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Ginseng; Recent Advances and Trends

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Abstract : Ginseng, the root of *Panax ginseng* C.A. Meyer, is well-known oriental herbal medicine. The number of paper reporting the effects on its physiological, pharmacological, and behavioral effects has been increased every year, since ginsenosides isolated from ginseng are known to be biologically active components. This brief review summarizes some of new findings from recently published papers on ginsenosides or ginseng saponins. Therefore, this paper includes the various effects of ginsenosides on neuronal cell growths, on behavior of experimental animals, on enzyme activities, on the release and uptake of neurotransmitters, on neuronal cell excitability, on the motility of intestine, on antitumor activity, on cardiovascular system and metabolism. In spite of various effects of ginsenosides on various cells or organs, it is still to date impossible for one to clearly explain the exact mechanism on the action of ginsenosides. However, in this article I will discuss several papers providing possible explanations on the physiological and pharmacological actions including signal transduction pathway of ginsenosides. The elucidation of the exact mechanism of ginsenosides on cellular or molecular level will not only give us a chance to explain why people have used ginseng as an elixir of life for several thousands of year but also give us a crucial chance to apply ginseng to modern medicine.

Key words : Panx ginsang C.A. Meyer, Physiology and pharmacology, Modern Medicine

Introduction

Ginseng is the root of Panax ginseng C. A. Meyer (Araliaceae), a well-known oriental folk medicine from long time ago and is used by far east, south east countries, Russia and even Europe. In Canada and United States, ginseng is also recently cultivated and is now in the markets for keeping one healthy or for naturopathic treatment. Ginseng is now one of the prototypical herbal medicines consumed in all around world.

Ginseng has been described to have many claims of medicinal functions such as anticancer, antihypertension, antidiabetes, antistress, facilitating learning, and improving the weak body conditions as tonics and even more, although its pharmacological effect is slow, subtle, and mild rather than strong compared with occidental medicine.[1] However, it is unwise to be indifferent to long history of ginseng or ignore the experiences of traditional oriental medicine related with ginseng.

Many scientists have investigated and analyzed ginseng vigorously in the last 30 years and have found new physiological or pharmacological effects of ginseng and also have isolated new pharamacoactive components. But it is still not proved exactly for its therapeutical efficacy. Moreover, the cellular or molecular mechanism of ginseng action is even not known. Recent publications on ginseng researchs provide the possibilities that ginseng or ginseng components will be soon developed as a modern medicine but not as a complementary medicine.

In this brief review article, I will go over the pharmacologically or physiologically active components of ginseng and main findings in recent ginseng researches, especially using ginsenosides, summarize these results, and finally consider the

future directions of ginseng study.

Active Components of Ginseng

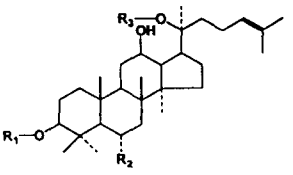
1. Ginsenosides (ginseng saponins)

Ginsenosides are main pharmacoactive molecules of ginseng. The name of "ginsenoside or ginseng saponins" was born, since it is found in ginseng and their properties are similar with saponins found in other plants as an aglycone.[2] However, ginsenosides are different from general saponins, since they are very mild in their effects and show much less toxicity even with high dose intake and do show a weak or little hemolysis. As shown Fig. 1, the back-bone structure of ginsenoside looks like that of steroids. In fact, ginsenoside is one of the derivatives of triterpenoid dammarane consisting of thirty carbon atoms. Three major types of ginsenosides are found in ginseng, called oleanolic acid, protopanaxadiol, and protopanaxatriol depending on their chemical constitution. Each type of ginsenoside has at least three side chain called R1, R2, and R3 and these R side chains are free or connected with sugar containing monomer, dimer, or trimer. These sugars components probably reduce toxicity of ginsenosides and provide specificity of ginsenoside effects. Total numbers of different ginsenosides found to date are at least twenty-nine. They are found in the root, root stock, stems, leaves, flowers, and fruits of ginseng plants. Interestingly, some of biologically active ginsenosides are found only in red ginseng and oriental ginseng.[3,4] They are probably formed during the steaming and hydrolysis in the process of red ginseng preparation from white ginseng.

The ginsenoside content in different parts of ginseng is in the sequence of bud and flower> leaf>root>rhizome>seed. These ginseng saponin content in root is 3~4% by weight in Panax ginseng C. A. Meyer.[1]

2. Other constituents of ginseng

Besides ginseng saponins, there are several minor components in ginseng. The reports on their



Ginsenoside	R_1	R_2	R_3
Protopanaxadiol type			
20S-protopanaxadiol	H	H	H
Ra_1	Glc-Glc	H	Xyl-Ara(pyr)-Glc
Ra_2	Glc-Glc	H	Xyl-Ara(fur)-Glc
Ra_3	Glc-Glc	H	Xyl-Glc-Glc
Rb_1	Glc-Glc	H	Glc-Glc
Rb_1-$COCH_2COOH$	Glc-Glc$COCH_2COOH$	H	Glc-Glc
Rb_2	Glc-Glc	H	Ara(pyr)-Glc
Rb_2-$COCH_2COOH$	Glc-Glc$COCH_2COOH$	H	Ara(pyr)-Glc
Rb_3	Glc-Glc	H	Xyl-Glc
Rc	Glc-Glc	H	Ara-Glc
Rc-$COCH_2COOH$	Glc-Glc	H	Ara-Glc
Rd	Glc-Glc	H	Glc
Rd-$COCH_2COOH$	Glc-Glc	H	Glc
Rg_3	Glc-Glc	H	H
Rh_2	Glc	H	H
Rs_1	Glc-Glc$COCH_3$	H	Glc-Ara(pyr)
Rs_2	Glc-Glc$COCH_3$	H	Glc-Ara(fur)
Protopanaxatriol type			
20S-protopanaxatriol	H	OH	H
Re	H	O-Rha-Glc	Glc
Rf	H	O-Glc-Glc	H
Rg_1	H	O-Glc	Glc
Rg_2	H	O-Rha-Glc	H
20S-glc-Rf	H	O-Glc-Glc	Glc
Rh_1	H	O-Glc	H
Notoginsenoside R_1	H	O-Xyl-Glc	Glc

Fig. 1. Structures of various ginseng saponins. They are different from three side chains attached to the common steroid ring. Abbreviations for carbohydrates are as follows: Glc, glucopyranoside; Ara(pyr) or Ara(fur), arabinopyranoside or arabinofuranoside; Rha, rhamnopyranoside.
Structures are given in Kaku *et al.* (2)

biological activities are not many so that I will go over them briefly.

(1) The lipophilic components

The lipophilic compounds found in ginseng root are several fatty acids such as stearic acid, palmitic acid, panacene, terpene, polyacetylene, phenolic acid. These lipid soluble compounds in ginseng are 1% about by weight. Polyacetylene and phenolic acid are known to have anticancer and antiaging activity, respectively (Figs. 2 and 3).[1]

(2) Alkaloids and polysaccharides

There is a report that ginseng roots also con-

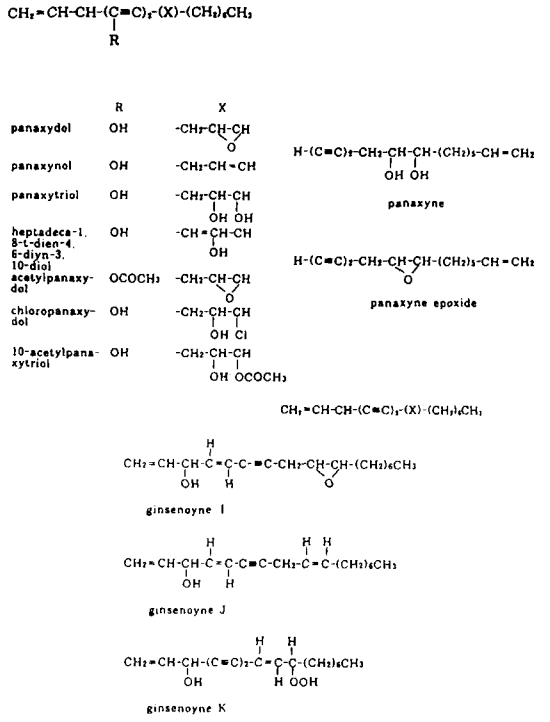
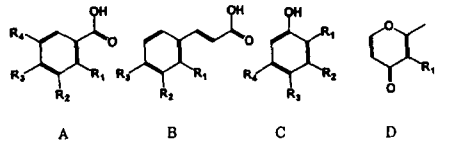


Fig. 2. Chemical structure of various polyacethylene isolated from ginseng. They are known to have anticancer and antiplatelet activities.



Compound name	Ring system	R^1	R^2	R^3	R^4
salicylic acid	A	OH	H	H	H
p-hydroxybenzoic acid	A	H	H	OH	H
gentisic acid	A	OH	H	H	OH
protocatechuic acid	A	H	OH	OH	H
vanillic acid	A	H	OCH_3	OH	H
syringic acid	A	H	OCH_3	OH	OCH_3
cinnamic acid	B	H	H	H	-
m-coumaric acid	B	H	H	OH	-
p-coumaric acid	B	H	H	OH	-
caffeic acid	B	H	OH	OH	-
ferulic acid	B	H	OCH_3	OH	-
maltol	D	OH	-	-	-

Fig. 3. Various phenolic acids isolated from ginseng. They are known to have antiaging and antoxidation activities.

	R_1	R_2
N_b-formyl-1-methyl-β-carboline	CHO	CH_3
1-carbobutoxy-β-carboline	H	$COOC_4H_9$
1-carboethoxy-β-carboline	H	$COOC_2H_5$
1-carbomethoxy-β-carboline	H	$COOCH_3$

Fig. 4. Chemical structure of alkaloids isolated from ginseng. It is not yet known to have biological activity.

tain a trace of alkaloids as shown in Fig. 4 but their pharmacological or physiological action is not clear and is under the investigation.

Five polysaccharides at least, called panaxan A, B, C, D, and E, have been isolated from ginseng root. As shown in Fig. 5, panaxan A is mainly consists of α-1→6 linked D-glucopyranose residues with a branching at the C-3 positions. Panaxan A conjugates with some amino acids such as histidine, leucine, alanine, tryptophan, glycine, asparagine, and threonine. These polysaccharides show some anticancer and hypoglycemic effects.[1] Ginseng also contain several peptides.[1]

Pharmacology and Physiology of Ginsenosides or Ginseng Saponins on Nervous System

Ginsenosides or ginseng saponins have shown to have a variety of effects on nervous system including several enzymes activities found in brain, neuronal cell growths, ion channels, intestinal contraction, and behaviors of experimental animal.

1. The neuronal cell growth and protection

Ginsenoside Rb_1 and malonylginsenoside Rb_1 induce the potentiation of the nerve growth factor (NGF)-mediated nerve fiber production prepared from chicken embryonic dorsal root ganglion and lumbar sympathetic ganglia, even though ginsenoside Rb_1 itself has no effect on nerve fiber production.[5,6] On the other hand, in neurons cultured from rat cortex, ginseng saponins enhance the extension of neurite and block the action of cytochalasin B, which is a polymerization inhibitor of actin.[7]

Ginsenoside Rg_1 prolongs the survival time of

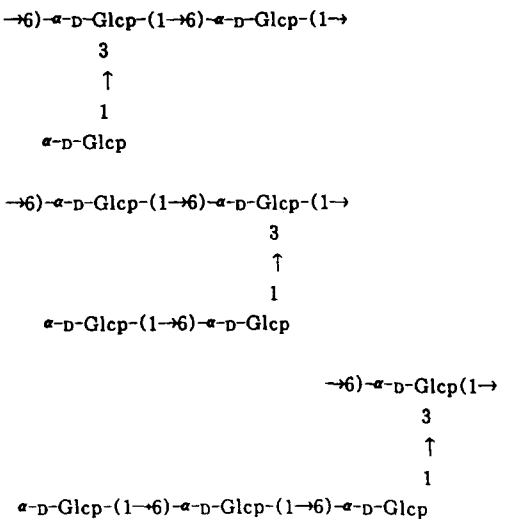


Fig. 5. Chemical structure of polysaccarides isolated from ginseng. They are known to have anticancer and to enhance immune activity.

neurons cultured from both chick and rat cerebral cortex.[8] Interestingly, various ginsenosides such as Rb_1, Rb_2, Rc, Rd, Re, Rf, and Rg_1 showed the protective effects from the impairment of brain growth following chronic ethanol treatment.[9] These protective effect could be originated from the proliferative and promoting effects of ginseng saponins on neurons. Recently, ginseng saponins also show the protection from ischemic injury and block the swelling of glia induced by glutamate treatment.[10]

2. Enzyme activity

There are not many papers on the effects of ginsenosides on activity of enzymes existing in nervous system. Recently, Sharma and Kalra (1993) reported using cell free system that ginseng root extracts and ginsenoside Rb_1, Rc, and Re inhibit potently the activity of purified calmodulin dependent phosphodiesterase isoenzymes from bovine brain.[11] The inhibitory effect of these ginsenosides on above isoenzymes attenuated by increasing the concentration of calmodulin. On the other hand, Stancheva and Alova (1993) studied the inhibitory effect of ginsenoside Rg_1 on cAMP phosphodiesterase activity prepared from various region of young and old rat brain. Ginsenoside Rg_1 inhibits cAMP phosphodiesterase activity both ages and the effect of ginsenoside Rg_1 is dose-dependent manner in the range of 5×10^{-5} to 5×10^{-4} M.[12] These reports suggest that some of ginsenosides are involved in the cAMP and Ca^{2+} metabolism as a calmodulin antagonist. In fact, Petcov (1978) reported that ginseng saponins increase cAMP formation at low concentration and inhibit cAMP formation at high concentration in rat brain.[13]

3. The uptake and release of neurotransmitters and neurohormones

In the experiment using animals fed with diet containing supplemented with ginseng saponins, the amount of norepinephrine and dopamine in brain was increased after at least 8 week feeding.[14] In experiments using rat pituitary cell culture, ginsenoside Rg_1 increases the secretion of adrenocorticotropin (ACTH), but ginsenoside Rb_1, Rc, Rd, and Re had no effect. The effect of ginsenoside Rg_1 is dose-dependent with half-maximal effect of 2.8 μM. The secretion of ACTH seems rapid after ginsenoside treatment.[15] Tsang *et al.* (1985) studied whether ginsenosides have effects on the uptake of various neurotransmitters such as GABA, glutamate, dopamine, norepinephrine, serotonin and 2-deoxy-D-glucose and leucine in rat brain synaptosomes. Total ginseng saponins inhibit above mentioned neurotransmitters but not 2-deoxy-D-glucose and leucine. Even higher concentration of ginseng saponins do not inhibit the uptake of 2-deoxy-D-glucose and leucine. Ginsenoside Rc and Rd among various ginsenosides show the strongest effects of uptake inhibition with sequence of GABA=NA>DA>Glu>5-HT. These results thus suggest that ginseng saponins act on only neurotransmitters selectively.[16] Tachikawa *et al.* (1995) reported that various ginsenosides inhibit acetylcholine (ACh)-evoked Na^+ influx and catecholamine secretion in adrenal chromaffin cells. Among them ginsenosides Rg_2 show the strongest effects. On the other hand, ginsenoside Rg_2 does not show the inhibition of secretion of catecholamines induced by depolarization (by high K^+ or veratridine) but in-

hibits both ACh-induced Na^+ and Ca^{2+} influxes in the cells. The inhibitory effects of ginsenoside Rg_2 was attenuated by increasing ACh or external Ca^{2+} concentration. These results seem that ginsenoside Rg_2 compete with ACh for ACh receptors or ACh binding sites or plays as a Ca^{2+} antagonist.[17]

On the other hand, ginsenoside Rb_1 even at low concentration increased the choline uptake but ginsenoside Rb_1 does not affect the affinity of the choline uptake carrier for choline in synaptosomes prepared from several regions of brain.[18] In brain slice ginsenoside Rb_1 also facilitates ACh release.[19] These results support that ginseng saponins have regulatory effects on neurotransmitter release or uptake in nervous system. It seems that a low concentration of ginseng saponins stimulates the release of neurotransmitters[15,19], whereas relatively high concentration of ginseng saponins shows inhibitory effects.[17] Interestingly, Kimura *et al.* (1994) reported that ginsenosides regulate GABAergic system in rat cortical membranes. They showed that ginsenosides Rb_1, Rb_2, Rc, Re, Rf, and Rg_1 inhibited specific [^{3}H] mucinol binding to the high-affinity site and ginsenoside Re and Rf enhanced specific [^{3}H] flunitrazepam binding without changes in the non-specific binding. Ginsenoside Rc inhibits the specific [^{3}H] baclofen binding.[20]

4. Ion channels and synaptic activity

The effects of ginseng saponins on ion channels or synaptic activity probably can provide a basis to explain the regulation of neurotransmitter release or uptake in nervous system as mentioned above. It was shown that ginseng root extract or several ginsenosides attenuate voltage-dependent Ca^{2+} channels in rat sensory neurons as well as adrenal chromaffin cells.[21-23] In sensory neuron the inhibitory effect of ginseng extract or ginsenoside Rf on Ca^{2+} channels is mediated through pertussis toxin sensitive GTP-binding proteins. These results suggest that ginseng components have its own novel receptor or exert as modulator of GTP-binding proteins which are coupled to Ca^{2+} channels. A line of evidences also supports the involvement of GTP or GTP-binding proteins in the action of ginsenosides. For example, ginsenosides inhibit adenylate cyclase activity stimulated by guanosine monophosphate (GMP).[24] Ginsenoside Rb_2 and Rc also inhibit adenylate cyclase activity but their inhibitory effects were attenuated by addition of GTP.[25] In rat chromaffin cells ginsenoside Rc including Re, Rf, and Rg1 induced the decrease of membrane capacitance following stimulation besides Ca^{2+} channel inhibition. These results suggest that ginsenosides regulate the release of stress neurotransmitter such as epinephrine from adrenal gland in peripheral nervous system.[24] In long-term potentiation (LTP) induced by strong tetanus, ginsenoside Rb_1 attenuated the magnitude of LTP but ginsenoside Rb_1 did not affect the basal synaptic responses evoked by low-frequency stimulation. In contrast, malonylginsenoside Rb_1 facilitated the generation of LTP by the weak tetanus. These results provide the evidences that ginsenoside Rb_1 and malonoylginsenoside Rb_1 are involved in the activity-dependent synaptic plasticity in brain.[26]

5. The intestinal contractility

The effects of various ginsenosides on electrical- or ligand-stimulated guinea pig ileum or mouse vas deferens contraction were performed in the earlier studies, since this bioassay is the prototype for finding a new biologically active compounds. Before two decades, Saito *et al.* (1973) and Nabata *et al.* (1973) showed that crude ginseng saponins isolated from ginseng leaves or root inhibit the stimulated contraction of guinea pig ileum by histamine, acetylcholine, serotonin, and nicotine.[27,28] Kaku *et al* (1978). also reported that ginsenoside Rb_1, Rc, Rd, Re, Rf, and Rg_1 inhibit the acetylcholine-induced contraction in isolated guinea pig ileum.[29] Among them ginsenoside Re shows the strongest inhibitory effect for ACh-induced contraction. Interestingly, the inhibitory effect of ginseng saponins on the electrically stimulated contraction of guinea pig ileum is not blocked by opioid receptor antagonist naloxone. These results show that the action of ginsenosides is not mediated

via opioid receptor.[30] Furthermore, ginseng saponins (protopanaxatriol but not protpanaxadiol) suppressed the development of morphine tolerance in a dose dependent manner in guinea pig ileum but ginseng saponins (protopanxatriol) did not show the suppression of the development of morphine tolerance in mouse vas deferens.[31] In the experiments using rabbit jejunum, which shows the spontaneous contractility without exogenous electrical or chemical stimuli as mentioned above, protopanaxatriols but not protpanaxadiols exert main inhibition of the spontaneous contractility of rabbit jejunum.[32]

6. The central nervous system (CNS) and behavior

Ginseng saponins isolated from ginseng root and ginseng leaves showed the various effects on central nervous system such as CNS-depressant action by inhibition of spontaneous and exploratory movements,[33] analgesic, anticonvulsant, and antipyretic effects.[27,28]

In further experiments on analgesic effects of ginseng saponins, Shin *et al.* (1996) showed the evidences that ginseng saponins depress the tonic pains rather than acute pains through the formalin, tail-flick, and writhing tests.[32] On the other hand, Kim *et al* (1990). reported that the oral administration of standardized ginseng extract inhibit the development of morphine-induced tolerance and physical dependence[34], although this treatment does not antagonize morphine-induced analgesia.[35] On the other hand, Ramaro and Bhagava (1990) showed that ginseng saponins administered by intraperitoneal injection produces not only weak analgesia and hypothermia but also antagonize the analgesia by morphine in the range of 25~50 mg/kg.[36] They also show that ginseng saponins have the inhibitory activity on the development of tolerance.[37]

In addition of the antagonism of ginseng saponins against morphine induced-tolerance to pain, Kim *et al.* (1995) also found that the pretreatment of total ginseng saponins not only attenuated cocaine-induced hyperactivity and conditioned place preference but also blocked methamphetamine-induced reverse tolerance and dopamine receptor supersensitivity.[38-40] It is possible to use ginseng as "an antidote" against various abused drugs. However, the exact antinarcotic mechanism is not known and requires more investigations.

As a psychotropic effect, ginseng saponins and ginsenoside Rb_1 show the suppression of aggressive action against intruder with dose-dependent manner as well as show the suppression of maternal aggression.[41,42] Ginseng saponins are also effective in stress-induced behavioral and physiological changes through their action on adrenocortical function.[43-45]

Antitumor activity

The efficacy of ginseng against cancer is known for a long time. But it is not known until now that which components of ginseng are effective for anticancer. Recently, *in vitro* experiments both ginsenoside Rh_2 and its aglycone (deglycosylation of Rh_2) are incoporated into cell membrane fraction and the growth of B16 melanoma cell was inhibited. The inhibitory effect by Rh_2 deglycosylated on the cell growth is stronger than that of ginsenoside Rh_2.[46] Besides the inhibition of B16 melanoma cell line, ginsenoside Rh_2 also inhibits the growth and proliferation of human ovarian cancer cell.[47] Furthermore, oral administration of ginsenoside Rh_2 induces the inhibition of human ovarian cancer cell mass growth inoculated into nude mice and prolongs survival time compared with untreated mice.[47] Ginsenoside Rh_2 also induce the differentiation of B16 melanoma cell and stimulates melanogenesis. However, ginsenoside Rh_1 does not inhibit the growth of B16 melanoma but stimulates melanogenesis.[48] Interestingly, ginsenoside Rh_2 shows the antimutagenesis effects by inhibiting the formation of sister chromatid exchanges, which is a sensitive indicator of DNA damage and has a correlationship with mutagenic activity of various chemicals induced by mutagens in human lymphocytes.[49] Furthermore, it

was also reported that the differentiation induced by both ginsenoside Rh_1 and ginsenoside Rh_2 is mediated via glucocorticoid receptors in F9 teratocarcinoma cells.[50]

Cardiovascular system

1. Antiplatelet action

Ginseng saponins or lipophilic components of ginseng show antiplatelet or antithrombin activity. In human platelets ginsenosides Rg_1 and Rd inhibit adrenalin- and thrombin-induced platelet aggregation as well as the release of 5-HT in the presence of fibrinogen but ginsenoside Rg_1 does not affect adrenaline- and thrombin-induced arachidonic acid release and diacylglycerol production.[51] Interestingly, ginsenoside Rg_1 also reduced the cytoplasmic free Ca^{2+} elevation induced by adrenalin and thrombin.[51] Teng *et al.* (1989) showed that panaxynol isolated from the diethyl ether layer of ginseng inhibits the aggregation of platelets induced by collagen, ADP, arachidonic acid, ionophore A23187, and thrombin but other ginsenosides have no effects. The inhibitory effect of on platelet aggregation by panaxynol is dependent on the incubation time. Panaxynol also inhibits the formation of thromboxane B stimulated by arachidonic acid, collagen, thrombin, and ionophore A23187 as well as reduces the cytoplasmic free Ca^{2+} elevation.[52] In addition, Park *et al.* (1995) showed that petroleum ether extract (lipophilic components of ginseng) inhibits the formation of the thromboxane A_2 stimulated by thrombin but also increase cGMP level by about three times compared to only thrombin treated platelets.[53]

2. Blood vessel and blood pressure

There are not many papers on regulations of blood pressure and heart activity by ginseng saponins or ginsenosides, although it is believed that ginseng is used for antihypertension or other heart-blood vessel related diseases. Recently, the administration of ginsenoside Rg_1 with intravenous injection induces the prolongation of ventricular refractoriness and repolarization in the experiments using dog.[54] Chen *et al.* (1984) reported that ginseng total saponins antagonize norepinphrine- or PGE_{2A}-induced contraction of rabbit pulmonary and intrapulmonary arteries.[55] Similarly, in rat the administration of various ginsenosides mixture also lowers blood pressure. These ginsenosides relaxed the aorta contracted by phenylephrine in the presence of endothelium and stimulate the formation of cGMP. The effects of ginsenosides on the relaxation of aorta and cGMP production are attenuated by the treatment with NO synthase inhibitor such as methylene blue or N-G-monomethyl-L-arginine.[56] In addition, ginseng saponins inhibit the vasoconstriction induced by thromboxane analogs, U 46619. Furthermore, ginseng total saponins also protect the electrolysis-induced pulmonary edema, which is derived by free radical production by electrolysis. On the other hand, Kang *et al.* (1995) reported that protopanxatriol and ginsenoside Rg_1 but not protopanxadiol and ginsenoside Rb_1 induce the relaxation of rat aorta with endothelium-dependent manner. They found that the mechanism of protopanaxatriol or ginsenoside Rg_1-induced aorta relaxation is through the production of nitric oxide (NO) and cGMP.[57,58]

Liver and metabolism

It is believed for a long time that ginseng or ginsenosides have the antidiabetic effect. Therefore, they are used for the alleviation of diabetes in folk medicine. In fact, maltol and panaxan, which are trace components of ginseng, show hypoglycemic activity in normal and diabetic animals.[1] In addition, ginsenoside Rb_2 also show the various effects related with metabolism of carbohydrates, lipids, and proteins in diabetic animal. For example, ginsenoside Rb_2 lowers blood glucose level and increases glycolysis, lipogenesis, and serum protein synthesis, and enhances protein synthesis in the subcellular protein synthesis in hepatic tissue.[59-62] Ginsenoside Rb_2 also increased nitrogen retention in the body.[63] In di-

abetic state, ATP content usually goes down, whereas AMP content increases, resulting in lowered energy charge. With various effects of ginsenoside Rb_2 in metabolism as mentioned above, the administration of ginsenoside Rb_2 gets back ATP content to normal level so that energy charge reaches normal condition.

On the other hand, ginsenoside Rg_1 stimulates enzyme activity of tyrosine aminotransferase, which converts ρ-hydroxyphenylpyruvic acid to tyrosine, in cultured hepatocytes. The enzyme is involved in protein metabolism and is induced by various hormones such as insulin, glucagon, adrenal corticoid hormones. Interestingly, the stimulatory effect of ginsenoside Rg_1 on tyrosine aminotransferase activity is attenuated by treatment of mifepristone, a high affinity glucocorticoid receptor antagonist.[64] Furthermore, Kang *et al.* (1994) showed that ginsenoside Rg_1 regulates the transcription of tyrosine aminotransferase gene in cultured hepatocytes.[65] The induction of tyrosine aminotransferase gene transcription reaches at maximum after 1 hour treatment of ginsenoside Rg_1 and dexamethasone. The induction gets back to control level after 3 hours. Both ginsenoside Rg_1 and dexamethasone treatment together do not show additive or synergistic effect on the induction of this gene transcription. This results suggest that the binding of both agents were probably saturated. Both effects on the induction of tyrosine aminotransferase gene transcription is partially blocked by mifepristone. This result suggests that both ginsenoside Rg_1 and dexamethasone use same signal pathway for the induction of this gene transcription, although the receptors for them may be different since mifepristone is less specific to distinguish glucocorticoid receptors from other steroid hormone receptor.[64, 65]

Discussion and Future Prospects

In the begining of ginseng study it seems that the main topics were on the efficacies of ginseng as a tonic, antidiabete, anticancer, antihypertension, and antiaging related with clinical or public health following the traditional medicine. During that time ginsenoside Rb_1 and ginsenoside Rg_1 were mainly used. With advance of techniques isolating minor ginsenosides the number of paper reporting the effects on other components of ginseng were increasing. Moreover, with advances of life science the researches using ginseng saponins also have been done on the more cellular and molecular level including the signal transduction pathway of ginseng saponins. For example, a particular single cell recordings using electrophysiogical technique provide us a basis to explain the entire organ or a biological system occuring after treatment of ginseng saponins.[21-23] The application of molecular biology also gave us chances to check the changes of gene regulations following ginseng saponins treatments.[65]

The ability that ginseng saponins has various biological effects as mentioned above still give us an open question on "how do ginseng saponins their job in a living cell or body", since the mechanism of ginsenoside action is not yet known and specific biological effects have not been ascribed to any one ginseng component. However, several research results to date make an answer possible on this question with at least several possibilities. One is that ginsenosides own their novel specific binding proteins (receptors). Some evidences support this possibility. Recently, ginsenoside Rf inhibits voltage-dependent Ca^{2+} channel mediated through pertussis toxin-sensitive GTP-binding protein.[21,22] The effects of ginsenosides on enzyme activity are also regulated by GTP or GMP concentration.[24,25] Other examples are that the induction of differentiation of F9 teratocarcinoma cell by ginsenoside Rh_1 and Rh_2 and the stimulatory effect of ginsenoside Rg_1 on the induction of tyrosine aminotransferase gene transcription is partially blocked by treatment of mifepristone (RU486), respectively which has relatively high affinity on glucocorticoid receptor.[50,64] These results show the possibility that ginsenoside Rh_1, Rh_2, or Rg_1 interact with glucocorticoid receptor as a partial

agonist or as subtypes of other steroid receptors. Interestingly, those reports also suggest that different ginsenoside possesses different signal transduction pathway as well as different location of binding site.

Second is that ginsenosides bind or interact with a portion of $GABA_A$, or nicotinic receptor complex coupled ligand-gated channels. Their binding to portion of ligand-gated channels not only affect ionic flux but also influence the affinity of the ligands to their receptors.[17, 20]

Third is that ginseng saponins or ginsenosides are just doing their job as second messenger antagonists like Ca^{2+} antagonist[11] or as release promotors of nitric oxide (NO) in smooth muscle, or are doing their job by inhibiting enzymes which are involved second messenger metabolism such as cAMP or cGMP.[53, 57] These regulations by ginsenosides in sequence influence the effector system following the physiological responses such as relaxation of blood vessel, antiplatelet activity, or modulation of neurotransmitter release.

When scientists observe so many actions of ginsenosides as mentioned above, they will have a curiosity. Are there any known compounds or biological systems having similar physiological or pharmacological effects or functions with ginsenosides? If there is a certain similar system, it can give us a lot of helps to explain the action of ginsenosides. Comparing the action of ginsenosides or ginseng saponins with already known biological compounds, opioid can be one of candidates with several evidences particularly in nervous system, although ginsenosides have a similar chemical structure with steroid. For example, both ginsenosides and opioids are good antistress agents. Opioids probably make people feel good or good mood, whereas ginsenosides may make people less stressful by regulating the release of stress hormones from adrenal glands or by increasing the release of ACTH from pituitary gland.[15, 17, 23] Second is that although opioids are much stronger analgesic agent than ginsenosides, both compounds have analgesic effects with probably different pain control pathway. Opioids usually induce analgesia by acting both peripheral nervous system and central nervous systems such as spinal cord or supraspinal level. Ginseng saponins or ginsenoside Rf not only inhibit Ca^{2+} channel activity of sensory neurons involved in peripheral pain pathway but also induce analgesia in several common algesiometric assays using experimental animals.[32]

Additional evidence for the interaction of a ginseng saponins with opioid's pain modulatory systems comes from the observation that ginsenosides can attenuate opioid antinociception and opioid tolerance.[34, 37] Third is that both compound inhibit the intestinal contractility. However, the inhibitory effect of ginsenosides is slow and does not induce desensitization of intestinal contractility, whereas the inhibitory effect of opioid is rapid and desensitized soon. However, the presence of ginsenosides suppresses the desensitization or tolerance induced by opioid.[31, 32] The evidences show that ginsenosides do not act through opioid receptor and just show similar pattern of action with opioids.

Although we look at the variety of effects of ginsenosides (ginseng saponins) reaching out whole physiology or pharmacology, many papers on ginseng are fragmentory and it is not easy for us to still draw or figure out a clear lines or schemes of ginseng action. It could derive that the study using ginseng saponins does not continue and stop in the middle. For the elucidation of ginseng's action or for making more advance ginseng study in future, we need the better suitable assay system with ginseng saponins but there are still several problems to solve. First, ginsenosides are not common materials to use and too expensive to buy with large quantity, since it is not easy to synthesize them and it is only isolated or purified from ginseng. It is not easy to obtain isotope-labelled ginsenoside (s) with these conditions. This also makes binding study difficult. Second, in most studies the amount of ginsenosides or concentration used is relatively high. That means that the affinity of ginsenosides to their binding site (s) is not high

even if ginsenoside receptors or bindig proteins exist in biological system. Therefore, it needs to modify ginsenosides or find synthetic analogs (i.e. synthetic ginsenoside agonist or antagonist) with high affinity. Third, many people with herbal medicine still believe that ginseng is not doing its job as a single component but ginseng is doing rather its job as a complexes with other compounds.[66]

요 약

인삼은 동양의 전통 의약으로서 잘 알려져 있다. 인삼 성분중에 진세노사이드 혹은 인삼 사포닌이 생물학적으로 활동성이 있는 물질로 알려진이래, 진세노사이드가 생리학적, 약리학적 및 행동에 미치는 영향에 대한 연구 보고들이 매년 늘고있다. 본 총설에서는 그동안 연구잡지에 발표된 논문들을 중심으로 요약하였다. 따라서 본 내용은 인삼사포닌이 신경세포성장, 실험동물의 행동, 효소의 활동성, 신경전달물질의 방출과 재흡수, 신경세포의 흥분과 이온채널, 장의 운동성, 항암, 심장 혈관계및 대사에 미치는 영향에 대하여 기술하였다. 현재까지 인삼사포닌이 여러 종류의 세포와 기관에 미치는 영향에도 불구하고, 아직 인삼 사포닌의 작용기전을 명확하게 설명하는 것은 불가능하다. 그러나 최근에 인삼사포닌 처리시 세포에서 일어나는 신호전달 과정과 인삼사포닌의 생리·약리학적 작용을 설명할 수 있는 논문들이 발표되었다. 앞으로 인삼사포닌에 의한 세포수준 혹은 분자수준에서의 작용기전이 밝혀질 경우 인삼이 왜 오랫동안 영약으로서 이용되어 왔는지가 밝혀질것이고, 더 중요한 것은 인삼을 현대 의약품으로 적용할 수 있는 중요한 계기를 제공할 것이다.

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