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E 2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。

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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)、金子篇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め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月よとり「ゲムシタビン投与膵がん患者に対する共生とした。しかしながら、適格規準を開始した。しかしながら、適格規準を開始した。しかしながら、適格規準を開始した。しかしながら、適格規準を満ったがした。しかしながら、適格規準を満ったとした。

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。

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 - 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ー無作為化第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

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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
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IV. 研究成果の刊行物・別刷

REVIEW ARTICLE

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

Kouichiro Minami · Yasuhito Uezono

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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 Gs- and Gicoupled 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

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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 $\boldsymbol{G}_{\boldsymbol{q}}$ 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

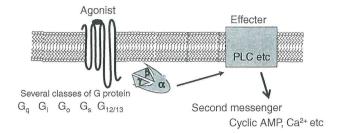


Fig. 1 Intracellular signaling of G protein coupled receptor

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	$IP_3 \uparrow DAG \uparrow$	cAMP↓	cAMP↑
Intracellar reaction	$PKC\uparrow$ $Ca^{2+}\uparrow$	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		\rightarrow		 ↓↑	
M_3				\rightarrow	\downarrow
5HT _{2A}	\downarrow				
5HT _{2C}		\downarrow	\downarrow		
mGluR1	\rightarrow				
mGluR5	\downarrow				
Substance P	\downarrow	\downarrow	1		\downarrow
Orexin 1	\downarrow	\downarrow	\downarrow		

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 [3H]methylscopolamine([3H]MS) binding, but did not affect the number of [3H]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



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

	Dex.	Ketamine	Propofol	Pent.	Alph.	Tramadol	ODT
$\overline{\mathrm{M_1}}$	\rightarrow	\downarrow			\downarrow	\downarrow	
M_3	1	1			\downarrow	\downarrow	\rightarrow
5HT _{2A}		\rightarrow	\rightarrow	\rightarrow			
$5\mathrm{HT}_{2\mathrm{C}}$	\rightarrow					\downarrow	\downarrow
mGluR1							
mGluR5							
Substance P	\rightarrow	1	\rightarrow	\downarrow		\rightarrow	\downarrow
Orexin 1	\rightarrow	\downarrow		\downarrow			

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

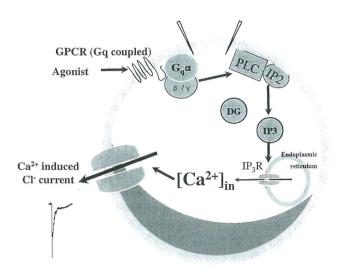


Fig. 2 Intracellular signaling of G_q coupled receptor expressing in Xenopus oocytes. Stimulation of G_q coupled receptors results in activation of Ca^{2+} -activated Cl^- currents in Xenopus oocytes; stimulation of G_q coupled receptors leads to G protein-dependent activation of phospholipase C, resulting 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 [3H]-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 [3H]-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-HTevoked Ca2+-activated Cl currents in oocytes that expressed 5-HT_{2C}R. ODT inhibited the specific binding of [³H]5-HT by 5-HT_{2C}R expressed in oocytes. ODT altered the apparent dissociation constant for binding of [3H]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 Ca²⁺-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 Ca²⁺-activated Cl⁻ currents. Moreover, ketamine and pentobarbital inhibited the specific binding of [³H]-substance P to SPR expressed in *Xenopus* oocytes. Scatchard analysis of [³H]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 Ca²⁺-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 Ca²⁺-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.

