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Insights into the Pharmacological Effects of Soy Isoflavones on Catecholamine System

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1. Introduction

Natural estrogens have a wide array of biological actions not only on the female reproductive system but also on metabolic homeostasis, cell proliferation and differentiation. The long-term genomic effects of estrogens are known to be mediated through classical nuclear receptors such as estrogen receptor-α (ER-α) and -β (ER-β) (Green et al., 1986; Krust et al., 1986; Mosselman et al., 1996). In addition to this established mechanism of action, much evidence has been accumulated that estrogens also have non-genomic actions via the activation of plasma membrane estrogen receptors (Wehling 1997; Falkenstein et al., 2000). Indeed, the cell membrane estrogen receptors have been extensively studied, resulting in the identification of several types of membrane estrogen receptors, such as ER-α, its S-palmitoylated ER variant (Li et al., 2003; Wyckoff et al., 2001), ER-X (Toran-Allerand et al., 2002; Qui et al., 2006), and GPR30 (Thomas et al., 2005; Revankar et al., 2005). Among these, GPR30 may be the most plausible candidate for a membrane estrogen receptor that regulates the various functions induced by estrogens (Funakoshi et al., 2006; Filardo et al., 2007), although the precise cellular localization and functions of GPR30 remain controversial (for review see, Mizukami 2010).

Soybeans have traditionally been consumed as food, especially in East Asian countries. Isoflavones such as daidzein and genistein are soy phytoestrogens and have a weak estrogenic activity due to the fact that their structures are similar to the primary structure of estrogens (Kurzer and Xu, 1997). Recent research attention has been paid to the high dietary intake of isoflavones because of their potentially beneficial effects associated with a reduction in the risk of developing cardiovascular diseases (Arjmandi et al., 1997), osteoporosis (Adlercreutz et al., 1993; Toda et al., 1999), menopausal symptoms (Adlercreutz et al., 1992), and some forms of cancers (Messina et al., 1994). These effects are considered to be mediated by binding to the nuclear estrogen receptors (Kurzer and Xu, 1997; Murkies et al., 1998).

Adrenal medullary cells are derived from the embryonic neural crest and share many properties with sympathetic postganglionic neurons. In cultured bovine adrenal medullary

cells, our previous studies have shown that carbachol, a derivative of acetylcholine, induced $^{22}Na^+$ influx via voltage-dependent Na^+ channels, and then increased $^{45}Ca^{2+}$ influx via voltage-dependent Ca^{2+} channels, a prerequisite for secretion (Wada et al., 1985; Yanagihara et al., 1996) and synthesis (Yanagihara et al., 1987) of catecholamines. Since the mechanism of stimulation of catecholamine synthesis and secretion in adrenal medullary cells are thought to be similar to those of noradrenaline in the sympathetic neurons, adrenal medullary cells have provided a good model for detailed analysis of the actions of cardiovascular drugs, such as α_2-adrenergic agonists (Yanagihara et al., 1987), natriuretic peptides (Yanagihara et al., 1991), carvedilol (Kajiwara et al., 2002) and pimobendan (Toyohira et al., 2005).

In our previous studies, treatment of bovine adrenal medullary cells with environmental estrogenic pollutants such as p-nonylphenol and bisphenol A stimulated catecholamine synthesis and tyrosine hydroxylase activity, probably through plasma membrane estrogen receptors (Yanagihara et al., 2005). Indeed, we demonstrated the occurrence and functional roles of unique estrogen receptors in the plasma membranes isolated from bovine adrenal medullary cells (Yanagihara et al., 2006). 17β-Estradiol stimulated catecholamine synthesis via activation of extracellular signal-regulated kinases (ERKs) through the plasma membrane estrogen receptors.

The present review summarizes the current knowledge of pharmacological effects of daidzein and genistein on catecholamine signaling, such as catecholamine synthesis and secretion in cultured bovine adrenal medullary cells and noradrenaline reuptake by SK-N-SH cells and by COS-7 cells transiently transfected with noradrenaline transporter.

2. Dual effects of daidzein on catecholamine synthesis and secretion

Incubation of bovine adrenal medullary cells with daidzein for 20 min resulted in a small increase in ^{14}C-catecholamine synthesis from [^{14}C]tyrosine (Fig. 1A). The stimulatory effect of daidzein on ^{14}C-catecholamine synthesis was observed to be concentration-dependent (10-1000 nM). Daidzein inhibited the specific binding of [^3H]17β-estradiol in a concentration (10-1000 nM)-dependent manner (Fig. 1B) similar to that of ^{14}C-catecholamine synthesis. From these results, it is likely that daidzein stimulates catecholamine synthesis via activation of membrane estrogen receptors in bovine adrenal medullary cells. Previous studies have shown that the serum concentrations of daidzein are around 200-350 nM in Japanese people older than 40 years (Morton et al., 2002) and that the serum levels of daidzein in humans consuming three meals per day, including one meal containing soybeans, can reach a maximum of 4.1 μM (King and Bursill, 1998). It seems that the concentrations of daidzein used in the present study are relevant in people's daily lives because these concentrations partially overlap with those in the plasma of individuals who consume soy products.

Daidzein (1 μM) and acetylcholine (0.3 mM) increased ^{14}C-catecholamine synthesis form [^{14}C]tyrosine by 31% and 245% over the control levels, respectively (Fig. 2A). Concurrent treatment of cells with daidzein and acetylcholine did not enhance but significantly inhibited the stimulatory effect of acetylcholine on ^{14}C-catecholamine synthesis (84% of acetylcholine). To determine which step of catecholamine synthesis was enhanced by daidzein, [^{14}C]DOPA was used as a substrate instead of [^{14}C]tyrosine (Fig. 2B). Neither daidzein nor acetylcholine increased ^{14}C-catecholamine synthesis from [^{14}C]DOPA, suggesting that the increase in catecholamine synthesis induced by daidzein and acetylcholine occurs predominantly upstream of the DOPA decarboxylase step, i.e., tyrosine hydroxylase step. Indeed, incubation of cells with daidzein (1 μM) for 10 min resulted in a significant increase in tyrosine

hydroxylase activity of 27% over the control (Fig. 3B). ICI182,780 (100 nM), an inhibitor of nuclear estrogen receptors when used alone, increased ^{14}C-catecholamine synthesis as well as tyrosine hydroxylase activity, and did not abolish but rather enhanced both stimulatory effects of daidzein (Fig. 3A and B). Furthermore, ICI182,780 enhanced the specific binding of [^{3}H]17β-estradiol to plasma membranes isolated from bovine adrenal medulla (data not presented). This gives rise to the possibility that daidzein and ICI182,780 act synergistically on different sites of the membrane estrogen receptors.

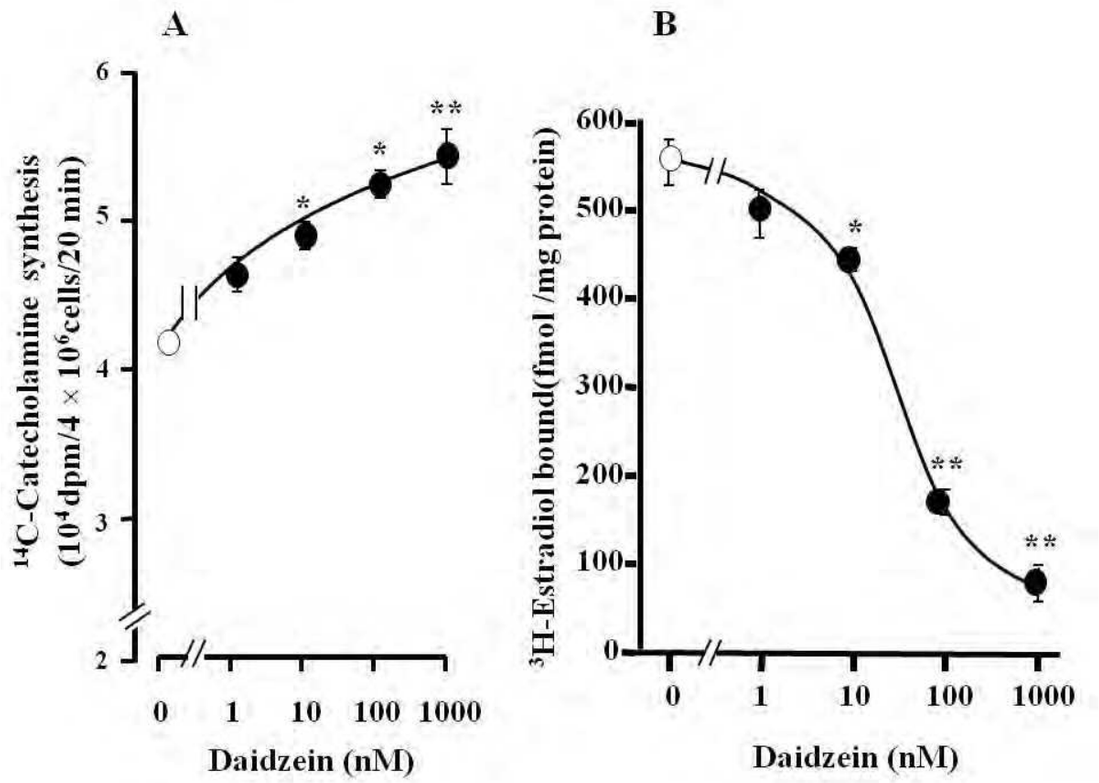


Fig. 1. Concentration–response curve of daidzein for ^{14}C-catecholamine synthesis from [^{14}C]tyrosine in cultured bovine adrenal medullary cells (A) and concentration-inhibition curve for specific binding of [^{3}H] 17β-estradiol to adrenal medullary plasma membranes (B). (A) Cultured bovine adrenal medullary cells (4x10^6 / dish) were incubated with (●) or without (○) various concentrations (1 – 1000 nM) of daidzein at 37 °C for 20 min in 1.0 ml KRP buffer containing L-[U-^{14}C]tyrosine (20 μM, 1 μCi). The ^{14}C-labeled catecholamines formed are measured and shown as the total ^{14}C-catecholamines (adrenaline, noradrenaline and dopamine). Date are expressed as the mean ± SEM of four experiments carried out in duplicate. *p < 0.05 and **p < 0.01, compared with control. (B) Plasma membranes isolated form bovine adrenal medulla were incubated at 4 °C for 30 min with various concentrations of daidzein in the presence of [^{3}H]17β-estradiol (5 nM, 0.1 μCi). Non-specific binding was determined in the presence 1 μM of 17β-estradiol and specific binding was obtained by subtracting non-specific binding from total binding. Values shown are means ± SEM of four separate experiments carried out in triplicate. *p < 0.05 and **p < 0.01, compared with control. Data from Liu et al. (2007) are modified.

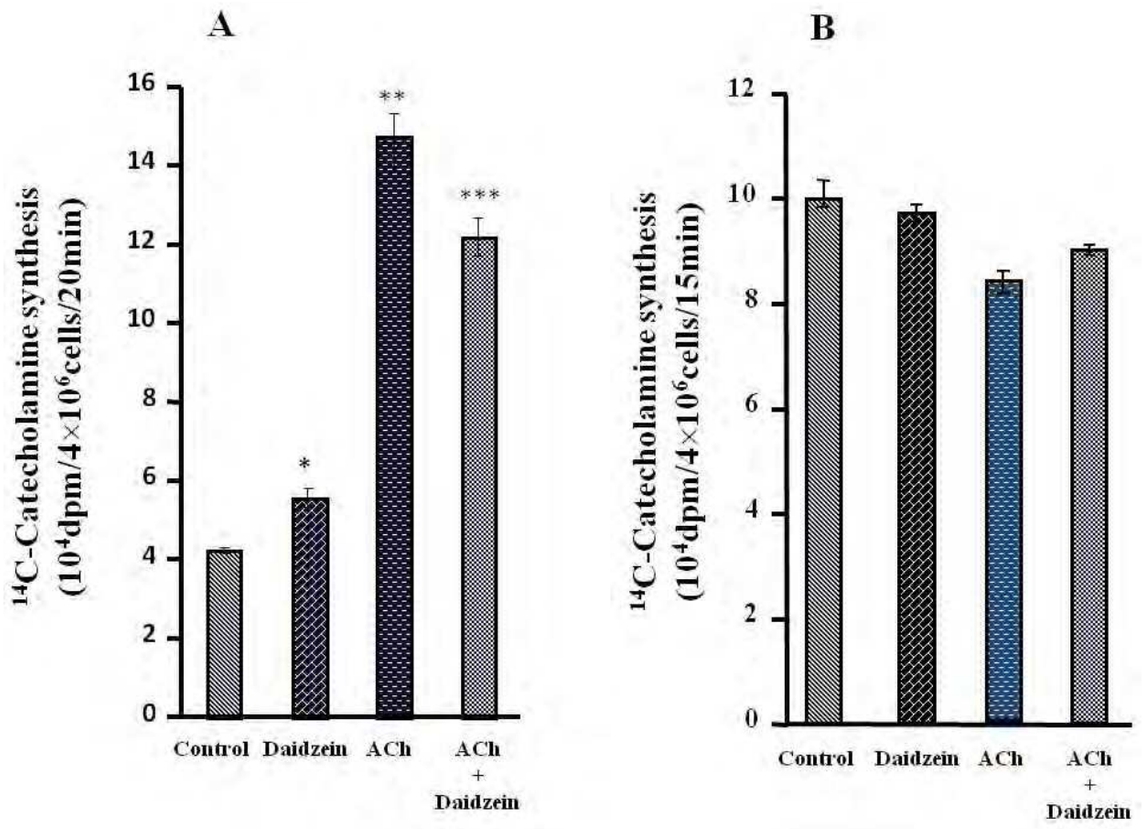


Fig. 2. Effects of daidzein on ^{14}C-catecholamine synthesis from [^{14}C]tyrosine (A) or [^{14}C]DOPA (B). The cells (4 x10^6/dish) were incubated with or without daidzein (1 μM) and acetylcholine (ACh)(0.3 mM) at 37 ˚C for 20 min or 15 min in the presence of L-[U-^{14}C]tyrosine (20 μM, 1 μCi) (A) or [^{14}C]DOPA (20 μM, 0.25 μCi) (B), respectively. The ^{14}C-catecholamines formed were measured. Data are expressed as the mean ± SEM of four experiments carried out in triplicate. *p < 0.05 and **p < 0.01, compared with control; ***p < 0.05, compared with acetylcholine alone. Data from Liu et al. (2007) are modified.

We next studied the effect of daidzein on catecholamine secretion induced by acetylcholine. The catecholamine secretion induced by acetylcholine corresponded to 13.5% of the total catecholamine content in the cells. Daidzein (1, 10, and 100 μM) significantly suppressed catecholamine secretion induced by acetylcholine to 94%, 88%, and 64% of that by acetylcholine alone (Fig. 4), respectively. These findings suggest that daidzein has dual effects on catecholamine synthesis and secretion, i.e., at low concentrations (10-100 nM) daidzein activates tyrosine hydroxylase activity and stimulates catecholamine synthesis, but at high concentrations (≧1 μM) it attenuates catecholamine synthesis and secretion induced by acetylcholine.

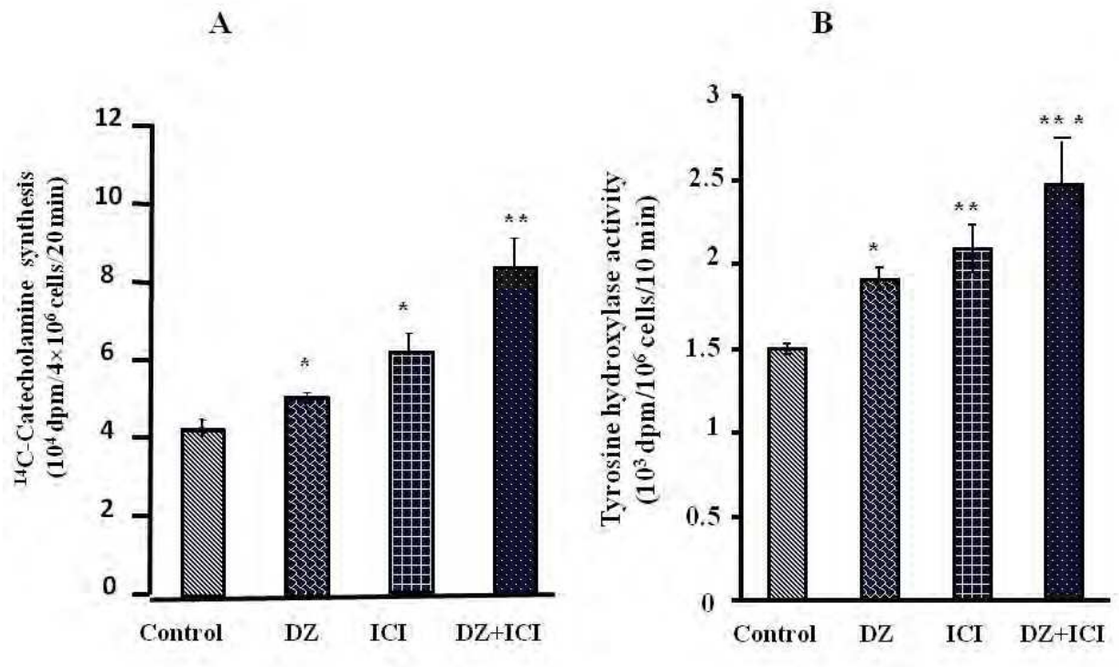


Fig. 3. Effects of daidzein and/or ICI182,780, an inhibitor of classical nuclear estrogen receptors, on ^{14}C-catecholamine synthesis (A) and tyrosine hydroxylase activity (B). (A) The cells (4x10^6/dish) were incubated with or without daidzein (DZ) (1 μM) and/or ICI182,780 (ICI) (100 nM) at 37 °C for 20 min in the presence of L-[U-^{14}C]tyrosine. Data are expressed as the means ± SEM of four experiments carried out in triplicate. *p < 0.05, compared with control; **p < 0.05, compared with daidzein alone. (B) Cells (10^6/well) were preincubated in 250 μl of KRP buffer with or without (1 μM) daidzein and/or ICI182,780 (100 nM) for 10 min and then incubated for another 10 min in the presence of L-[1-^{14}C]tyrosine (18 μM, 0.2 μCi), and tyrosine hydroxylase activity was measured. Data are the mean ± SEM of four separate experiments carried out in triplicate. *p < 0.05 and **p < 0.01, compared with control; ***p < 0.05, compared with daidzein. Data from Liu et al. (2007) are modified.

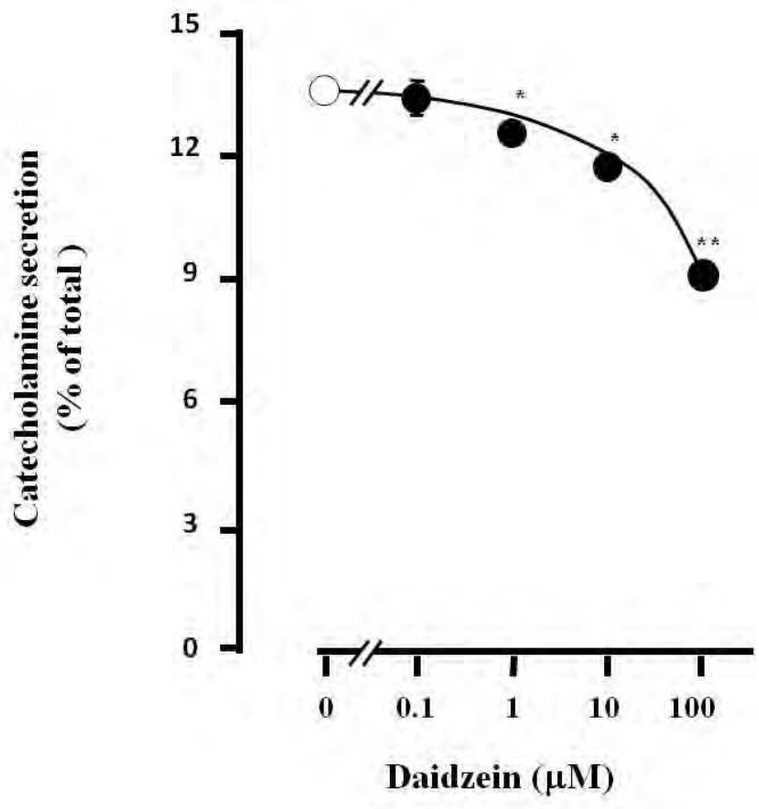


Fig. 4. Effects of daidzein on catecholamine secretion induced by acetylcholine in bovine adrenal medullary cells. Cells ($2x10^6$/dish) were incubated with acetylcholine (0.3 mM) in the presence (●) or absence (○) of various concentrations (0.1-100 μM) of daidzein for 10 min at 37 °C. Catecholamines secreted into the medium were measured, and expressed as percentage of total catecholamines. Data are means ± SEM of four experiments carried out in duplicate. *p <0.05, compared with control (0 μM daidzein). Data from Liu et al. (2007) are modified.

3. Up-regulation of noradrenaline transporter function by genistein

Treatment of SK-N-SH cells (a human neuroblastoma cell line) with genistein, another soy isoflavone, for 20 min stimulated [^{3}H]noradrenaline uptake by the cells in a bell-shaped concentration-dependent manner (0.1-10 μM), whereas neither daidzein nor cumestrol, another phytoestrogen, did so (Fig. 5A). Genistein (0.01-10 μM) also stimulated [^{3}H]noradrenaline uptake by COS-7 cells transiently transfected with noradrenaline transporter (Fig.5B). In Japanese middle-aged women, the dietary intake of genistein was reported to be 111.6 μmol/day/capita (30.1 mg/day/capita), and the median plasma concentration of genistein was 206 nM (Arai et al., 2000). Since Asian individuals generally consume more soy foods than do people in developed Western countries, the mean concentrations of genistein in Japanese and UK men were 493 nM and 33 nM, respectively (Morton et al., 2002). Furthermore, a previous paper (Adlercreutz et al., 1993) reported that the plasma concentration of genistein exceeded 2400 nM in one Japanese man. Therefore, it

seems that the genistein concentrations used in the present study are nutritionally (or pharmacologically) relevant.

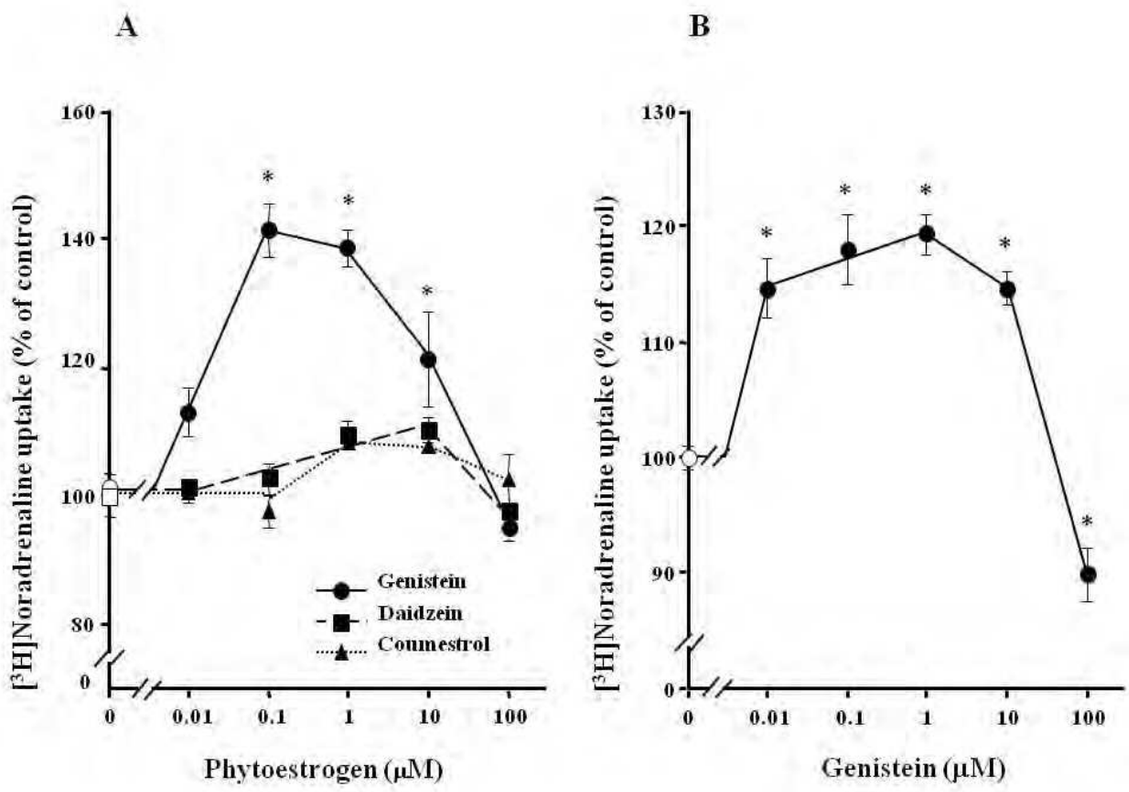


Fig. 5. Effects of various phytoestrogens on [^{3}H]noradrenaline uptake by SK-N-SH cells (A) and COS-7 cells transfected with bovine noradrenaline transporters (B). (A) SK-N-SH cells were pretreated for 20 min with or without various concentrations (0.01 – 100 μ M) of genistein (●), daidzein (■), or coumestrol (▲), and then incubated for another 10 min with [^{3}H]noradrenaline (0.1 μM, 0.1 μCi) in the presence or absence of phytoestrogens (0.01 - 100 μM). Results are presented as percentage of control values (62.3 ± 4.2 fmol/10^6 cells/min). Data are means ± SEM from three separate experiments. *p < 0.05, compared with control. (B) The bovine noradrenaline transporter transfected COS-7 cells were pretreated for 20 min with various concentrations of genistein (0.01 – 100 μM), and then the desipramine-sensitive uptake of [^{3}H] noradrenaline by the cells was measured. *p < 0.05, compared with control. Data from Toyohira et al. (2010) are modified.

From Eadie-Hofstee analysis of [^{3}H] noradrenaline uptake, genistein (10 μM) caused a significant increase in the maximal velocity (V_{max}) of noradrenaline transport with little change in the Michealis-Menten constant (K_m) value (Fig. 6A). Scatchard analysis of [^{3}H]nisoxetine binding to COS-7 cells transiently transfected with noradrenaline transporter showed that genistein increases the maximal binding (B_{max}) without any change in the dissociation constant (K_d) (Fig. 6B).

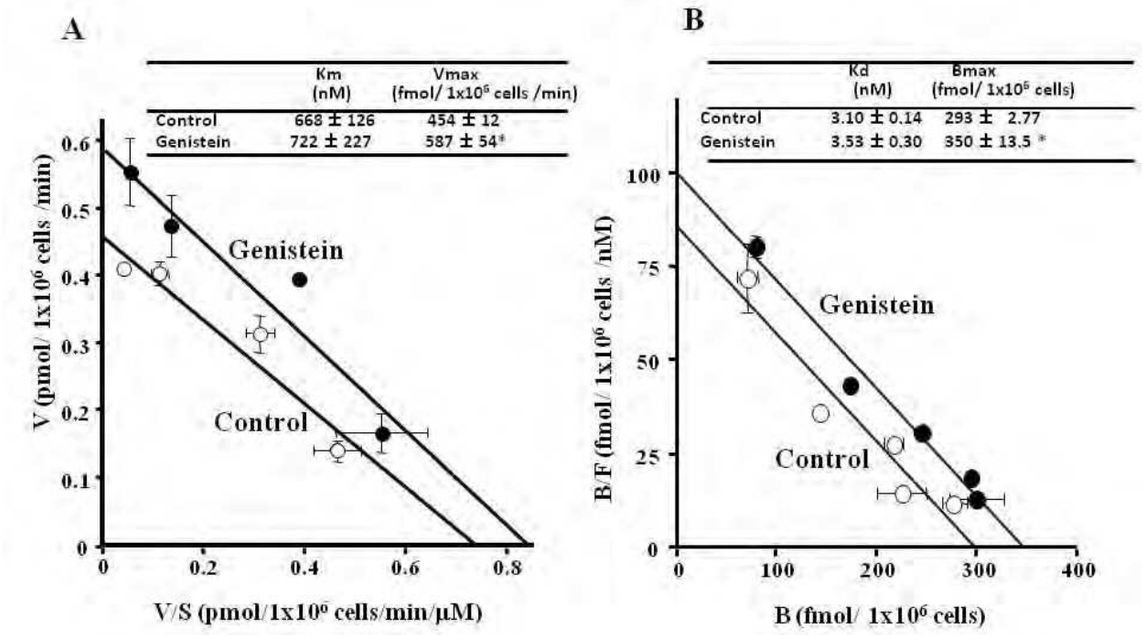


Fig. 6. Eadie-Hofstee plots of [^{3}H] noradrenaline uptake (A) and Scatchard plots of specific [^{3}H]nisoxetine binding (B) in bovine noradrenaline transporter transfected COS-7 cells. (A) Cells were pretreated with or without genistein (10 μM) for 20 min at 37 ˚C. Desipramine-sensitive [^{3}H] noradrenaline uptake was measured with various concentrations (0.1 - 10 μM) of [^{3}H] noradrenaline and analyzed by Eadie-Hofstee method of [^{3}H] noradrenaline uptake. Data are means ± SEM from three separate experiments. Inset: V_{max} and K_m values were calculated by Eadie-Hofstee analysis of the saturation curves in the absence (control) or presence of 10 μM genistein. *p < 0.05, compared with control. (B) The bovine noradrenaline transporter transfected COS-7 cells were incubated with increasing concentrations of [^{3}H]nisoxetine (1 - 24 nM) in the presence or absence of genistein (10 μM) at 4 ˚C for 2 h. Non-specific binding was determined in the presence of 10 μM nisoxetine. The specific binding was 30-40% of the total binding at the K_d concentration of [^{3}H]nisoxetine. The data are plotted by Scatchard plot analysis of the saturation curves of [^{3}H]nisoxetine specific binding in the absence (control) or presence of 10 μM genistein. Data are means ± SEM from three separate experiments. *p < 0.05, compared with control. Data from Toyohira et al. (2010) are modified.

To test the involvement of nuclear estrogen receptors (ER-α and ER-β) in the stimulatory effect of genistein on noradrenaline transport, we used ICI182,780, an inhibitor of both ER-α and ER-β. COS-7 cells transfected with noradrenaline transporters were preincubated with ICI182,780 (100 nM), and then incubated for another 10 min with [^{3}H]noradrenaline in the presence or absence of genistein (100 nM) or 17β-estradiol (100 nM). ICI182,780 by itself stimulated [^{3}H]noradrenaline uptake by the cells (data not presented). ICI182,780 did not suppress but rather enhanced genistein-induced [^{3}H]noradrenaline uptake. Sodium orthovanadate (50 μM), an inhibitor of protein tyrosine phosphatase, significantly inhibited [^{3}H]noradrenaline uptake (data not shown). Although genistein is known to be an inhibitor of tyrosine kinases, daidzein, an inactive analogue of genistein against tyrosine kinase, had little effect on [^{3}H]noradrenaline uptake by SK-N-SH cells (Fig. 5A), suggesting an involvement of tyrosine kinase, but not of membrane estrogen receptors. Furthermore, the

stimulatory effects on [^{3}H]noradrenaline uptake were observed by treatment with tyrophostin 25, an inhibitor of epidermal growth factor receptor tyrosine kinase (Fig. 7A), whereas PP2, an inhibitor of the soluble-type src-family of tyrosine kinases, did not affect it (Fig. 7B). From these findings, it is suggested that genistein increases the activity of noradrenaline transporter, probably through processes involving receptor-type protein tyrosine phosphorylation.

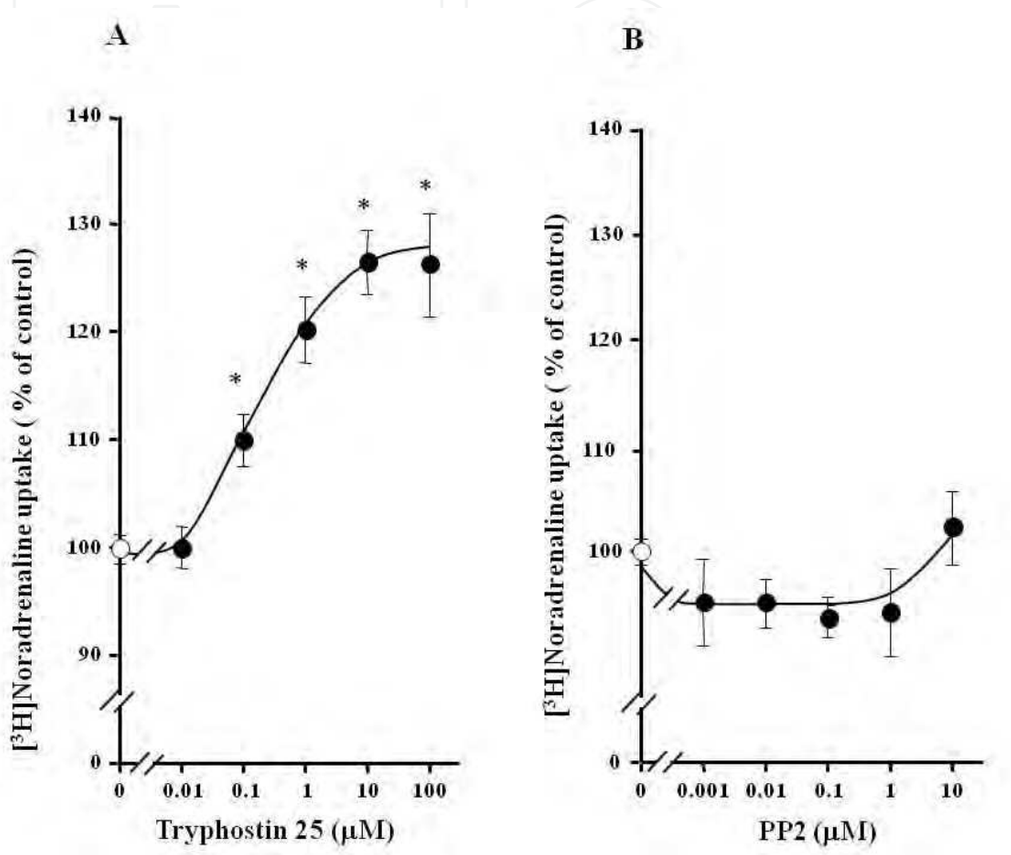


Fig. 7. Effects of tyrphostin 25 (A) or PP2 (B) on [^{3}H] noradrenaline uptake by COS-7 cells transfected with bovine noradrenaline transporters. The bovine noradrenaline transporter transfected COS-7 cells were pretreated for 20 min with tyrphostin 25 (0.01 – 100 μM) (A) or PP2 (0.001 – 10 μM) (B), and then the desipramine-sensitive uptake of [^{3}H] noradrenaline by the cells was measured. Results are presented as percentage of control values. Data are means ± SEM from three separate experiments. *p < 0.05, compared with control. Data from Toyohira et al. (2010) are modified.

4. Pharmacological significance of soy isoflavone's effects on catecholamine system

Soy isoflavones (daidzein and genistein) are present at high concentrations as a glycoside in many soybeans and soy foods such as miso, tofu, and soy milk. Several lines of accumulating evidence have indicated that soy isoflavones play a role in the prevention of cardiovascular diseases, reproductive cancers, and menopausal symptoms (Potter et al.,

1998; Cassidy et al., 1999; Upmalis et al., 2000; Ishimi et al., 1999). The cardioprotective ability of these isoflavones has been attributed partially to their ability to lower cholesterol (Wong et al., 1998; Yamakoshi et al., 2000) and cardiovascular disease risk (Lichtenstein 1998). In the present review, daidzein (0.01-1.0 μM) stimulated catecholamine synthesis by 20~30% over the control, suggesting that daidzein at nutritionally relevant concentrations strengthens the catecholamine system in the adrenal medulla and probably in the sympathetic neurons.

On the other hand, daidzein at high concentrations (over 1.0 μM) suppresses catecholamine synthesis and secretion induced by the physiological secretagogue acetylcholine, suggesting that daidzein attenuates the catecholamine synthesis and secretion induced by stress and emotional excitation, thus causing the stimulation of sympathetic nerves and the adrenal medulla. Genistein up-regulates the noradrenaline transporter function. This suggests that genistein also stimulates the termination of neurotransmission by the reuptake of noradrenaline released into the extracellular milieu and suppresses the sympathetic nerve activity. Although catecholamines play a pivotal role in the regulation of normal functions in cardiovascular systems, prolonged stress-induced over-expression of endogenous catecholamines may contribute to the involvement and augmentation of cardiovascular diseases such as heart failure, atherosclerosis, coronary heart disease, and hypertension. Indeed, chronic heart failure is associated with activation of the sympathetic nervous system as manifested by increased circulating catecholamines and increased regional activity of the sympathetic nervous system (Freedman and Lefkowitz, 2004; Westfall and Westfall 2005). Furthermore, it has been shown that up-regulation of adrenal medullary G protein-coupled receptor kinase 2 is a very important mechanism for mediating the sympathetic hyperactivity and circulating catecholamine levels that accompany and aggravate chronic heart failure (Lymperopoulos et al., 2007). The present findings on the effects of daidzein and genistein in catecholamine system may partially explain the cardiovascular protective effects of soy isoflavones.

5. Future perspectives

What are the major pending problems or questions revealed by the present study? While the *in vitro* effects of soy isoflavone have been well clarified using cultured bovine adrenal medullary cells, SK-N-SH cells or COS-7 cells transiently transfected with noradrenaline transporter, the *in vivo* effects are not as clear. Therefore, to confirm the effects of soy isoflavone on catecholamine synthesis, secretion and reuptake, further *in vivo* studies on the effects of administration of daidzein and genistein to animals or humans will be needed in the near future.

Finally, a question arises as to how best to demonstrate the protective effects of soy isoflavone on stress-induced catecholamine synthesis and secretoin? The anti-depressive or anxiolytic effects of soy isoflavone should be examined using laboratory animals under various stress conditions. Analysis with *in vivo* studies will provide more conclusive information and add new pharmacological actions of soy isoflavone on catecholamine signaling.

6. Concluding remarks

Daidzein and genistein are major natural phytoestrogens found in soybeans. In the present review, we have demonstrated that daidzein stimulates catecholamine synthesis at low

concentrations similar to those at which daidzein inhibits the specific binding of [^{3}H]17β-estradiol to the membrane receptors, suggesting that daidzein at low concentrations enhances catecholamine synthesis probably through plasma membrane estrogen receptors (Liu et al., 2007). However, daidzein at high concentrations (1-100 μM) inhibited catecholamine synthesis and secretion induced by acetylcholine, the physiological secretagogue. The latter findings suggest that daidzein at high concentrations suppresses the catecholamine synthesis and secretion induced by stress or emotional excitation that induces the stimulation of the splanchnic nerves and subsequently the adrenal medulla. In addition to daidzein's effects, genistein also increases the activity of the noradrenaline transporter, suggesting an enhancement of termination of noradrenaline transmission at the sympathetic nerve terminals. Although endogenous catecholamines play an important role in the regulation of normal functions in the cardiovascular system, stress-induced over expression of catecholamines may contribute to the involvement and augmentation of cardiovascular disorders The present findings would support the idea that soy isoflavone suppress excessive stress-induced hyperactivity of the sympatho-adrenal system and thereby protect the cardiovascular system (Yanagihara et al., 2008).

7. Funding

This work was supported in part by a grant from Grant-in-Aids (11839030, 20611020, and 20590129) for Scientific Research (C) from the Japan Society for the Promotion of Science, and a grant from the University of Occupational, Environmental Health for Advanced Research and the Smoking Research Foundation.

8. Conflict of interest

The authors have declared no conflict of interest.

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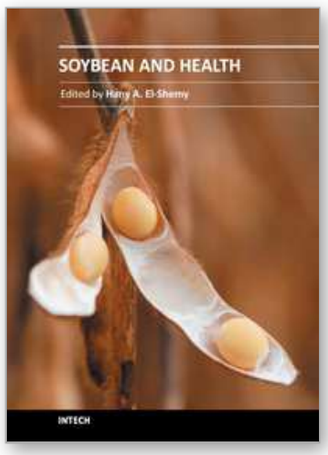
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Soybean and Health

Edited by Prof. Hany El-Shemy

ISBN 978-953-307-535-8
Hard cover, 502 pages
Publisher InTech
Published online 12, September, 2011
Published in print edition September, 2011

Worldwide, soybean seed proteins represent a major source of amino acids for human and animal nutrition. Soybean seeds are an important and economical source of protein in the diet of many developed and developing countries. Soy is a complete protein, and soy-foods are rich in vitamins and minerals. Soybean protein provides all the essential amino acids in the amounts needed for human health. Recent research suggests that soy may also lower risk of prostate, colon and breast cancers as well as osteoporosis and other bone health problems, and alleviate hot flashes associated with menopause. This volume is expected to be useful for student, researchers and public who are interested in soybean.

How to reference

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Nobuyuki Yanagihara, Yumiko Toyohira, Minhui Liu, Susumu Ueno, Masato Tsutsui and Han Zhang (2011). Insights into the Pharmacological Effects of Soy Isoflavones on Catecholamine System, Soybean and Health, Prof. Hany El-Shemy (Ed.), ISBN: 978-953-307-535-8, InTech, Available from: http://www.intechopen.com/books/soybean-and-health/insights-into-the-pharmacological-effects-of-soy-isoflavones-on-catecholamine-system

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