Hormetic response to B-type procyanidin ingestion involves stress-related neuromodulation via the gut-brain axis: Preclinical and clinical observations

Naomi Osakabe¹,²*, Taiki Fushimi¹ and Yasuyuki Fujii¹

¹Functional Control Systems, Graduate School of Engineering and Science, Shibaura Institute of Technology, Saitama, Japan, ²Department of Bio-Science and Engineering, Shibaura Institute of Technology, Saitama, Japan

B-type procyanidins, a series of catechin oligomers, are among the most ingested polyphenols in the human diet. Results of meta-analyses have suggested that intake of B-type procyanidins reduces cardiovascular disease risk. Another recent focus has been on the effects of B-type procyanidins on central nervous system (CNS) function. Although long-term B-type procyanidin ingestion is linked to health benefits, a single oral intake has been reported to cause physiological alterations in circulation, metabolism, and the CNS. Comprehensive analyses of previous reports indicate an optimal mid-range dose for the hemodynamic effects of B-type procyanidins, with null responses at lower or higher doses, suggesting hormesis. Indeed, polyphenols, including B-type procyanidins, elicit hormetic responses in vitro, but animal and clinical studies are limited. Hormesis of hemodynamic and metabolic responses to B-type procyanidins was recently confirmed in animal studies, however, and our work has linked these effects to the CNS. Here, we evaluate the hormetic response elicited by B-type procyanidins, recontextualizing the results of intervention trials. In addition, we discuss the possibility that this hormetic response to B-type procyanidins arises via CNS neurotransmitter receptors. We have verified the direction of future research for B-type procyanidins in this review.

KEYWORDS
B-type procyanidin, hormesis, sympathetic nervous system (SNS), central nervous system, hemodynamics, stress

Introduction

B-type procyanidins are characterized by a series of heteropolyflavan-3-ols, with a single interflavan bond between carbon-4 of the B-ring and either carbon-8 or carbon-6 of the C-ring (1–3). B-type procyanidins can be categorized by their degree of polymerization: monomers form linkages leading to oligomers. The most common
monomeric unit is (−)-epicatechin, and the C4−C8 bond (Figure 1A) is the most prominent. B-type procyanidins containing 2−7 monomeric units are defined as oligoprocyanidins which are abundant in cocoa (4−6), apples (7, 8), grape seeds (9, 10), and red wine (11−13).

Results of meta-analyses have suggested that intake of foods rich in B-type procyanidins is linked to reduced risk for cardiovascular disease, including coronary heart disease, myocardial infarction, and stroke (14−20). Randomized controlled trials and subsequent meta-analyses have confirmed that dark chocolate containing large amounts of B-type procyanidins can mitigate states related to the metabolic syndrome, including hypertension (21−23), dyslipidemia (24, 25), and glucose intolerance (25, 26). In addition, the latest large-scale randomized trial found a 27% reduction in cardiovascular death by ingestion of cocoa flavanol fraction, which is rich in B-type procyanidin monomer and oligomers, for 3.6 years (27). Recent studies have focused on the benefit of B-type procyanidin ingestion for the central nervous system (CNS). A few intervention trials have reported that B-type procyanidin might be effective in improving cognitive function (28−31).

Almost all B-type procyanidins ingested in food move into the colon, and some are degraded by the microbiome (32−34). Consequently, changes in the gut microbiome induced by ingestion of B-type procyanidins for a comparatively long period may alter the composition of metabolites in the colon (32, 35−38). One hypothesis is that these colon changes associated with gut microbiota contribute to the beneficial effects of B-type procyanidins.

Acute physiological changes have been reported to follow a single intake of foods rich in B-type procyanidins. These changes are related to hemodynamics (39−43), metabolism (44, 45), the autonomic nervous system (46), and cognitive function or cerebral blood flow (28, 47−54). These findings highlight the need to evaluate the acute and chronic physiological effects of B-type procyanidin ingestion.

In addition, the acute hemodynamic changes following ingestion of B-type procyanidin, such as flow-mediated dilatation (FMD), do not show a monotonic dose response (55). Instead, these physiological changes follow a pattern of hormesis, with peak benefit at mid-range doses and less benefit at higher or lower doses. Comprehensive analyses of many earlier findings suggest that there is likely a mid-range optimal dose for the effects of B-type procyanidins on hemodynamics.

Polyphenols, including B-type procyanidins, elicit hormetic responses in cell culture (56−59). Cellular proliferation occurs at relatively low concentrations, but cytotoxicity is detected at high concentrations (60). In vivo animal and human dose-response findings for B-type procyanidins are relatively limited. Recently, however, results from animal studies confirmed that hemodynamics and metabolism show a hormetic dose-response to B-type procyanidin, and we found that these changes arise through sympathetic nerve activation, driven by CNS activation. Here, we review data from human intervention trials supporting a hormesis pattern of response to B-type procyanidins. Furthermore, we discuss the possibility that B-type procyanidins elicit this response via neurotransmitter receptors expressed in the CNS.

Hormesis

Bioactive compounds are expected to yield a monotonic dose-dependent response in terms of efficacy or toxicity (Figure 1B). In some cases, however, the pattern is characterized by an inverted U-shaped dose-response (Figure 1C). This pattern of hormesis can also reflect an adaptive response. For example, exposure to low amounts of a substance or stressor can induce resistance to higher doses of the same trigger. This exposure to mild levels of harmful factors can precondition a cell or an organism, inducing activation of stress resistance pathways and expanding maintenance and repair capacities (61, 62).

As an example, a moderate exercise program yields various benefits, such as decreased risk of cardiovascular disease, stronger bones and skeletal muscle, and longevity. An overly intense exercise program, however, can lead to harmful effects (63), so that the response to exercise “dose” shows a hormetic pattern. Exercise-related enhancement of cognition and mood also shows a hormetic response (64) that is reported to relate closely to adult hippocampal neurogenesis (65). Furthermore, moderate physical activity is generally accepted to be associated with cardiovascular (66−68) and metabolic benefits through sympathetic nervous system (SNS) (69−71). Recent evidence also links CNS plasticity to the effects of moderate exercise on SNS activity (72).

Polyphenols elicit a hormetic response in cell culture (73); curcumin (74), resveratrol (75) and B-type procyanidins (76). The hormesis effect of other polyphenols also has been confirmed in vitro, and these activities are considered to arise from modulation of a number of redox-based signaling pathways. Abundant evidence thus supports a hormesis effect of polyphenols in in vitro studies, but limited data illustrate these effects in vivo.

Hormetic response to B-type procyanidin in intervention and animal studies

As mentioned above, repeated ingestion of B-type procyanidins is reported to reduce the risk of cardiovascular diseases. Besides numerous intervention trials have been examined following the single ingestion of foods rich in B-type procyanidins. Regarding hemodynamics, a single ingestion
was associated with increased FMD at about 2 h following ingestion (23). These results indicated that a single treatment of B-type procyanidin might improve vascular endothelial cell function. Sun et al. assessed the dose-response pattern of human endothelial function to B-type procyanidin in cocoa (55). They concluded that cocoa flavanols could significantly improve endothelial function, with an optimal dose of about 710 mg. They also observed a non-linear association (inverted U-shape) between cocoa flavanols and FMD. There were no notable adverse effects in the intervention studies using 1.4 times (1,008 mg) or 1.76 times (1,248 mg) the effective dose (710 mg) shown by Sun et al. (55). Since these intervention studies used cocoa drinks or chocolate as the test food, it was limited intake amount. Therefore, the toxicity of type B-type procyanidins may not detect.

In addition, results of a recent intervention trial indicate that repeated supplements of B-type procyanidins are associated with improvement on memory tasks that depend on dentate gyrus functions (52). Intervention trials have been conducted in young adults, examining the effects on a memory task of a single ingestion of cocoa flavanols at doses from 172 to 994 mg (77). In almost all cases, cocoa flavanols were associated with enhanced working memory or mood and reduced fatigue, but evidence of dose-response in CNS studies is limited.

These results, taken together, suggest that a hormetic physiological response following a single intake of B-type procyanidins is likely. Studies of other polyphenols, such as curcumin and resveratrol, are too limited to allow for interpretations regarding dose response (78).

Repeated oral gavage with 10 mg/kg body weight (bw) of cocoa flavanol in rats resulted in significantly decreased blood pressure and markedly increased aortic endothelial nitric oxide synthase expression (eNOS), indicating this dose as optimal (79). On the other hand, a single oral administration of 10 mg/kg cocoa flavanol, resulted in a transient increase in mean blood pressure (BP) and heart rate (HR), along with a marked increase in blood flow in the cremaster muscle arteriole soon after treatment. A significant increase in eNOS phosphorylation was also observed in aorta dissected 60 min after this treatment. Similar but weaker alterations were observed at a dose of 1 mg/kg cocoa flavanol but 100 mg/kg cocoa flavanol did not trigger any changes in hemodynamics or eNOS phosphorylation.

We also compared B-type procyanidins such as the monomer [(-)-epicatechin; EC], dimer (procyanidin B2; B2), trimer (procyanidin C1; C1), and tetramer (cinnamtannin A2; A2) on hemodynamics (80). At a dose of 10 µg/kg, A2 and B2 were associated with a marked increase in cremasteric arteriole

![FIGURE 1]

Chemical structure of B-type procyanidin (C4–C8) bond, (A), and dose-response curves: (B) monotonic and (C) hormesis.
blood flow, C1 was linked to a slight increase, and EC did not trigger any change. Based on these findings, a relative efficacy of B-type procyanidins on hemodynamics was suggested as follows: A2 > B2 > C1 > > EC (Figure 2). A dose-response study of A2 showed increased blood flow with a single dose of 10 µg/kg, but not with a dose of 100 µg/kg. In our dose-response study for A2 induction of thermogenic uncoupling protein (UCP)-1 expression in brown adipose tissue (BAT), we found that a single oral dose at 1 µg/kg was associated with significantly increased UCP-1 mRNA expression (Figure 2), but more than 1 µg/kg A2 (10 to 1,000 µg/kg) did not show any change (81).

Taken together, the results of animal studies of cocoa flavanol or the B-type procyanidins are consistent with those of intervention studies following a single intake of food rich in B-type procyanidin. The implication is that this polyphenol elicits an inverted U-shaped dose-response.

Target organ of B-type procyanidins from the perspective of bioavailability

B-type procyanidins show poor bioavailability, and intact forms in foods are hardly present in the blood (82). For this reason, how these polyphenols exert beneficial effects remains unclear. Recent studies suggest that the physiological changes following repeated B-type procyanidin ingestion may be related to alterations in gut microflora and/or their metabolites, but the mechanism for changes arising immediately after a single dose is unclear. Considering that most B-type procyanidins are present in the feces, the target organ of them is the gastrointestinal tract, including the oral cavity.

Single doses of B-type procyanidins do not draw a monotonic dose-response, and benefits are seen at the mid-range doses but not at lower or higher doses. Among various pharmacological agents, those that support social interactions or memory are reported to show biphasic reactions (83) and enhance memory (84). A single oral ingestion of cocoa flavanol has been also reported to improve cognition and mood in intervention studies. As noted, the primary target organ of B-type procyanidins appears to be the digestive tract, but activation of the CNS may be crucial to the mechanism of action.

Sympathetic nerve activation by B-type procyanidins

A single oral optimal dose of cocoa flavanol triggers an increase in blood flow in the cremaster arteriole soon after treatment in rats (85). Such a rapid response likely does not depend on absorption or distribution in the blood. The SNS is a well-known regulator of hemodynamic reflection, exerting its influence through adrenergic receptors (AdR) expressed in the myocardium, vascular smooth muscle, and vasomotor center in the medulla oblongata (86). Activation of myocardial β1 AdR, which are expressed predominantly in cardiac tissue, causes increased cardiac output and HR. Activation of the α1 AdR in vascular smooth muscle contracts blood vessels, leading to elevated BP (Figure 3) (87). For this reason, we used adrenaline blockers to examine whether the SNS is involved in the hemodynamic changes induced by B-type procyanidins. We found that a transient increase in HR caused by an optimal dose of cocoa flavanol could be markedly decreased by co-treatment with a β1 AdR blocker in rats. In addition, co-treatment with an α1 blocker inhibited the transient elevation in BP that a single oral dose of cocoa flavanol induced.

Sympathetic nervous system also regulates non-shivering thermogenesis through β3 AdR in BAT via UCP-1 (88). We have found that UCP-1 mRNA upregulation in BAT after an optimal dose of cocoa flavanol is markedly attenuated by co-administration of β3 blocker. These results implicate the SNS in the acute hemodynamic and metabolic changes following a single oral dose of B-type procyanidins.
In hormesis, effects at high doses can be less than effects at optimal doses. We evaluated the hormetic pattern of response to B-type procyanidins in vivo and found that a single oral administration of 10-fold the optimal dose of cocoa flavanol in rats yielded no transient hemodynamic alterations (79). In addition, as noted, an optimal dose of cocoa flavanol increased UCP-1 mRNA expression in BAT, but this change was markedly dampened at doses 10-fold the optimal level (89). Based on our findings linking the hemodynamic and thermogenic effects of B-type procyanidins to SNS activation, we focused on why optimal dose elicit these effects but not high doses.

Blood pressure and heart rate are regulated competitively by inhibitory and activating AdR. Activation of the β2 receptor relaxes vascular smooth muscle as a competitive effect against the vasoconstrictive action of α1 AdR and thus decreases BP (Figure 3) (87). In our co-administration study with a high dose of B-type procyanidins and α1 blocker in rats, although, we found no changes in BP (79). Besides, inhibitory α2 AdR, which are present in the preganglionic sympathetic fibers and vasomotor center in the CNS, down-regulate the SNS. Yohimbine is an α2 blocker that is reported to be more effective in CNS than SNS. Given this pattern, we conducted a co-administration study with a high dose of cocoa flavanol (100 mg/kg) and yohimbine. A single high dose of cocoa flavanol alone elicited no change in BP, but BP increased markedly and transiently by co-administered with yohimbine. Similar results were observed co-administration of B-type procyanidin tetramer A2 (100 µg/kg) and yohimbine (80).

As mentioned above, whereas a single oral dose of 1 µg/kg of A2 significantly increased UCP-1 mRNA expression in BAT, doses from 10 to 1,000 µg/kg A2 did not (81). In contrast, co-administration of a high dose (100 µg/kg) of A2 and yohimbine markedly increased UCP-1 mRNA expression. A recent report suggested that the premotor neurons controlling thermogenic effector activation lie primarily within the medullary rostral raphe pallidus (90). Non-shivering thermogenesis through the β3 receptor is inhibited by α2AR activation in this region (91).

α2 AdR are present on noradrenergic terminals in the peripheral nervous system and the CNS (92). α2 adrenergic autoreceptors lie in the presynaptic membrane of adrenergic neurons, inhibiting exocytosis of their neurotransmitters (mostly noradrenaline) as part of a negative feedback loop (93, 94) (Figure 3). Feedback inhibition of noradrenaline release from sympathetic nerves by α2-autoreceptors limits its exocytosis and protects heart under normal conditions (95). The reduced hemodynamic and metabolic output at a high dose of B-type procyanidins observed in our previous studies may cause activation of autoreceptor α2. Thus, SNS deactivation may be induced by a high dose of B-type procyanidins.
Stress and hormetic response to B-type procyanidins

The relationship between stress and hormetic responses is well known. Various factors induce the stress response, which involves rapid activation of the sympathetic–adrenal–medullary (SAM) axis and the hypothalamus–pituitary–adrenal (HPA) axis (96). In the SAM, rapid physiological adaptation mediated mainly by noradrenaline results in transient responses, such as alertness, and appraisal of the situation, enabling a strategic decision. Sympathetic modulations induced by stressors rely on direct projections from the paraventricular nucleus of the hypothalamus (PVN), locus coeruleus, and rostral ventrolateral medulla to pre-ganglionic sympathetic neurons present in the dorsal intermediolateral cellular column of the spinal cord (97). As a result, noradrenaline is secreted from sympathetic nerve terminals, leading to activation of signaling pathways that evoke changes in blood vessels, glands, visceral organs, and smooth muscle. Considering the previous results following a single oral administration of B-type procyanidins, these changes may be induced by activation of the SNS.

The PVN, which also has a role in eliciting activation of the HPA, synthesizes oxytocin, vasopressin, and corticotropin-releasing hormone (CRH), depending on the target (98). CRH excreted from the PVN to the anterior pituitary induces release of adrenocorticotropic hormone, which drives the responses associated with release of cortisol (corticosterone in rodents) from the adrenal gland in the hours following stress. When blood cortisol exceeds a certain level, it exerts negative feedback on the hypothalamic release of CRH and the pituitary release of adrenocorticotropic hormone (99). Activation of these pathways results in adaptive conditions that mediate long-term memories of the experience. Therefore, HPA activation induced by optimal stress has a strong positive effect on memory, cognition, and stress resilience (100).

If the outcome following a single dose of B-type procyanidins arises as stress response, HPA activation is expected to occur at the same time as sympathetic hyperactivity. Therefore, we examined the activation of HPA following a single dose of B-type procyanidins. In mouse PVN, the optimal dose of cocoa flavanol (10 mg/kg bw) markedly upregulated CRH mRNA, as detected by in situ hybridization, 240 min after administration. A dose of 50 mg/kg cocoa flavanol also showed similar alterations 60 min after administration, with a significant elevation in plasma corticosterone (101). In addition, CRH mRNA in mouse PVN was increased significantly 60 min after administration of an optimal dose of A2 (10 µg/kg), and a similar change only 15 min after administration of a 10-fold oral dose of A2 (102). Few reports have described the relationship between stress intensity and the duration of response, but our results suggested that the reaction is faster with exposure to more severe stress. Taken together, these findings indicate that stimulation with an oral dose of B-type procyanidin might be a stressor for mammals, resulting in SNS activation (Figure 2).

Conclusion

Various stressors such as radiation, reactive oxygen species, calorie restriction, temperature, chemicals, and exercise elicit hormetic responses (103). Hormesis and the underlying biochemical pathways induced by the stressors confer protection against a range of pathological or aging processes (62). In this review, we especially focused on the hormetic alterations induced by B-type procyanidins, which are electrophilic compounds that easily cause redox reactions. The relationship between CNS activation and the chemical characteristics of B-type procyanidins remains unclear and requires further clarification. B-type procyanidins or related compounds may contribute to the beneficial effects of eating fruits and vegetables through hormetic responses induced by neuromodulation.

Author contributions

TF and YF collected the sources and drafted this manuscript. NO constructed the conception and finally approved of this manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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