Secoisolariciresinol Diglucoside (SDG) Isolated from Flaxseed, an Alternative to ACE Inhibitors in the Treatment of Hypertension

Kailash Prasad, MBBS (Hons.), MD, PhD, FRCPC, FACC, FIACS, FICA[1]

[1] Department of Physiology, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

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Address for correspondence Kailash Prasad, MBBS (Hons.), MD, PhD, FRCPC, FACC, FFACS, FICA, Department of Physiology, College of Medicine, University of Saskatchewan, 107 Wiggins Road, Saskatoon, Saskatchewan, Canada S7N 5E5 (e-mail: k.prasad@usask.ca).

Abstract

Secoisolariciresionol diglucoside (SDG) is a plant lignan isolated from flaxseed and is phytoestrogen. SDG is a potent and long-acting hypotensive agent. Plant phytoestrogens have inhibitory effects on angiotensin-converting enzyme (ACE). The hypotensive effects of SDG, a phytoestrogen, may be mediated through inhibition of ACE. The objective of this study was to investigate if SDG-induced hypotension is mediated through inhibition of ACE. The Sprague Dawley male rats were anesthetized and trachea was cannulated. The right jugular vein was cannulated to administer the drug and the carotid artery was cannulated to record arterial pressures using PIOEZ-1 miniature model transducer (Becton, Dickinson and Company, Franklin Lakes, NJ) and Beckman dynograph (Beckman Instruments, Inc., Schiller Park, IL). The effects of angiotensin I (0.2 µg/kg, intravenously [IV]) in the absence and presence of SDG (10 mg/kg, IV), and SDG alone on systolic, diastolic, and mean arterial pressures were measured before and after 15, 30, and 60 minutes of drug administration. SDG decreased the systolic, diastolic, and mean arterial pressure by 37, 47, and 43%, respectively, at 15 minutes and 18.8, 21.2, and 20.3%, respectively, at 60 minutes. Angiotensin I increased the arterial pressure. SDG decreased angiotensin I-induced rise in the systolic, diastolic, and mean arterial pressures by 60, 58, and 51%, respectively, at 15 minutes and 48, 46, and 30%, respectively, at 60 minutes. The data suggest that SDG reduced the angiotensin I-induced rise in the arterial pressures and hence SDG is a potent ACE inhibitor.

Keywords
- arterial pressures
- angiotensin I
- angiotensin-converting enzyme inhibitor
- secoisolariciresinol diglucoside
- flaxseed

Flaxseed comprises 32 to 45% of its mass as oil of which 51% is α-linolenic acid and 15 to 18% is linoleic acid.[1,2] Flaxmeal which is devoid of oil is approximately 55 to 68% of the total flaxseed and contains approximately 16.4 mg/g of secoisolariciresional diglucoside (SDG).[3] SDG content of flaxseed varies between 0.6 and 1.8 g per 100 g.[4] SDG has been isolated from flaxseed.[5] SDG is a phytoestrogen,[6] and phytoestrogens from dietary soy have been shown to have mild hypotensive effect.[7] Prasad[8] has reported that SDG administered intravenously (IV) has a dose-dependent hypotensive effects in Sprague Dawley male rats. He also reported that hypotensive effect starts immediately reaching to a maximum within 15 minutes, after which the pressure tended to recover, but the recovery was not complete even after 4 hours of SDG administration. He also reported that the hypotensive effects of SDG is mediated through the stimulation of guanylate cyclase enzyme. Plant flavonoids have inhibitory effects on angiotensin-converting enzyme (ACE).[9] Substances derived from soy are ACE inhibitors.[10] The renin-angiotensin-aldosterone system (RAAS) plays a major role in the regulation of blood pressure. Within RAAS, ACE converts angiotensin I to angiotensin II which increases the blood pressure by vasoconstriction and by stimulating the production of aldosterone, which promotes sodium and water retention. The ACE

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Table 1 Sequential changes in the systolic, diastolic, and mean arterial pressures with SDG (10 mg/kg, IV)

Arterial pressure (mm Hg)	Control (0 minute)	SDG (15 minutes)	SDG (30 minutes)	SDG (60 minutes)
Systolic	137.5 ± 3.82	86.5 ± 7.6[a]	93.6 ± 6.7[a]	111.7 ± 6.9[a,b]
Diastolic	104.8 ± 7.01	55.3 ± 5.9[a]	67.0 ± 6.5[a]	82.6 ± 7.3[a,b]
Mean	115.8 ± 5.4	65.7 ± 5.9[a]	76.0 ± 6.1[a]	92.3 ± 6.6[a]

Abbreviations: IV, intravenous; SDG, secoisolariciresionol diglucoside.
[a]$p < 0.05$, control vs. SDG treatment.
[b]$p < 0.05$, 15 vs. 30 or 60 minutes.
Note: The results are expressed as mean ± standard error.

inhibitors are known to reduce arterial pressures. Since SDG is phytoestrogen and phytoestrogens are ACE inhibitors, it is possible that the hypotensive effects of SDG may be mediated through inhibition of ACE.

The objective of this investigation was to determine if SDG-induced decreases in the blood pressures is mediated through inhibition of ACE.

Methods

The experiments were performed on Sprague Dawley male rats weighing between 450 and 500 g. The rats were in cages under 12-hour light and 12-hour dark cycle and were cared for according to approved standards for laboratory animal care. Food and water were given ad libitum. The rats were anesthetized with Nembutal Sodium (45 mg/kg, intraperitoneally) and the trachea was cannulated. The right jugular vein was cannulated for administration of drugs. The carotid artery was cannulated with catheter to record arterial pressure. The catheter was connected to a PIOEZ-1 miniature model transducer (Becton, Dickinson and Company, Franklin Lakes, NJ) coupled to Beckman R611) dynograph recorder (Beckman Instruments, Inc., Schiller Park, IL) to monitor, systolic, diastolic, and mean arterial pressures.

Protocol

Effects of IV SDG on Arterial Pressures

This study was performed to determine if SDG lowers arterial pressure. Effects of SDG in the dose of 10 mg/kg, IV on arterial pressure were monitored for 60 minutes ($n = 6$).

Effect of Angiotensin I (0.2 µg/kg, IV) in the Absence or Presence of SDG on Arterial Pressures

This study was designed to determine if the effect of angiotensin I is blocked by SDG. The effects of angiotensin I (0.2 µg/kg, IV) in the absence or presence of SDG (10 mg/kg, IV) on arterial pressures were observed for 60 minutes ($n = 6$).

Statistical Analysis

The values of the arterial pressures with SDG are presented as mean ± standard error (SE). The arterial pressures with angiotensin I in the absence or presence of SDG have been shown as mean ± SE of absolute changes. Repeated measure analysis of variance followed by post hoc test was used for statistical analysis. A p value of less than 0.05 was considered significant.

Results

Hypotensive Effects of SDG

The effects of IV administration of 10 mg/kg of SDG on the systolic, diastolic, and mean arterial pressure in anesthetized rats are shown in ►**Table 1**. SDG decreased the systolic, diastolic, and mean arterial pressure by 37, 47, and 43%, respectively, at 15 minutes after SDG administration. At 1 hour after SDG administration, the systolic, diastolic, and mean arterial pressure decreased by 18.8, 21.2, and 20.3%, respectively. The data suggest that SDG is a very potent and long-acting hypotensive agent and the effect is more on the diastolic than the systolic arterial pressure.

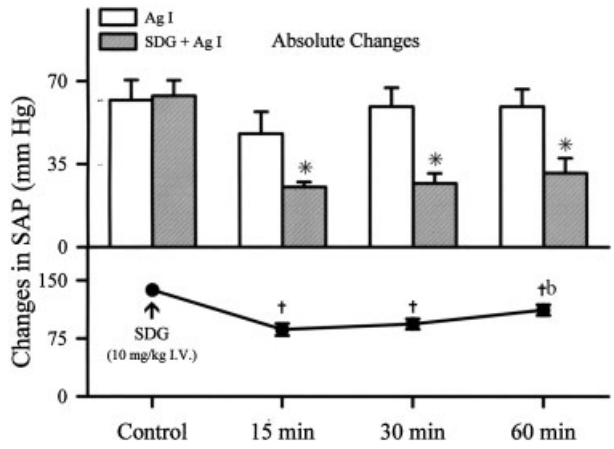

Fig. 1 Effects of angiotensin I (0.2 µg/kg, IV) on the absolute changes in the systolic arterial pressure in the absence or presence of SDG (10 mg/kg, IV) at various time intervals in the bar diagram. Line plot shows the effects of SDG on systolic arterial pressure for 60-minute duration. The results are expressed as mean ± SE. *$p < 0.05$, comparison of the values at various time intervals with respect to the values of control before any drug treatment in the bar diagram. †$p < 0.05$, comparison of values at different times with respect to control (line diagram). [a]$p < 0.05$, 15 versus 30 or 60 minutes (line diagram). Ag I, angiotensin I; SDG, secoisolariciresionol diglucoside; SE, standard error.

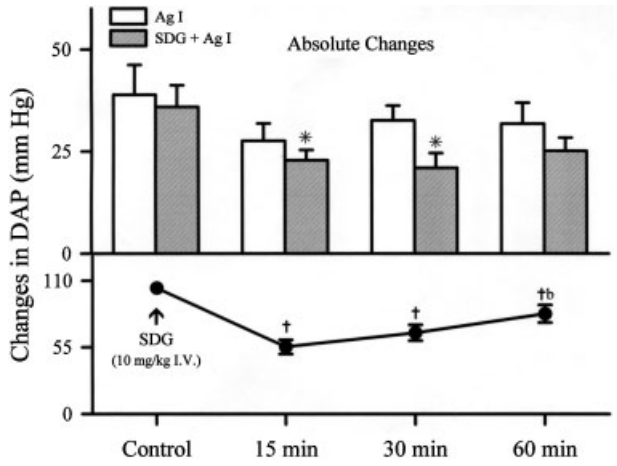

Fig. 2 Effects of angiotensin I (0.2 µg/kg, IV) on the diastolic arterial pressure (expressed as absolute changes) in the absence or presence of SDG (10 mg/kg, IV) at various time intervals. Line diagram shows the effects of SDG on diastolic arterial pressure for 60-minute duration. The results are expressed as mean ± SE. $^{*}p < 0.05$, comparison of the values at different time intervals with respect to control (bar diagram). $^{\dagger}p < 0.05$, comparison of values at different time intervals with respect to control (line diagram). $^{b}p < 0.05$, 15 versus 30 or 60 minutes (line diagram). Ag I, angiotensin I; SDG, secoisolariciresionol diglucoside; SE, standard error.

Effect of Angiotensin I is the Presence or Absence of SDG

The effects of angiotensin I (0.2 µg/kg, IV) on the arterial pressure for 60 minutes are summarized in ►**Figs. 1–3**. SDG reduced the systolic, diastolic, and mean arterial pressures. Angiotensin I increased systolic, diastolic, and mean arterial pressures throughout 60 minutes. The increases in the pressures remained unchanged during the whole period of study. The arterial pressures with angiotensin I decreased significantly in the presence of SDG, the decreases in systolic, diastolic, and mean arterial pressures being 60, 58, and 51%, respectively, at 15 minutes. The decreases in the systolic, diastolic, and mean arterial pressures with angiotensin I in the presence of SDG at 60 minutes were 48, 46, and 39%, respectively. The data show that SDG reduced the angiotensin I-induced rise in arterial pressures, suggesting that the hypotensive effect of SDG is mediated through inhibition of angiotensin-converting enzyme.

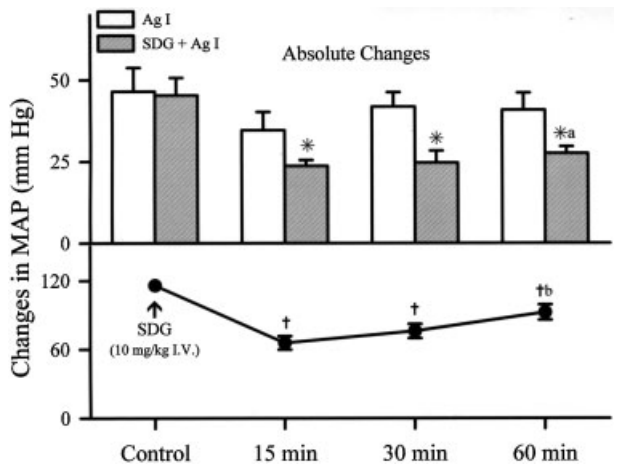

Fig. 3 Effects of angiotensin I (0.2 µg/kg, IV) on the mean arterial pressure (expressed as absolute changes) in the absence or presence of SDG (10 mg/kg, IV) at various time intervals. Line diagram shows the effects of SDG on the mean arterial pressure for 60-minute duration. The results are expressed at mean ± SE. $^{*}p < 0.05$, comparison of values at different time intervals with respect to control (bar diagram). $^{a}p < 0.05$ comparison, 15 versus 30 or 60 minutes (bar diagram). $^{\dagger}p < 0.05$, comparison of the values at different times with respect to control (line diagram). $^{b}p < 0.05$, 15 versus 30 or 60 minutes (line diagram). Ag I, angiotensin I; SDG, secoisolariciresionol diglucoside; SE, standard error.

Discussion

SDG in the dose of 10 mg/kg produced marked decreases in the arterial pressures in anesthetized rats, the decreases being more in diastolic than in the systolic pressures. Similar findings have been observed earlier by Prasad.[8] Angiotensin I increased the arterial pressure in the present study. Similar effects of angiotensin I have been reported on the arterial pressures of rat.[11] SDG significantly reduced the angiotensin I-induced increase in the arterial pressure, the reduction being greater in diastolic as compared with systolic arterial pressures. This could be due to inhibition of ACE. The reasoning being as follows: Renin released from the specialized cells in the kidney acts on renin substrate, angiotensinogen to produce biologically inactive decapeptide, angiotensin I which in turn is converted to the octapeptide angiotensin II by ACE. Angiotensin II is a powerful vasoconstrictor through binding to angiotensin II (AT_1) receptor. Since SDG reduced the pressure response to angiotensin I, it might have inhibited the ACE resulting in decreased conversion of angiotensin I to angiotensin II and hence reduction in angiotensin I-induced rise in the arterial pressure. ACE inhibitors are well known to reduce arterial pressure and have been used extensively for patients with hypertension. ACE inhibitors have been used to reduce blood pressure in animal models[12–14] and human hypertension.[15–19]

In conclusion, these results suggest that hypotensive effects of SDG isolated from flaxseed is mediated through inhibition of angiotensin-converting enzyme. SDG may prove to be an alternative to other ACE inhibitors for the treatment of hypertension.

Acknowledgments

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