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Potential Implications of the Phytohormone Abscisic Acid in Human Health Improvement at the Central Nervous System

Gastón Alfredo Pizzio*[1,2]

[1]*Instituto de Biología Molecular y Celular de Plantas, Universidad Politécnica de Valencia (UPV-CSIC), CP46022 Valencia, Spain.*

[2]*CIT-RIO NEGRO Sede Atlántica, Universidad Nacional de Río Negro (UNRN-CONICET), Viedma CP8500, Río Negro, Argentina.*

***Corresponding Author(s): Gastón Alfredo Pizzio**

Institute of Molecular and Cellular Biology of Plants, Polytechnic University of Valencia (UPV-CSIC), CP46022 Valencia, Spain.

Tel: +34-963-877-856; Email: gpizzio@gmail.com & gaspiz@ibmcp.upv.es

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Abstract

The plant hormone Abscisic Acid (ABA) has applications not only in agriculture, but also in human health. ABA is established as the key hormonal regulator of plant stress physiology, and it is also involved in plant growth and development under normal conditions. This phytohormone is present in the human body from dietary sources as well as from endogenous production through the carotenoid biogenesis pathway. ABA in mammals has both autocrine and paracrine function, and targets cells of the innate immune response, mesenchymal and hemopoietic stem cells and cells involved in the regulation of systemic glucose homeostasis, among others. Moreover, ABA increases glucose uptake in skeletal muscle and adipose tissue through an insulin-independent mechanism. Besides, ABA increases the energy expenditure in the brown and white adipose tissues. In this article, we review the potential of ABA to treat or ameliorate brain and spinal cord disorders, such as sleep disorders, depression, pain and Alzheimer derived memory impairments. Dietary ABA administration shows benefits in humans, as well as extensive data obtained in different mammal models and cell lines. Finally, future perspectives in nutraceutical use of ABA are discussed.

Introduction

Plants are central to our well-being, principally as food and medicine source. The coevolution between plants and humans is complex but long standing. Hominids have achieved different morphological and biochemical adaptations to plant material ingestion [1]. An interesting connection between plants and humans came from small signaling molecules called phytohormones [2]. Recent studies suggest that plant hormones also work in mammalian systems, and have the potential to reduce human diseases such as cancer and diabetes [3]. In particular, we want to focus this review in the relationship between the phytohormone Abscisic Acid (ABA) and mammalian physiology at the central nervous system level. Extensive data obtained from people and different animal models and cell lines suggests a myriad of benefits of ABA in human health.

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Abscisic acid machinery in plants

The phytohormone Abscisic Acid (ABA) is a key player in the plant stress response. The most studied role of ABA has been the induction of drought resistance, among other biotic and abiotic stresses, in both model plants and crops [4,5]. ABA also plays a role in different physiological processes, such as seed germination and early seedling growth, shoot and root growth and development, stomata closure, senescence, fruit ripening, fruit and leaf abscission, and bud dormancy [6].

In plants, abiotic stress (e.g., drought or salinity) induces ABA synthesis and active hormonal level increases notably. ABA synthesis in plants starts from the precursor carotene and follows the carotenoid pathway [7,8]. The initial steps, from carotene to xanthoxin are rendered in plastids and different enzymes are involved, for instance in *Arabidopsis thaliana*: viviparous (VPs), zeaxanthin epoxidase (ZEP/ABA1), abscisic acid (ABA)-deficient 4 (ABA4) and nine-cis-epoxycarotenoid dioxygenase (NCEDs). Then in the cytosol, ABA2 and ABA3 turn xanthoxin into active ABA. The rate-limiting step for ABA synthesis is the cleavage of 9-cis-epoxycarotenoid into xanthoxin by the NCEDs enzymes [9]. Moreover, transgenic plants with constitutive expression of NCEDs have high levels of ABA [10].

Net active ABA levels are set by the rate of synthesis and degradation/inactivation. In turn, ABA catabolism follows two different pathways: reversible conjugation or irreversible hydroxylation [7,11]. For instance, in *Arabidopsis thaliana* ABA can be glycosylated/inactivated by UGT71C5 to form ABA-glucose ester (ABA-GE), which is stored in vacuoles or in the endoplasmic reticulum. ABA-GE can be deconjugated to restore the active ABA by glycosidases, such as BG1 and BG2 [12-14]. This mechanism allows plants to promptly adapt to changes in the environment through ABA-mediated responses. By contrast, ABA can be irreversible converted to an inactive form as dihydrophaseic acid (DPA) by CYP707As and ABH2 [15,16].

In plants ABA is perceived inside the cell through the family of soluble receptors pyrabactin resistance 1 (PYR1)/PYR1-like (PYL)/regulatory components of ABA receptors (RCAR) [17-19] **(Figure 1a)**. The PYL family has several members and has been identified in many crops, for instance 12 PYLs in palm [20], 14 PYLs in tomato [21], 20 PYLs in quinoa [22], 23 PYLs in benthamiana [23], 38 PYLs in wheat [24] and 46 PYLs in canola [25]. Upon ABA perception, the clade A protein phosphatases type 2Cs (PP2Cs) are inhibited through the formation of a ternary complex: ABA-PYL-PP2CA. This PP2CA inactivation relieves the inhibition of the ABA-activated subclass III SNF1-related protein kinases 2 (SnRK2s) [26,27]. Then, activated SnRK2 induces the activation of a battery of ABA effectors from transmembrane channels to transcription factors [28,29] **(Figure 1a)**. In a second layer of regulation, the activity and half-life of components of this ABA core signaling pathway are regulated by different mechanisms such as the ubiquitin- 26S proteasome system, the endocytic/vacuolar degradation pathway, the circadian system and multiple secondary kinases [30-33].

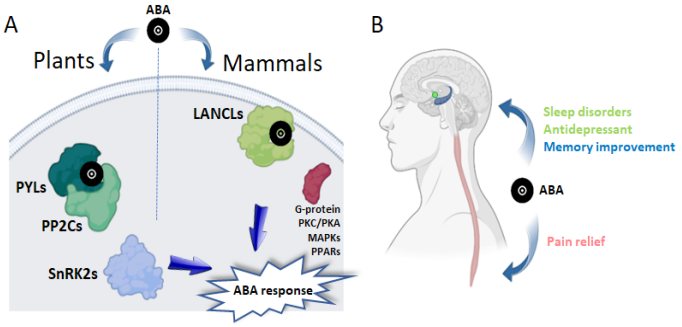

Table 1: ABA perception and its role in the central nervous system. A) ABA is perceived by the PYR/PYL receptors in plants and by the LANCL receptors in mammals. B) In the central nervous system ABA plays a role in sleep, depression, memory and pain. In green: hypothalamus. In blue: hippocampus. In red: spinal cord. Icons were obtained from Biorender.

ABA Signaling in Mammals

One of the first reports describing the presence of ABA in mammals found the phytohormone in the central nervous system of pigs and rats [34]. The molecule purified from mammalian brain had the same biochemical properties than abscisic acid. Moreover, this brain factor inhibited stomatal apertures in *Setcreasea pallida Rose* (Commelinaceae) leaves. Later on, the endogenous synthesis of ABA by human granulocytes was also demonstrated [35]. Moreover, an increase of intracellular ABA levels after heat-stress (fever-like temperatures), and its release triggered by phagocytosis was also reported. For this reason ABA was proposed as a new endogenous pro-inflammatory cytokine in humans [35]. This idea of a phytohormone with a role in inflammation represents the first example of signaling module conservation, including the stress signal molecule and its transduction pathway, from plants to mammals. Moreover, this concept is also important from a clinical perspective, given that the identification of a new inflammation cytokine would magnify the possibility of development of new anti-inflammatory drugs (e.g. ABA antagonists molecules). Several other observations support the conclusion that ABA is endogenously produced by human and murine cells: granulocytes [35,36], macrophages and monocytes [37,38], insulin-releasing cells [39], mesenchymal stem cells (MSCs) [40], hemopoietic progenitors (HP) [41], adipocytes [42], keratinocytes [36], and fibroblasts [43], all have been shown to produce and release ABA when exposed to cell-specific stimuli.

Regarding ABA recognition in mammals, it was firstly reported that lanthionine synthetase C-like protein 2 (LANCL2) binds ABA and regulates cell glucose uptake and metabolism [44,45] (figure 1a). Later it was also shown that LANCL1 binds ABA, inducing the transcriptional expression of the glucose transporters GLUT4 and GLUT1 and the signaling proteins AMPK/PGC-1a/Sirt1, and also stimulates mitochondrial respiration and the expression of the skeletal muscle uncoupling proteins sarcolipin and UCP3 [46]. LANCL protein family, which includes LANCL1, 2 and 3, shares properties typical of a peptide and steroid hormone receptors. Both LANCL1 and LANCL2 bind ABA, although LANCL2 with higher affinity than LANCL1, with a Kd of 3 nM and 1 µM, respectively [46,47]. Of note, none of the mammalian LANCL proteins are involved in lanthionine synthesis, even if the name includes “lanthionine synthetase” [48]. LANCL2 binds to the intracellular side of the plasma membrane through a myristoyl anchor [49], while LANCL1 and 3 are cytosolic soluble proteins [50]. On the other hand, LANCL1 and 2 are highly expressed in mammals, particularly in the brain, heart and germinal cells, with LANCL3 having the lowest expression levels of the LANCL proteins [46].

Upon ABA reception, LANCLs activates a G protein; in addition, as other steroid hormone receptors, they are capable of nuclear translocation after detachment from the membrane when de-myristoylated [46]. As proposed recently, this combination of peptide receptors (G protein coupling) and steroid hormone

receptors (with nuclear translocation), points to a heritage of the primordial origin of the hormone, or a consequence of ABA solubility properties [46]. In muscle cells, ABA recognition by LANCLs receptors lead to an insulin-independent glucose transport activation via the AMPK/PGC-1a pathway [51,52]. It was also reported that LANCL2 mediates akt activation via mTORC2 in human liver cells [53]. Besides, LANCL2 interacts with PPARɣ in white adipocytes, leading to PPARɣ-mediated activation of adipogenic genes after insulin-stimulated triglyceride accumulation [54]. In fact, LANCL2-_/-_ mice show a reduction in muscle activation and adipocyte glucose transport and metabolism, with the concomitant limitation in glucose tolerance [54]. Additionally, LANCL2 is also involved in the transcriptional activation of different browning genes in brown adipocytes [55]. The ABA signaling pathway in mammals also includes the cAMP-dependent activation of PKA and CD38 phosphorylation, leading to a cyclic ADP-ribose (cADPR)-mediated intracellular Ca^{2+} increase [35,38,39,56].

ABA Role in Brain Health

ABA in sleep disorders

Sleep disorders increase health problems such as anxiety or forgetfulness [58,59]. Different therapies have been implemented to ameliorate insomnia, using GABA, melatonin and orexin receptors as pharmacological targets [60]. However, the drugs administered can cause dependency and other serious side effects [61,62]. An interesting alternative is the application of natural compounds such as ABA **(Figure 1b)**.

It is well established that GABAergic neurotransmission has fundamental roles in boosting pentobarbital-induced sleep and relieving insomnia [63]. Indeed, ABA is involved in neurotransmitter release and regulates the activation of second messengers in both neural and non-neural cells [64-66]. On the other hand, the mammalian ABA receptor LANCL2 is related to plasma membrane and peroxisome proliferator activated receptors (PPARs) , which are members of a nuclear hormone receptor superfamily with three subtypes (PPARα, PPARβ and PPARβ/δ) [44,67]. PPARs are located in different parts of the CNS, particularly in hypothalamic neurons [68] which are involved in sleep/wake regulation [64]. Clinical and behavioral investigations have shown that PPARs have significant effects in sleep-wake cycle regulation [69]. Besides, it has been demonstrated that circadian locomotor activity is also affected by PPARs [70]. Sleep physiology and the circadian network are connected [71,72] and ABA-LANCL2-PPARγ axis could be one of the links.

The efficacy of ABA to boost pentobarbital-induced sleep, and the involvement of GABA-A, PPARβ and PPARγ receptors in this process was recently demonstrated [73]. An ABA-induced promotion of sleep onset in rats was reported, with levels comparable to diazepam treatment [73]. On the other hand, it was reported that vitamin A plays a role in sleep cycle regulation and also has functional effects on the pineal gland [74,75]. ABA is a vitamin A-like lipophilic substance and has beneficial regulatory effects on brain physiology [76], with the potential to induce pro-hypnotic effects. Several reports show the ability of ABA to perform as a neuromodulator in the central nervous system, directly or indirectly interfering with synaptic neurotransmission due to changes in ion currents [65,66]. For instance, ABA interacts with neurotransmitters and second messengers such as glutamate, calcium and nitric oxide at synaptic levels [35,66,77]. The ABA hypnotic effect is probably induced by neurotransmitter regulation. However, this issue needs to be further investigated, and, above all, experiments in humans would be very welcome.

ABA as an antidepressant

Following with the role of ABA in the central nervous system, some antidepressant effects of this phytohormone were also proposed [78,79] **(Figure 1b)**. ABA is produced and released by the brain itself. Indeed, the brain contains much more ABA than any other type of tissue [34]; although with asymmetric distribution, and the hypothalamus showed the highest ABA concentration. Depression is a stress-related disorder and affects more than 10% of the world population [80,81]. The stress response in mammals is mainly regulated by the hypothalamus and a dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis is usually involved in depression symptoms [82,83]. The ABA abundance in the hypothalamus suggests a role of ABA in the stress and depression response.

An association between retinoic acid (RA) and depressive symptoms has also been reported [84,85]. For instance, RA chronic administration induces HPA axis hyperactivity and depression-like behavioral changes in rats [86]. In addition, depressed patients exhibit a dysregulation in brain retinoid [87,88]. Interestingly, ABA and RA are carotenoid derivatives [7,89], and both molecules share a similar structure, specially a key carboxyl group in the isoprene-composed side chain involved in their bioactivity [84,90].

The corticotrophin-Releasing Hormone (CRH) in the paraventricular nucleus of the hypothalamus plays a central role in the regulation of HPA axis activity [82,83]. The release of corticosterone and stimulus-induced c-fos expression are widely used as markers in studies of neuronal activation after stress [91,92]. Interestingly, the ABA concentration significantly increased in the serum after stress treatments, and correlates with elevated corticosterone and c-fos levels [78]. By contrast, a decrease in ABA concentration was found in the hypothalamus of the rats under acute stress. These results are suggesting ABA may play a role in the stress response. Indeed, chronic ABA administration in rats showed a downregulation in CRH mRNA expression in the hypothalamus. Moreover, lower corticosterone concentrations in the serum were found after ABA treatment. These results indicate that ABA inhibits the HPA axis activity under physiological conditions.

On the other hand, chronic ABA treatment induces sucrose intake in rats. Sucrose intake correlates with the motivation to seek out a pleasurable experience, and this is connected with the capacity to feel interest or pleasure in mammals [93]. The ABA- induced higher sucrose intake and the downregulated HPA axis activity suggest that this phytohormone may play a role in the pathogenesis of depression. Indeed, the antidepressant effect of ABA was recently demonstrated in rats and mice under Chronic Unpredictable Mild Stress (CUMS) and Forced Swimming Test (FST) [78,79]. CUMS successfully decreased sucrose intake and increased immobility in the FST in rats, while ABA improved these depression-like behaviors [78]. Anhedonia is another behavior related with depression symptoms and sucrose intake [93,94]. ABA-treated rats spent a longer time swimming in the FST compared with the CUMS rats, although this accordance could not alleviate anxiety-related behaviors [78]. In agreement, ABA induces the normalization of CRH expression in the hypothalamus to control levels, and decreases corticosterone levels in serum. These results demonstrate the anti-depressant activity of ABA at the central nervous system,

and underscore the potential of this phytohormone for novel therapeutic strategies development to treat depression.

ABA improves memory in mammals

An interesting ABA function described in mammals is the positive effect that this phytohormone plays on spatial learning and memory performance [64,66] (Figure 1b). Indeed, this role of ABA is also involved in the amelioration of cognitive impairment in diseases such as obesity induced type 2 diabetes [95,96], Alzheimer disease [97-99] and essential tremor [100]. ABA not only readily permeates the brain when applied peripherally [64], but is also produced and released by the brain itself [34,56]. Moreover, the high ABA levels seen in the hippocampus suggest a connection between this phytohormone and learning/memory processes. This is also supported by the fact that ABA and Retinoic Acid (RA) share similar molecular structures, and RA has been reported to improve spatial memory in rodents [101-103]. Indeed, ABA has a positive effect on spatial learning and memory performance [66]. Furthermore, the PI3K/PKC signaling pathway is involved in this mechanism given that its inhibitors suppress the ABA-induced learning and memory improvement [66]. The serine/threonine kinase PKC also participates in memory related disorders such as Alzheimer's disease [104].

Alzheimer's disease is a type of dementia related to neurodegenerative processes in the elderly,; and neuroinflammation is one of the most important pathological causes [105,106]. ABA treatment improves memory impairment in Alzheimer's disease 5xFAD model mice, through neuroinflammation inhibition and LANCL2/CREB upregulation in the cortex and hippocampus [97]. Furthermore, this role of the phytohormone was also observed in the triple transgenic mice (3xTg-AD), another murine model of Alzheimer's disease [99]. Even more, ABA also ameliorates cognitive impairments in a streptozotocin-induced rat model of Alzheimer's disease [98]. Streptozotocin central injection produces neuroinflammation and oxidative stress in the brain, leading to learning and memory impairments [107], and ABA administration attenuates these deficits through activation of PPARβ/δ and PKA signaling [98]. These results together illustrate that ABA is an effective treatment to improve cognitive health.

Role of ABA in pain treatment

It was recently demonstrated that ABA elicits antinociceptive effects and reduces neuropathic pain at spinal cord level [108-110] **(Figure 1b)**. The spinal cord plays a key role in pain transmission, regulation and processing. In particular, the dorsal horn parts and laminas have a paramount importance in pain control and transmission [111]. Injury and dysfunctional-related neuropathic pain treatment in the nervous system represents a current clinical challenge given the relative lack of potent and safe analgesics [112]. Neuropathic pain originates from an aberrant neuronal activity along the pain signaling pathway, and neurons in the spinal dorsal horn are involved in this process [113,114]. Furthermore, neuroinflammation in the spinal dorsal horn is a prerequisite for a dysfunction of spinal neuronal activation and the genesis of neuropathic pain [115-117]. Moreover, neuroinflammation involves leukocytes infiltration, microglia and astrocytes activation, and pro-inflammatory cytokines over-production [115-116]. As already stated, identifying signaling molecules controlling neuroinflammation would provide novel molecular targets for the development of novel analgesics [108].

The presence of ABA in the spinal dorsal horn was recently reported [108] ABA concentrations in this tissue are not significantly altered by peripheral nerve injury- induced neuroinflammation. Moreover, ABA treatment ameliorates spinal inflammation and chronic pain in rats [108]. On the other hand, it was shown that the mammalian ABA receptor LANCL2 is expressed in immune cells such as T cells, macrophages, dendritic cells and spinal microglia [61,108]. Furthermore, knockdown of the LANCL2 gene with siRNA in the spinal dorsal horn recapitulates the nerve injury induced spinal neuroinflammation and nociceptive behaviors [108]. In addition, spinal microglia cells respond to ABA treatment [56]. Indeed, the abundance of LANCL2 was reduced in the spinal cord with nerve injury- induced neuroinflammation, and this reduction was reverted by ABA treatment [108]. Moreover, ABA treatment prevented the reduction in LANCL2 protein expression in the cortex of an Alzheimer's disease mouse model [97].

The role of the ABA and LANCL2 signaling on mammalian inflammatory signaling pathways is controversial, given that both pro-inflammatory and anti-inflammatory effects of this axis have been reported [35,36,95,97,109,118]. Possibly, the ABA/LANCL2 function on inflammation is tissue/organ-specific. For instance, pro-inflammatory activity was reported in ABA treated granulocytes that showed an increment in phagocytosis, production of reactive oxygen species (ROS) and nitric oxide (NO) [35]. In accordance, an increment of TNFα, NO, and ROS dependent of ultraviolet light induced ABA release from granulocytes and keratinocytes has been demonstrated [36]. On the contrary, an anti-inflammatory ABA activity was induced in animals with inflammatory bowel disease, since this treatment reduces TNFα expression and macrophage infiltration in white adipose tissue [118]. Besides, an ABA- induced reduction of glial activation and production of TNFα and IL-1β was reported, leading to an improvement of cognitive function in the brain of a murine model of Alzheimer's disease [97]. In this sense, ABA treatment also reduces high fat diet- induced microglial activation and TNFα production in the hypothalamus of rats [95]. Moreover, ABA treatment attenuates spinal neuroinflammation induced by nerve injury in the spinal cord, and reduces Iba1 and TNFα expression [108]. An explanation proposed elsewhere, is that two different signaling pathways may be working for the opposite inflammatory ABA induced responses [119]. Supporting this idea, it was shown that ABA- induced pro-inflammatory responses in granulocytes is mediated by a pertussis toxin (PTX)-sensitive G-protein [35]. In contrast, ABA- induced anti-inflammatory activity is not affected by PTX, given that ABA treatment still attenuated lipopolysaccharide- induced microglial activation and TNFα production in the spinal cord, suggesting that G-protein is dispensable in this scenario [108].

In another line of evidence, intrathecal ABA administration in rats lead to analgesia in tail-flick and hot-plate tests [110]. Furthermore, intracerebroventricular ABA application showed a potent pain-relieving activity in rats under formalin tests [109]. The molecular mechanism of these phenotypes is PKA-dependent and involves p-ERK down-regulation, as well as the peroxisome proliferator-activated receptors (PPAR β/δ) and opioid signaling activation [109-110]. Interestingly, opioids induce antinociception via PTX- sensitive inhibitory G-proteins [120]. Of note, ABA is structurally similar to the PPARγ agonist thiazolidinediones and both compounds ameliorate insulin resistance and inhibit systemic inflammation [67,121]. Besides, PPAR receptors are members of the nuclear receptor superfamily [122].

ABA plays a critical role in the genesis of neuropathic pain and showed antinociceptive effects [108-110]. The fact that deficiencies in ABA reception and signaling in mammals can be remedied by exogenous ABA application provides a rationale to explore neuropathic pain treatments with this phytohormone. Moreover, given that ABA is present in a vegetable and fruit-based diet, it is also conceivable to explore the nutraceutical application of ABA in the neuropathic pain field.

Conclusion and future perspectives

There is substantial evidence to argue that ABA plays a neurotrophic role in the mammalian central nervous system, related with sleep, depression, pain and memory **(figure 1b)**. While these evidences are mostly based on animal models and cell lines, further insight into ABA functions in the human brain would be necessary in order to determine its potential therapeutic effect.

Despite the fact that ABA is produced and released by the brain itself [34], it is also conceivable to study the nutraceutical application of this phytohormone given that it readily permeates the blood brain barrier [64]. A fruit and vegetable rich food diet represents a natural source of ABA [123]. In particular avocados (2.0 mg/kg), citrus (1.25 mg/kg), soybean (0.79 mg/kg) and figs (0.72 mg/kg) contain high ABA levels [123]. An interesting field of research would be to generate crops with magnified ABA levels through abiotic stress treatments or genome editing. Alternatively, the feasibility of ABA production in bioreactors was recently demonstrated, using the oleaginous yeast *Yarrowia lipolytica* [124].

Finally, an increasingly used tool in agriculture is the use of ABA agonists to combat the severe drought episodes induced by the climate change [125-126]. Some of these agonists are even more potent and persistent than ABA in crops. Studies using ABA agonists in mammals have not been reported yet, representing a long and promising road ahead in this field.

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