器外科と漢方　消化器外科　36(8),1299-1305, 2013
15. 河野　透、武田　宏司、上園保仁　外科医のための Kampo EBM UP-TO DATE 抗癌剤の副作用と漢方薬　日本外科学会雑誌 114(5), 251-255, 2013

2. 学会発表

1. Kono, T., Kaneko, A., Matsumoto, C., Miyagi, C., Ohbuchi, K., Mizuhara, Y., Miyano, K., Uezono, Y. Multi-target prevention of chemotherapy-induced oral mucositis by hangeshashinto:PGE2 and cell migration in human oral keratinocytes. Digestive Disease Week (DDW) 2013 Orland, USA. (2013 年 5 月)
2. Kono, T., Nishiyama, M., Kaneko A., Yamamoto, M., Ueno, N., Kohgo, Y., Uezono, Y. Small intestinal microbiota of colonic IBD patients may have the altered gut microenvironment enabling selective enrichment of certain bacterial populations : Implications of microbiome analysis on ileal effluent samples collected from ileostomy patients. Digestive Disease Week (DDW) 2013 Orlando, USA. (2013 年 5 月)
3. Kubota, K., Ohbuchi, K., Sudo, Y., Miyano, K., Yamamoto, M., Kono, T., Uezono, Y. Prokinetic effect via blocking of two-pore domain potassium channels (KCNKs): a

novel mechanism of enhanced colonic motility by local anesthetics and a traditional Japanese medicine daikenchuto (TU-100). Digestive Disease Week (DDW) 2013 Orlando, USA. （2013 年 5 月）

4. Ueno, N., Musch, M.W., Kono, T., Wang, Y., Kaneko, A., Omiya, Y., Yamamoto,M., Fujiya, M., Uezono, Y., Kohgo, Y., Chang, E.B. Multitargeted treatment of Crohn's disease by traditional Japanese herbal medicine TU-100: an endogenous adrenomedullin enhancer. 37th World Congress of the International Union of Physiological Sciences (IUPS) 2013 Birmingham, UK. (2013 年 7 月)
5. Kono, T., Kaneko, A., Nozaki, R., Matsumoto, C., Miyagi, C., Ohbuchi, K., Omiya, Y., Mizuhara, Y., Miyano, K., Uezono, Y.Multitargeted therapy of chemotherapy-induced oral mucositis by hangeshashinto (TJ-14), a multicomponent traditional Japanese herbal medicine: effect on prostanoid synthesis and cell migration. 37th World Congress of the International Union of Physiological Sciences (IUPS) 2013 Birmingham, UK. (2013 年 7 月)
6. 河野　透、久保田訓世、山本雅浩、上園保仁　Two-pore domain カリウムチャネル（KCNKs）の腸管運動メカニズムへの関与　大建中湯の大腸運動亢進メカニズム　第 55 回日本平滑筋学会総会, 旭川（2013 年 8 月）
7. 河野　透　漢方はオーケストラ　医療用漢方製剤の海外進出　日本生薬学会第 60 回年会, 札幌（2013 年 9 月）
8. 河野　透　がん化学療法に伴う末梢神経障害の発現機序とその対処法：臨床研究と基礎研究の融合点　第 7 回日本緩和医療薬学会年会, 千葉（2013 年 9 月）
9. Kono, T., Kaneko, A., Yamamoto, M., Nozaki, R., Kitagawa, S., Takeda, H. Administration of daikenchuto (TU-100), a traditional Japanese medicine, through a long tube ameliorates postoperative ileus via inhibition of prostaglandin E2. European Society of Coloproctology (ESCP) 2013 Belgrade, Serbia (2013 年 9 月)
10. 山本雅浩、久保田訓世、河野　透、上園保仁　KCNKs 阻害による消化管運動亢進作用：局所麻酔薬および大建中湯による大腸運動促進の新規メカニズム　第 15 回日本神経消化器病学会, 島根、（2013 年 11 月）
11. Kono, T., Kaneko, A., Omiya, Y., Miyano, K., Uezono, Y. Traditional Japanese oral mucositis medicine hangeshashinto upregulates antimicrobial peptides in human salivary gland cells. 2014 Gastrointestinal Cancers Symposium San Francisco, USA.（2014 年 1 月）
12. Kono, T., Kubota, K., Ohbuchi, K., Mase, A., Sudo, Y., Miyano, K., Yamamoto, M., Uezono, Y. Hydroxy- α-sanshool evokes unique colonic migrating motor complex in rat proximal colon via blocking of a two-pore domain potassium channel, KCNK9, in myenteric neurons. Digestive Disease Week 2014, Chicago, USA (2014 年 5 月)

G．知的財産権の出願・登録状況（予定を含む。）

1. 特許取得

特許タイトル：アドレノメデュリン産
生増強剤
発明者：　河野透 1)、金子篤 2)、
大宮雄司 2)
出願人:1) 独立行政法人旭川医科大学、
2)株式会社ツムラ
特許登録番号：　特許第 5451403 号

2. 実用新案登録

なし

3.その他

なし

厚生労働科学研究費補助金（第３次対がん総合戦略研究事業）
分担研究報告書

六君子湯を用いたがん患者のQOL向上のための研究

研究分担者　大西　俊介　北海道大学消化器内科　助教

研究要旨　がん患者のQOL向上のための六君子湯のエビデンスを確立するため、臨床研究を立案し、「ゲムシタビン投与膵がん患者における軽度悪液質または前悪液質状態に対する六君子湯の悪液質進行抑制効果− 無作為化第Ⅱ相比較試験」が平成24年8月より登録開始となった。平成25年10月にプロトコール改正を行い、臨床研究を継続して行っている。

A．研究目的

我々はこれまでに、動物モデルを用いて六君子湯の食欲増進作用およびそのメカニズムを明らかにし、がん患者のQOL向上のためのエビデンスを確立するため、平成２４年８月より「ゲムシタビン投与膵がん患者における軽度悪液質または前悪液質状態に対する六君子湯の悪液質進行抑制効果− 無作為化第Ⅱ相比較試験」を開始した。しかしながら、適格規準を満たす症例に乏しかったため、プロトコールを改正して試験を継続することとした。

B．研究方法

当研究班で組織されるデータセンターならびに統計専門家らとともに、「ゲムシタビン投与膵がん患者における軽度悪液質または前悪液質状態に対する六君子湯の悪液質進行抑制効果− 無作為化第Ⅱ相比較試験」の改正作業を行った。

（倫理面への配慮）
臨床研究であるため、倫理面には特に配慮し、完成したフルプロトコールはプロトコール審査委員会に諮り承認を得たのち、各参加施設の倫理審査委員会での承認を得ることとした。また、被験者には十分な説明を行い、説明同意文書に署名をいただいてから開始し、補償のための保険にも加入した。

C．研究結果

臨床試験名を「ゲムシタビン投与膵がん患者における悪液質発症および進行に対する六君子湯の抑制効果− 無作為化第Ⅱ相比較試験」に変更し、適格基準のうち「食欲不振症状」および「CRP」の項目を削除した。また、研究参加施設を２施設追加した。この改正プロトコールが平成２５年１０

月に独立データモニタリング委員会に承認され、各施設で倫理委員会の承認を得て、再度登録開始となった。平成２６年３月までに１１例の登録が得られた。

D．考察

膵がんにおいて、軽度悪液質または前悪液質状態にある患者は非常に少ないことが明らかになり、症例登録が進まない一因となった。今年度の改正により、症例登録数の増加を見込んでいる。

六君子湯はがん患者の悪液質の進行を抑制し、 QOL や予後を改善する可能性があるため、本臨床研究において探索的な試験を行い、有用な評価項目が認められれば第Ⅲ相の臨床試験を計画して検証していく。

E．結論

がん患者の QOL 向上のための六君子湯のエビデンスを確立するため、臨床試験を開始したが。プロトコールの改正を経て現在も継続中である。

F．研究発表

1. 論文発表

1. Nahata M, Muto S, Nakagawa K, Ohnishi S, Sadakane C, Saegusa Y, Iizuka S, Hattori T, Asaka M, Takeda H. Serotonin 2C receptor antagonism ameliorates novelty-induced hypophagia in aged mice. **Psychoneuroendocrinology** 2013:38(10);2051-64.
2. Yamada C, Saegusa Y, Nakagawa K, Ohnishi S, Muto S, Nahata M, Sadakane C, Hattori T, Sakamoto N, Takeda H. Rikkunshito, a Japanese Kampo medicine, ameliorates decreased feeding behavior via ghrelin and serotonin 2B receptor signaling in a novelty stress murine model. **BioMed Research International** 2013:2013;792940.
3. Takeda H, Nakagawa K, Okubo N, Nishimura M, Muto S, Ohnishi S, Sakamoto N, Hosono H, Asaka M. Pathophysiologic basis of anorexia: Focus on the interaction between ghrelin dynamics and the serotonergic system. **Biological & Pharmaceutical Bulletin** 2013:36(9);1401-5.
4. 武田宏司，武藤修一，大西俊介，河野透．抗癌剤に伴う cachexia とその治療．**栄養− 評価と治療**，2013:30(4);283-6.

2. 学会発表

1. 大西俊介，武藤修一，坂本直哉，武田宏司．新奇環境ストレスによる老齢動物の摂食低下における 5-HT2C 受容体の関与と六君子湯の効果．第 15 回日本神経消化器病学会，スポンサードシンポジウム，出雲，2013 年 11 月．
2. 大西俊介，武藤修一，武田宏司．ストレスによる老齢動物の摂食低下には 5-HT2C 受容体の機能亢進が関与する．第 21 回日本消化器関連学会週間，シンポジウム，東京，2013 年 10 月．

G．知的財産権の出願・登録状況
（予定を含む。）

1. 特許取得

該当なし。

2. 実用新案登録

該当なし。

3.その他

該当なし。

厚生労働科学研究費補助金（第３次対がん総合戦略研究事業）
分担研究報告書

六君子湯を用いたがん患者のQOL向上のための研究

研究分担者　櫻木　範明　北海道大学大学院医学研究科
生殖内分泌・腫瘍学分野　教授

研究要旨　がん患者のQOL向上のための六君子湯の有効性に関するエビデンスを確立することを目的に臨床研究のプロトコールを作成し、「シスプラチンを含む化学療法を施行される子宮がん患者の食欲不振に対する六君子湯の効果− 無作為化第Ⅱ相比較試験」が平成２５年１２月より登録開始となり、現在も臨床研究を継続して行っている。

A．研究目的

これまでに動物モデルを用いて六君子湯の食欲増進作用およびそのメカニズムが科学的に明らかとなってきた。がん患者のQOL向上のための六君子湯の有効性のエビデンスを確立するため、臨床試験として「シスプラチンを含む化学療法を施行される子宮がん患者の食欲不振に対する六君子湯の効果− 無作為化第Ⅱ相比較試験」を行う。

B．研究方法

当研究班で組織されるデータセンターならびに統計専門家らとともに、「シスプラチンを含む化学療法を施行される子宮がん患者の食欲不振に対する六君子湯の効果− 無作為化第Ⅱ相比較試験」プロトコールの作成を行った。

（倫理面への配慮）
臨床研究であるため、倫理面には特に配慮し、完成したフルプロトコールはプロトコール審査委員会に諮り承認を得たのち、各参加施設の倫理審査委員会での承認を得ることとした。また、被験者には十分な説明を行い、説明同意文書に署名をいただいてから開始することとしている。また、補償のための保険にも加入した。

C．研究結果

「シスプラチンを含む化学療法を施行される子宮がん患者の食欲不振に対する六君子湯の効果− 無作為化第II相比較試験」のフルプロトコールを作成し、平成２５年７月に倫理承認を受けた。しかしながら、シスプラチン以外の併用薬の投与スケジュールについて参加施設間での調整が必要となったため、３回のメモランダムの発

行を要した。最終的には平成２５年１２月より症例登録を開始することができ、平成２６年３月末までに９例の症例登録が行われた。

D．考察

４ヶ月で９例の登録があったことから、１カ月あたり２例のペースで症例集積できている。２０１５年１２月までに４０例の登録を予定しているが、概ね順調に推移していると考える。

六君子湯はシスプラチンを含む化学療法を受けるがん患者において観察される嘔吐や食欲不振を抑制することで患者の QOL を改善し、治療のコンプライアンスを高める可能性があるため、本臨床研究において探索的な試験を行い、有用な評価項目が認められれば第Ⅲ相の臨床試験を計画して検証していく。

E．結論

がん患者の QOL 向上のための六君子湯の有効性のエビデンスを確立するため、臨床試験を開始し、現在も継続中である。

F．研究発表

1．論文発表

1. Watari H, Todo Y, Kang S, Odagiri T, Sakuragi N. Proposal of a concept and design of a randomized phase III trial investigating the survival effect of para-aortic lymphadenectomy in endometrial cancer. J Obstet Gynaecol Res, 40 (2): 312-316, 2014.
2. Todo Y, Watari H, Kang S, Sakuragi N. Tailoring lymphadenectomy according to the risk of lymph node metastasis in endometrial cancer. J Obstet Gynaecol Res, 40 (2): 317-321, 2014.
3. Dong P, Kaneuchi M, Watari H, Sudo S, Sakuragi N. MicroRNA-106b modulates epithelial-mesenchymal transition by targeting TWIST1 in invasive endometrial cancer cell lines. Mol Carcinog, 53 (5): 349-359, 2014.
4. Kato T, Watari H, Takeda M, Hosaka M, Mitamura T, Kobayashi N, Sudo S, Kaneuchi M, Kudo M, Sakuragi N. Multivariate prognostic analysis on the patients with adenocarcinoma of the uterine cervix treated with radical hysterectomy and systematic lymphadenectomy. J Gynecol Oncol, 24: 222-228, 2013.
5. Dong P, Kaneuchi M, Konno Y, Watari H, Sudo S, Sakuragi N. Emerging therapeutic biomarkers in endometrial cancer. Biomed Res Int, 2013: 130362, 2013.
6. Mitamura T, Watari H, Wang L, Kanno H, Hassan MK, Miyazaki M, Katoh Y, Kimura T, Tanino M, Nishihara H, Tanaka S, Sakuragi N. Downregulation of miRNA-31 induces taxane resistance in ovarian cancer cells through increase of receptor tyrosine kinase MET. Oncogenesis, 25 (2): e40, 2013.
7. Todo Y, Watari H, Okamoto K, Hareyama H, Minobe S, Kato H, Sakuragi N. Tumor volume successively reflects the state of disease progression in endometrial cancer. Gynecol Oncol, 129: 472-477, 2013.
8. Sakuragi N. Recent advances in research on epigenetic alterations and clinical significance of para-aortic lymphadenectomy in endometrial

cancer: an introduction. Int J Clin Oncol, 18 (2): 183-185, 2013.

2. 学会発表

なし。

G. 知的財産権の出願・登録状況
（予定を含む。）

1. 特許取得

該当なし。

2. 実用新案登録

該当なし。

3.その他

該当なし。

Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Minami K, Uezono Y.	The recent progress in research on the effects of anesthetics and analgesics on G protein-coupled receptors.	J Anesthesia	27 (2)	284-292	2013
Yanagihara K, Takigahira M, Mihara K, Kubo T, Morimoto C, Morita Y, Terawaki K, Uezono Y.	Inhibitory effects of isoflavones on tumor growth and cachexia in newly established cachectic mouse models carrying human stomach cancers.	Nutr Cancer	65 (4)	578-589	2013
Narita M, Imai S, Nakamura A, Ozeki A, Asato M, Rahmadi M, Sudo Y, Hojo M, Uezono Y, Devi LA, Kuzumaki N, Suzuki T.	Possible involvement of prolonging spinal μ-opioid receptor desensitization in the development of antihyperalgesic tolerance to μ-opioids under a neuropathic pain-like state.	Addict Biol	18 (4)	614-622	2013
上園保仁.	日本の「統合医療」のゆくえ-『厚生労働省「統合医療」のあり方に関する検討会』による今後の指針は？-.	がん患者と対症療法	24 (1)	74-82	2013
上園保仁.	モデル動物からみたcachexia（悪液質）.	栄養-評価と治療	30 (4)	272-274	2013
Motoyama N, Morita K, Kitayama T, Shiraishi S, Uezono Y, Nishimura F, Kanamatsu T, Dohi T.	Pain-releasing action of platelet-activating factor (PAF) antagonists in neuropathic pain animal models and the mechanisms of action.	Eur J Pain	17 (8)	1156-1167	2013
上園保仁.	がん患者の生活の質の向上をめざすがん疼痛およびがん悪液質症状改善のための研究-がん患者へ届ける基礎から臨床へのトランスレーショナルリサーチ-.	がん患者と対症療法	24 (2)	158-164	2013
Terawaki K, Sawada Y, Kashiwase Y, Hashimoto H, Yoshimura M, Suzuki M, Miyano K, Sudo Y, Shiraishi S, Higami Y, Yanagihara K, Kase Y, Ueta Y, Uezono Y.	Novel cancer cachexia model by peritoneal dissemination-derived cell line established from human stomach cancer cell.	Am J Physiol Endocrinol Metab	306 (4)	E373-E387	2014
Okura D, Horishita T, Ueno S, Yanagihara N, Sudo Y, Uezono Y, Sata T.	The endocannabinoid anandamide inhibits voltage-gated sodium channels $Na_V1.2$, $Na_V1.6$, $Na_V1.7$ and $Na_V1.8$ in *Xenopus* Oocytes.	Anesth Analg	118 (3)	554-562	2014
Morita K, Shiraishi S, Motoyama N, Kitayama T, Kanematsu T, Uezono Y, Dohi T.	Palliation of bone cancer pain by antagonists of platelet-activating factor receptors.	PLOS ONE	9 (3)	e91746	2014
Fujii H, Hayashida K, Saitoh A, Yokoyama A, Hirayama S, Iwa T, Nakata E, Sudo Y, Uezono Y, Yamada M, Nagase H.	Novel delta opioid receptor agonists with oxazatricyclodecane structure.	ACS Med Chem Lett	5	368-372	2014
Horishita T, Yanagihara N, Ueno S, Sudo Y, Uezono Y, Okura D, Minami T, Kawasaki T, Sata T.	Neurosteroids allopregnanolone sulfate and pregnanolone sulfate have diverse effect on the α subunit of the neuronal voltage-gated sodium channels NaV1.2, $Na_V1.6$, $Na_V1.7$ and $Na_V1.8$ in *Xenopus* Oocytes.	Anesthesiology	epub ahead of print		2014

Suzuki H, Asakawa A, Amitani H, Fujitsuka N, Nakamura N, Inui A.	Cancer cachexia pathophysiology and translational aspect of herbal medicine.	Jpn J Clin Oncol	43 (7)	695-705	2013
Suzuki H, Asakawa A, Amitani H, Nakamura N, Inui A.	Cancer cachexia--pathophysiology and management.	J Gastroenterol	48 (5)	574-594	2013
Amitani M, Asakawa A, Amitani H, Inui A.	Control of food intake and muscle wasting in cachexia.	Int J Biochem Cell Biol	45 (10)	2179-2185	2013
鈴木甫, 浅川明弘, 網谷東方, 乾明夫.	Cachexiaの診断、病態と治療.	栄養-評価と治療	30 (4)	268-271	2013
網谷真理恵, 網谷東方, 浅川明弘, 乾明夫.	Cachexiaの新しい治療.	栄養-評価と治療	30 (4)	293-297	2013
米田孝一, 浅川明弘, 乾明夫.	緩和ケアチームからみたcachexiaへのアプローチ.	栄養-評価と治療	30 (4)	298-300	2013
Yoshimura M, Matsuura T, Ohkubo J, Ohno M, Maruyama T, Ishikura T, Hashimoto H, Kakuma T, Yoshimatsu H, Terawaki K, Uezono Y, Ueta Y.	The gene expression of the hypothalamic feeding-regulating peptides in cisplatin-induced anorexic rats.	Peptides	46	13-19	2013
Yoshimura M, Ohkubo J, Katoh A, Ohno M, Ishikura T, Kakuma T, Yoshimatsu H, Murphy D, Ueta Y.	A c-fos-monomeric red fluorescent protein 1 fusion transgene is differentially expressed in rat forebrain and brainstem after chronic dehydration and rehydration.	J Neuroendocrinol	25 (5)	478-487	2013
Yoshimura M, Hagimoto M, Matsuura T, Ohkubo J, Ohno M, Maruyama T, Ishikura T, Hashimoto H, Kakuma T, Yoshimatsu H, Terawaki K, Uezono Y, Toyohira Y, Yanagihara N, Ueta Y.	Effects of food deprivation on the hypothalamic feeding-regulating peptides gene expression in serotonin depleted rats.	J Physiol Sci	64 (2)	97-104	2014
Yoshimura M, Matsuura T, Ohkubo J, Maruyama T, Ishikura T, Hashimoto H, Kakuma T, Mori M, Ueta Y.	A role of nesfatin-1/NucB2 in dehydration-induced anorexia.	Am J Physiol Regul Integr Comp Physiol	epub ahead of print		2014
Horiuchi K, Okamoto T, Iihara M, Tsukada T.	An analysis of genotype- phenotype correlations and survival outcomes in patients with primary hyperparathyroidism caused by multiple endocrine neoplasia type 1: the experience at a single institution.	Surg Today	43 (8)	894-899	2013
Ataka K, Asakawa A, Nagaishi K, Kaimoto K, Sawada A, Hayakawa Y, Tatezawa R, Inui A, Fujimiya M.	Bone marrow-derived microglia infiltrate into the paraventricular nucleus of chronic psychological stress-loaded mice.	PLoS One	8 (11)	e81744	2013
Chiba H, Ataka K, Iba K, Nagaishi K, Yamashita T, Fujimiya M.	Diabetes impairs the interactions between long-term hematopoietic stem cells and osteopontin-positive cells in the endosteal niche of mouse bone marrow.	Am J Physiol Cell Physiol	305 (7)	C693-C703	2013
Nagaishi K, Ataka K, Echizen E, Arimura Y, Fujimiya M.	Mesenchymal stem cell therapy ameliorates diabetic hepatocyte damage in mice by inhibiting infiltration of bone marrow-derived cells.	Hepatology	59 (5)	1816-1829	2014

Matsuo T, Miyata Y, Sagara Y, Higami Y, Tobu S, Matsuo M, Noguchi M, Shimokawa I, Kanetake H, Sakai H.	Renoprotective effects of telmisartan after unilateral renal ablation in rats.	Int J Nephrol Renovasc Dis	6	207-214	2013
Okita N, Yoshimura M, Watanabe K, Minato S, Kudo Y, Higami Y, Tanuma S.	CHK1 cleavage in programmed cell death is intricately regulated by both caspase and non-caspase family proteases.	Biochim Biophys Acta	1830 (1)	2204-2213	2013
Chujo Y, Fujii N, Okita N, Konishi T, Narita T, Yamada A, Haruyama Y, Tashiro K, Chiba T, Shimokawa I, Higami Y.	Caloric restriction- associated remodeling of rat white adipose tissue: effects on the growth hormone/insulin-like growth factor-1 axis, sterol regulatory element binding protein-1, and macrophage infiltration.	Age (Dordr)	35 (4)	1143-1156	2013
土屋拓郎, 沖田直之, 須藤結香, 樋上賀一.	カロリー制限が白色脂肪組織における脂肪酸合成に及ぼす影響の経時的解析.	基礎老化研究	37 (3)	29-31	2013
須藤結香, 沖田直之, 樋上賀一.	カロリー制限による抗老化・寿命延伸効果のメカニズム ～脂肪組織のリモデリングと脂質代謝の活性化～.	自律神経	50 (3)	192-195	2013
Okita N, Ishikawa N, Mizunoe Y, Oku M, Nagai W, Suzuki Y, Matsushima S, Mikami K, Okado H, Sasaki T, Higami Y.	Inhibitory effect of p53 on mitochondrial content and function during adipogenesis.	Biochem Biophys Res Commun	446 (1)	91-97	2014
Kono T, Kaneko A, Omiya Y, Ohbuchi K, Ohno N, Yamamoto M.	Epithelial transient receptor potential ankyrin 1 (TRPA1)-dependent adrenomedullin up-regulates blood flow in rat small intestine.	Am J Physiol Gastrointest Liver Physiol	304 (4)	428-436	2013
Kono T, Hata T, Morita S, Munemoto Y, Matsui T, Kojima H, Takemoto H, Fukunaga M, Nagata N, Shimada M, Sakamoto J, Mishima H.	Goshajinkigan Oxaliplatin Neurotoxicity Evaluation (GONE): a phase 2, multicenter, randomized, double-blind, placebo-controlled trial of goshajinkigan to prevent oxaliplatin-induced neuropathy.	Cancer Chemo Pharm	72 (6)	1283-1290	2013
Munekage M, Ichikawa K, Kitagawa H, Uehara H, Watanabe J, Kono T, Hanazaki K.	Population pharmacokinetic analysis of daikenchuto, a traditional Japanese medicine (kampo) in Japanese and US health volunteers.	Drug Metab Dispos	41 (6)	1256-1263	2013
Sakatani A., Fujiya M, Ito T, Inaba Y, Ueno N, Kashima S, Tominaga M, Moriichi K, Okamoto K, Tanabe H, Ikuta K, Ohtake T, Kono T, Furukawa H, Ashida T, Kohgo Y.	Infliximab extends the duration until the first surgery in patients with Crohn's disease.	BioMed Res Int	2013		2013
河野透, 武田宏司, 上園保仁, 島田光生.	消化器外科と漢方.	消化器外科	36 (9)	1299-1305	2013
河野透, 武田宏司, 上園保仁.	外科医のためのKampo EBM UP-TO DATE 抗癌剤の副作用と漢方薬.	日本外科学会雑誌	114 (5)	251-255	2013
前田耕太郎, 勝野秀稔, 河野透	外科医のためのKampo EBM UP-TO DATE 周術期における大建中湯の有用性と作用メカニズム	日本外科学会雑誌	114 (5)	232-235	2013
河野透, 上園保仁, 武田宏司, 笠井章次, 佐藤宏彦, 島田光生	オキサリプラチンによるしびれ-牛車腎気丸	臨床外科	68 (12)	1319-1323	2013
Mizuno K, Kono T, Suzuki Y, Miyagi C, Omiya Y, Miyano K, Kase Y, Uezono Y.	Goshajinkigan, a traditional Japanese medicine, prevents oxaliplatin-induced acute peripheral neuropathy by suppressing functional alteration of TRP channels in rat.	J Pharmacol Sci	125	91-98	2014

Aoyama T, Nishikawa K, Takiguchi N, Tanabe K, Imano M, Fukushima R, Sakamoto J, Oba MS, Morita S, Kono T, Tsuburaya A.	Double-blind, placebo-controlled, randomized phase II study of TJ-14 (hangeshashinto) for gastric cancer chemotherapy-induced oral mucositis.	Cancer Chemother Pharmacol	73 (5)	1047-1054	2014
Watanabe K, Karasaki H, Mizukami Y, Kawamoto T, Kono T, Imai K, Einama T, Taniguchi M, Kohgo Y, Furukawa H.	Cyst infection of intraductal papillary mucinous neoplasms of the pancreas: management of a rare complication: report of 2 cases.	Pancreas	43 (3)	478-481	2014
Kaneko A, Kono T, Miura N, Tsuchiya N, Yamamoto M.	Preventive effect of TU-100 on a type-2 model of colitis in mice: Possible involvement of enhancing adrenomedullin in intestinal epithelial cells.	Gastroenterol Res Pract	2013	384057	2013
Kono T, Takeda H, Shimada M, Kase Y, Uezono Y.	Novel therapeutics for adverse effects of antitumor therapy: the promise of multicomponent, traditional Japanese herbal remedies.	J Carcinog Mutagen	epub ahead of print		2014
Kono T, Kaneko A, Matsumoto C, Miyagi C, Ohbuchi K, Mizuhara Y, Miyano K, Uezono Y.	Multitargeted effects of hangeshashinto for treatment of chemotherapy-induced oral mucositis on inducible prostaglandin E2 production in human oral keratinocytes.	Integr Cancer Ther	epub ahead of print		2014
Shimada M, Morine Y, Nagano H, Hatano E, Kaiho T, Miyazaki M, Kono T, Kamiyama T, Morita S, Sakamoto J, Kusano M, Saji S, Kanematsu T, Kitajima M.	Effect of TU-100, a traditional Japanese medicine, administered after hepatic resection in patients with liver cancer: a multi-center, randomized, double-blind, placebo-controlled phase II trial (JFMC40-1001).	Int J Clin Oncol	epub ahead of print		2014
Ueno N, Hasebe T, Kaneko A, Yamamoto M, Fujiya M, Kohgo Y, Kono T, Wang CZ, Yuan CS, Bissonnette M, Chang EB, Musch MW.	TU-100 (daikenchuto) and ginger ameliorate anti-CD3 antibody induced T cell-mediated murine enteritis: microbe-independent effects involving Akt and NF-κB suppression.	PloS ONE	epub ahead of print		2014
Nahata M, Muto S, Nakagawa K, Ohnishi S, Sadakane C, Saegusa Y, Iizuka S, Hattori T, Asaka M, Takeda H.	Serotonin 2C receptor antagonism ameliorates novelty-induced hypophagia in aged mice.	Psychoneuro-endocrinology	38 (10)	2051-2064	2013
Yamada C, Saegusa Y, Nakagawa K, Ohnishi S, Muto S, Nahata M, Sadakane C, Hattori T, Sakamoto N, Takeda H.	Rikkunshito, a Japanese Kampo medicine, ameliorates decreased feeding behavior via ghrelin and serotonin 2B receptor signaling in a novelty stress murine model.	BioMed Res Int	2013	792940	2013
Takeda H, Nakagawa K, Okubo N, Nishimura M, Muto S, Ohnishi S, Sakamoto N, Hosono H, Asaka M.	Pathophysiologic basis of anorexia: focus on the interaction between ghrelin dynamics and the serotonergic system.	Biol Pharm Bull	36 (9)	1401-1405	2013
武田宏司, 武藤修一, 大西俊介, 河野透.	抗癌剤に伴うcachexiaとその治療.	栄養-評価と治療	30 (4)	283-286	2013

Kato T, Watari H, Takeda M, Hosaka M, Mitamura T, Kobayashi N, Sudo S, Kaneuchi M, Kudo M, Sakuragi N.	Multivariate prognostic analysis on the patients with adenocarcinoma of the uterine cervix treated with radical hysterectomy and systematic lymphadenectomy.	J Gynecol Oncol	24 (3)	222-228	2013
Dong P, Kaneuchi M, Konno Y, Watari H, Sudo S, Sakuragi N.	Emerging therapeutic biomarkers in endometrial cancer.	Biomed Res Int	2013	130362	2013
Mitamura T, Watari H, Wang L, Kanno H, Hassan MK, Miyazaki M, Katoh Y, Kimura T, Tanino M, Nishihara H, Tanaka S, Sakuragi N.	Downregulation of miRNA-31 induces taxane resistance in ovarian cancer cells through increase of receptor tyrosine kinase MET.	Oncogenesis	25 (2)	e40	2013
Todo Y, Watari H, Okamoto K, Hareyama H, Minobe S, Kato H, Sakuragi N.	Tumor volume successively reflects the state of disease progression in endometrial cancer.	Gynecol Oncol	129 (3)	472-477	2013
Sakuragi N.	Recent advances in research on epigenetic alterations and clinical significance of para-aortic lymphadenectomy in endometrial cancer: an introduction.	Int J Clin Oncol	18 (2)	183-185	2013
Watari H, Todo Y, Kang S, Odagiri T, Sakuragi N.	Proposal of a concept and design of a randomized phase III trial investigating the survival effect of para-aortic lymphadenectomy in endometrial cancer.	J Obstet Gynaecol Res	40 (2)	312-316	2014
Todo Y, Watari H, Kang S, Sakuragi N.	Tailoring lymphadenectomy according to the risk of lymph node metastasis in endometrial cancer.	J Obstet Gynaecol Res	40 (2)	317-321	2014
Dong P, Kaneuchi M, Watari H, Sudo S, Sakuragi N.	MicroRNA-106b modulates epithelial-mesenchymal transition by targeting TWIST1 in invasive endometrial cancer cell lines.	Mol Carcinog	53 (5)	349-359	2014

Ⅳ. 研究成果の刊行物・別刷

J Anesth (2013) 27:284–292
DOI 10.1007/s00540-012-1507-2

REVIEW ARTICLE

The recent progress in research on effects of anesthetics and analgesics on G protein-coupled receptors

Kouichiro Minami · Yasuhito Uezono

Received: 15 February 2012 / Accepted: 9 October 2012 / Published online: 26 October 2012

Abstract The exact mechanisms of action behind anesthetics and analgesics are still unclear. Much attention was focused on ion channels in the central nervous system as targets for anesthetics and analgesics in the 1980s. During the 1990s, major advances were made in our understanding of the physiology and pharmacology of G protein coupled receptor (GPCR) signaling. Thus, several lines of studies have shown that G protein coupled receptors (GPCRs) are one of the targets for anesthetics and analgesics and especially, that some of them inhibit the functions of GPCRs, i.e,, muscarinic receptors and substance P receptors. However, these studies had been focused on only G_q coupled receptors. There has been little work on G_s- and G_i-coupled receptors. In the last decade, a new assay system, using chimera $G_{i/o}$-coupled receptor fused to Gq_{i5}, has been established and the effects of anesthetics and analgesics on the function of G_i-coupled receptors is now more easily studied. This review highlights the recent progress of the studies regarding the effects of anesthetics and analgesics on GPCRs.

Keywords Anesthetics · Analgesics · G protein-coupled receptor

Introduction

In the 1990s, the effects of anesthetics on voltage- and ligand-gated ion channels have been the focus of several studies [1–4]. However, the mechanisms of anesthetics and analgesics actions are still not known well. The G protein coupled receptors (GPCRs) are not only the largest protein family in the human genome but are also the single biggest target for many drugs (Fig. 1; Table 1). Recent research about GPCRs is therefore growing at a fast pace and the range of techniques that can be applied to GPCRs is vast and continues to grow in our understanding of the physiology and pharmacology of G protein coupled receptor (GPCR) signaling. Further studies have shown that GPCRs are targets for anesthetics [5]. As compared with ion ligand-gated ion channels, less is known about the mechanisms of action of anesthetics on GPCRs. In this review, we present the recent progress of the research on the effects of anesthetics and analgesics on GPCRs.

The effect of anesthetics and analgesics on G_q protein coupled receptors

The main focus of GPCR anesthetics and analgesics research has often been concentrated on G_q-coupled receptors (Tables 2, 3). Because G_q coupled receptors leads to intracellular Ca^{2+} elevation, the effects of anesthetics and analgesics on G_q coupled receptors have been well studied using the *Xenopus* oocyte expression system (Fig. 2). The *Xenopus* oocyte expression system has been used to study a multiplicity of brain receptors with pharmacological properties that mimic those of native brain receptors [2]. Stimulation of G_q coupled receptors results in activation of Ca^{2+}-activated Cl^- currents in *Xenopus* oocytes [6–9]; stimulation of G_q coupled receptors leads to G protein-dependent activation of phospholipase C, resulting in the formation of IP_3 and diacylglycerol. The IP_3 causes the release of Ca^{2+} from the endoplasmic

K. Minami (✉) · Y. Uezono
Cancer Pathophysiology Division, National Cancer Center Research Institute, Tokyo 104-0045, Japan
e-mail: kminami@med.uoeh-u.ac.jp

K. Minami
Department of Anesthesiology and Critical Care Medicine, Jichi Medical University, Tochigi 329-0483, Japan

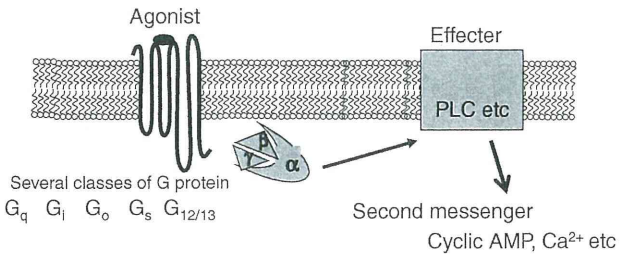

Fig. 1 Intracellular signaling of G protein coupled receptor

Table 1 Signaling of G protein coupled receptor

G protein	G_q	$G_{i/o}$	G_s
Effecter	PLC↑	Adenylate cyclase↓	Adenylate cyclase↑
Second messenger	IP_3 ↑ DAG↑	cAMP↓	cAMP↑
Intracellar reaction	PKC↑ Ca^{2+}↑	PKA↓	PKA↑
Receptor	M_1	M_2	β-Adrenergic
	M_3	μ Opioid	
	Substance P		
	Orexin 1		
	$5HT_{2A}$		
	mGluR1		
	mGluR1		

Table 2 The effects of volatile anesthetics on Gq coupled receptor function

	Halothane	Isoflurane	Enflurane	Desflurane	Sevoflurane
M_1	↓	→		↓↑	↓
M_3	↓	↓		→	↓
$5HT_{2A}$	↓				
$5HT_{2C}$		↓	↓		
mGluR1	→				
mGluR5	↓				
Substance P	↓	↓	↓		↓
Orexin 1	↓	↓	↓		

reticulum, which in turn triggers the opening of Ca^{2+}-activated Cl^- channels in *Xenopus* oocytes. This system has been well characterized, and has proven useful for studying the effects of anesthetics and analgesics on G_q coupled receptors.

Muscarinic acetylcholine receptors

In G_q coupled receptors, muscarinic acetylcholine receptors (MRs) have been paid much attention to as the target of the anesthetics and analgesics. This is because MRs are involved in various neuronal functions in the central nervous system (CNS) and the autonomic nervous system [10]. Cholinergic antagonism interferes with learning behavior, whereas cholinesterase inhibitors enhance learning [11]. Furthermore, the inhibition of MRs lead to sedation or non-rapid eye movement sleep [12]. The therapeutic potential of muscarinic antagonists is compromised by several effects on the autonomic nervous system, including dry mouth, tachycardia, constipation, urinary retention, and pupillary dilation [13]. Recent molecular cloning studies have revealed the existence of five subtypes of MRs (M1R-M5R) [14, 15]. Using pharmacological techniques, many of the muscarinic responses in peripheral tissues have been studied thoroughly. However, relatively little is known about the functional roles of individual subtypes of MRs in the CNS. Recent studies of their anatomic distribution have been used to predict their functions in the CNS. For example, cortical and hippocampal M1R are involved in memory and learning [16].

To date, several investigators have studied the effects of anesthetics on MRs. Anthony et al. [17] reported that chloroform, enflurane, isoflurane and halothane increased the affinity of [^{3}H]methylscopolamine([^{3}H]MS) binding, but did not affect the number of [^{3}H]MS binding sites in the rat brainstem. Isoflurane inhibits muscarinic receptor-evoked cyclic GMP production in cultured bovine adrenal medullary cells, suggesting that isoflurane inhibits M1R [18]. Lin et al. [19] showed that enflurane inhibits the function of mouse and human brain phosphatidylinositol-linked MRs expressed in *Xenopus* oocytes.

There have been several reports on the effects of volatile anesthetics on recombinant MRs using the *Xenopus* oocyte expression system. Halothane inhibits signaling via M1R expressed in *Xenopus* oocytes [6–12]. Desflurane has a biphasic effect on M1R signaling, enhancing it at lower concentrations, but depressing it at higher concentrations and a similar, although not significant, trend was observed with M3R signaling [20]. Isoflurane has no effect on M1R signaling, but inhibits M3R signaling [20, 21]. Sevoflurane depresses the function of M1R and M3R signaling in a dose-dependent manner [22]. Similar to its known effect on M1R signaling, halothane also depresses M3R function dose-dependently [22].

There are several reports on the inhibitory effects of intravenous anesthetics, ketamine, propofol, thiopental, alphaxalone and an α_2-adrenoceptor agonist, dexmedetomidine. Durieux [23] reported that ketamine profoundly inhibits muscarinic signaling. Nagase et al. [24] reported that propofol inhibits M1R-mediated signal transduction at the receptor site or the site of interaction between the receptor and associated G proteins. Shiraishi et al. [25] recently reported the inhibitory effects of alphaxalone on M1R and M3R expressed in *Xenopus* oocytes. Dexmedetomidine has little effect on the M1R function expressing in

Table 3 The effects of Intravenous anesthetics and analgesics on Gq coupled receptor function

	Dex.	Ketamine	Propofol	Pent.	Alph.	Tramadol	ODT
M_1	→	↓	↓		↓	↓	↓
M_3	↓	↓			↓	↓	→
$5HT_{2A}$		→	→	→			
$5HT_{2C}$	→					↓	↓
mGluR1							
mGluR5							
Substance P	→	↓	→	↓		→	↓
Orexin 1	→	↓		↓			

Dex. dexmedetomidine, *Pent.* pentobarbiturate, *Alph.* alfaxalone, *ODT O*-desmethyl tramadol

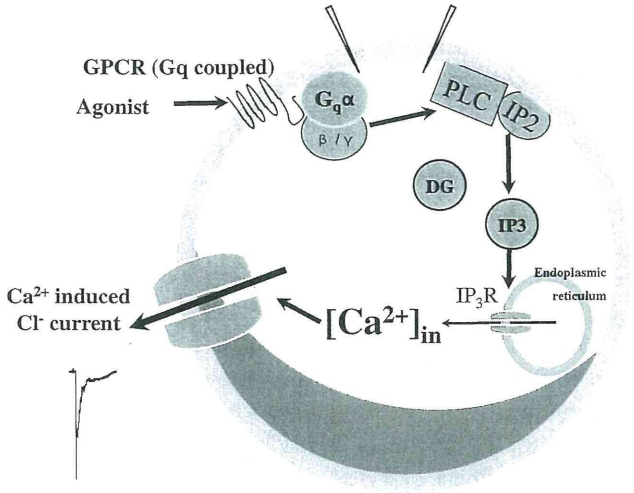

Fig. 2 Intracellular signaling of Gq coupled receptor expressing in *Xenopus* oocytes. Stimulation of G_q coupled receptors results in activation of Ca^{2+}-activated Cl^- currents in *Xenopus* oocytes; stimulation of G_q coupled receptors leads to G protein-dependent activation of phospholipase C, resulting in the formation of IP_3 and diacylglycerol. The IP_3 causes the release of Ca^{2+} from the endoplasmic reticulum, which in turn triggers the opening of Ca^{2+}-activated Cl^- channels in *Xenopus* oocytes

Xenopus oocytes expressing M1Rs. In contrast, dexmedetomidine inhibited the ACh-induced currents in *Xenopus* oocytes expressing M3Rs [26].

Local anesthetics also inhibit MRs. Clinically relevant concentrations of lidocaine inhibit M1R signaling [27–29]. Hollmann et al. [27–30] suggested that the major site of action is an extracellular domain of the muscarinic receptor; the N-terminus and third extracellular loop of the M1R molecule were identified as necessary for extracellular inhibition by charged LA, and the intracellular effect of LA most likely takes place at the $G_{\alpha q}$-subunit.

There have been several reports with evidence that showed the effects of analgesics. The effects of tramadol on MRs have been well studied. Information on the effects of tramadol on MRs is scarce. In a rat brain binding experiment, Frink et al. [31] showed that tramadol and its metabolite, *O*-desmethyl tramadol (ODT), have no affinity for M1R. We investigated the effects of tramadol on M1R in two different systems, a *Xenopus* oocyte expression system and on cultured bovine adrenal medullary cells. Tramadol competitively inhibited acetylcholine (ACh)-induced currents in *Xenopus* oocytes expressing the M1R [32]. In cultured bovine adrenal medullary cells, tramadol suppressed muscarine-induced cyclic GMP accumulation and inhibited the specific binding of [^{3}H]-quinuclidinyl benzilate (QNB) [32]. These findings suggest that tramadol inhibits MR function via QNB-binding sites. We also investigated the effects of tramadol on M3R using the *Xenopus* oocytes expression system [33]. Tramadol inhibited ACh-induced currents in oocytes expressing the M3R and the specific binding of [^{3}H]-QNB, suggesting that tramadol inhibits M3R function via QNB-binding sites. This may explain the modulation of neuronal function and the anticholinergic effects of tramadol in clinical situations. To confirm the anticholinergic action of tramadol, we investigated the effects of tramadol on the pH of gastric juices during anesthesia in order to determine whether tramadol inhibits the secretion of gastric juices from gastric glands [34]. After anesthesia was induced, the gastric pH was measured using pH test paper; then tramadol (100 mg), famotidine (20 mg), or saline was injected into the deltoid muscle. The gastric pH was increased by the same amount in both the tramadol and famotidine groups at 3 h after drug administration, suggesting that tramadol inhibits the secretion of gastric acid. The effects of the metabolite ODT on M1R and M3R functions in the *Xenopus* oocytes expression system have been reported [35]; the inhibitory effects of ODT on muscarinic receptors are different from those of tramadol. ODT inhibits M1R function but has little effect on M3R function [35].

As mentioned above, there is much evidence that MRs are the targets of anesthetics and analgesics. By contrast, a recent report pointed out that MRs do not seem to mediate the immobilization caused by inhaled anesthetics [36]. Previous studies have focused on G_q-coupled receptors (M1R and M3R), although, there has been little information on the other MRs, such as M2R. More studies are necessary to reveal the roles of individual MRs in the mechanisms of anesthetics and analgesics.

5-Hydroxytryptamine (5-HT; serotonin) receptors

5-Hydroxytryptamine (5-HT; serotonin) is a neurotransmitter that is essential for a large number of physiological processes, including the regulation of vascular and non-vascular smooth muscle contraction, modulation of platelet aggregation, and the regulation of appetite, mood, anxiety, wakefulness, and perception [37, 38]. To mediate this astonishing array of functions, no fewer than 15 separate receptors have evolved, of which all but two (5-HT_{3A} and 5-HT_{3B}) are GPCRs [37, 38].

Although seven different families of 5-HT receptors (5-HTR) have been identified, there is little information on the effects of anesthetics on G-protein-coupled 5-HTRs. Several investigators recently studied the effects of anesthetics on two types of metabotropic 5HTR. Enflurane inhibited the function of phosphatidylinositol-linked acetylcholine and 5-HTR [19]. We previously reported the inhibitory effects of anesthetics on 5-HT_{2A}R in detail. Halothane decreased 5-HT_{2A}R-mediated responses in a concentration-dependent manner, and the inhibitory effects of halothane were attenuated by treatment with the protein kinase C (PKC) inhibitor GF109203X. These findings imply that metabotropic 5-HTRs are affected by halothane, and that these actions may be dependent on the activity of PKC.

By contrast, the intravenous anesthetics propofol, ketamine, pentobarbital, and etomidate did not affect the functions of 5-HT_{2A}R. Dexmedetomidine has little effect on the 5-HT_{2C} receptors function expressing in *Xenopus* oocytes [7]. Tramadol inhibited 5-HT-induced Cl^- currents at pharmacologically relevant concentrations, and the mechanism of this inhibitory effect seems to involve competitive displacement of the 5-HT binding to the 5-HT_{2C}R, rather than via activation of the PKC pathway. ODT is a more potent analgesic than tramadol. ODT, at pharmacologically relevant concentrations, inhibited 5-HT-evoked Ca^{2+}-activated Cl^- currents in oocytes that expressed 5-HT_{2C}R. ODT inhibited the specific binding of [^{3}H]5-HT by 5-HT_{2C}R expressed in oocytes. ODT altered the apparent dissociation constant for binding of [^{3}H]5-HT by 5-HT_{2C}R without changing maximum binding, which indicated competitive inhibition [39].

There have been several findings with evidence that 5-HTR is a one of the targets of volatile anesthetics, but intravenous anesthetics do not seem to have an effect on them. By contrast, a recent report pointed out that tramadol and metabolite ODT would have inhibition.

Substance P receptors

Substance P receptors (SPR) are widely distributed in the CNS and peripheral nerves. SP is a neurotransmitter that is released from C-fibers within nociceptive primary afferent neurons to the spinal cord and mediates part of the excitatory synaptic input to nociceptive neurons at this level [40–42]. A recent study of mice lacking the gene encoding SPR showed that the mice had altered pain sensitivity; nociceptive responses to certain somatic and visceral noxious stimuli are reduced in SPR knockout mice [43–45]. Accordingly, much attention has been paid to the role of SPR in anesthetic mechanisms.

Recently, we reported the effects of halothane, isoflurane, enflurane, and diethyl ether on substance P-induced currents mediated by SPR expressed in *Xenopus* oocytes [9]. All of the volatile anesthetics tested inhibited SPR-induced Ca^{2+}-activated Cl^- currents at pharmacologically relevant concentrations. The PKC inhibitor GF109203X enhanced the substance P-induced Cl^- currents. However, GF109203X abolished the inhibitory effects of the volatile anesthetics examined on SPR. These results demonstrate that halothane, isoflurane, enflurane and diethyl ether inhibit the function of SPR and suggest that activation of PKC is involved in the mechanism of action of anesthetics and ethanol on the inhibitory effects of SPR.

The intravenous anesthetics ketamine and pentobarbital inhibit SPR-induced currents at pharmacologically relevant concentrations, while propofol has little effect on the currents [46]. By contrast, GF109203X did not abolish the inhibitory effects of ketamine and pentobarbital on substance P-induced Ca^{2+}-activated Cl^- currents. Moreover, ketamine and pentobarbital inhibited the specific binding of [^{3}H]-substance P to SPR expressed in *Xenopus* oocytes. Scatchard analysis of [^{3}H]SP binding revealed that ketamine and pentobarbital decreased the apparent dissociation constant for binding and maximal binding, indicating noncompetitive inhibition. The results suggest that ketamine and pentobarbital inhibit SPR function.

In contrast to anesthetics, there has been little information about the effects of analgesics on SPR. Tramadol has little effect on SPR expressed in *Xenopus* oocytes [46]. On the other hand, we recently reported that inhibitory effects of ODT have much greater analgesic potency than tramadol itself on SPR [47]. In this study, we investigated the effects of ODT on SPR expressed in *Xenopus* oocytes by examining substance P-induced Ca^{2+}-activated Cl^- currents. ODT inhibited the SPR-induced Cl^- currents at pharmacologically relevant concentrations, however, GF109203X did not abolish the inhibitory effects of ODT on SP-induced Ca^{2+}-activated Cl^- currents. The results suggest that the ODT inhibits the SPR functions, which may be independent of activation of PKC-mediated pathways.

These findings imply that SPR are affected by most volatile anesthetics and some intravenous anesthetics. Propofol and tramadol have little effect on the currents.