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REVIEW

Salicylic acid receptor in plants and humans

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A NAD(P)H-reductase like protein that undergoes conformational changes in the presence of salicylic acid, aspirin, and 2,6-dihydroxybenzoic acid has been purified. The protein is evolutionarily conserved and was found in plants and humans. A strong relationship between the protein conformation and temperature of plants, human neuroblastoma cell line, SK-N-SH, and mouse brain tissue has been demonstrated. These findings create a common ground for studying thermoregulation in plants and humans.

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Introduction

Aspirin (ASA) and salicylic acid (SA) are of considerable interest because of their multiple effects in humans as well as plants. SA is a naturally occurring compound in many plants [1]. The acid, in addition to triggering a rise in temperature in plants [2], also acts as a signal in plant resistance to various pathogens [3]. In humans, ASA (acetylsalicylic acid) and SA inhibit the synthesis of prostaglandins [4], reduce the risk of cardiovascular diseases [5], and the development of colon-cancer [6]. In children, both drugs can cause a disorder known as the Reye's syndrome [7].

Thermoregulation in plants

One striking example of thermoregulation in plants is provided by the inflorescences of several arum lily species such as *Sauromatum guttatum*. On the day of inflorescence opening, the *Sauromatum* appendix (a 20 cm-long, slender organ) becomes hot, reaching a 32°C [8, 9]. In the *Sauromatum* appendix and other thermogenic plants, the temperature rise can be triggered by three phenolic compounds: SA, ASA, and 2,6 dihydroxyben-zoic acid [2].

The current concept on thermoregulation in the *Sauromatum* appendix is that heat is generated by the mitochondria via an alternative, cyanide-resistant oxidase [10, 11]. The activity of this oxidase, which is present in the mitochondria of many plants, does not generate a proton-motive force, and energy is thus released as heat, whereas the activity of the cytochrome pathway generates a proton-motive force that leads to ATP production. The saturation of the cytochrome pathway controls the electron flux through the alternative oxidase and consequently, it controls the amount of heat that is generated.

Thermoregulation in humans

Human core body temperature is maintained within a narrow range, around the set point of ~37ºC, whereas the temperature of the skin and extremities can vary over

several ºC. Many factors such as metabolism, behavior, and hormones can affect body temperature [12, 13]. There are three major energy sources within the human body that generate heat as a by-product and they contribute to core body temperature. These sources are cellular respiration, muscular activity [14], and diet-induced thermogenesis [15]. Other sources of heat are ATPases such as, Na^+, K^+ ATPase [16] and Ca^{2+}-ATPase [17].

Adaptive thermogenesis (non-shivering thermogenesis) is an induced mechanism that ensures the maintenance of core body temperature in cold exposure and during arousal from hibernation. In these cases heat is generated via the mitochondrial uncoupling proteins in brown adipose tissue [18]. Another source of heat, especially in a cold environment, is shivering that results from the increase in the metabolism of the skeletal muscles (shivering thermogenesis) [19].

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The *Sauromatum* appendix is rich in oil bodies and lipophilic deposits that are depleted during thermogenesis [20]. To isolate hydrophobic proteins associated with the lipophilic material, a combination of water and an organic solvent was used as an extraction solution [21]. The major protein that was purified from these extracts was a NADP(H)-reductase like protein. The protein was present in two charge state distributions that have been detected using electrospray ionization-mass spectrometry. One conformation, state A (an extended state) appeared prior to heat-production, and state B (a compact state) began appearing one day prior to heat-production. The protein transition to state B was complete on the day of heat-production. In contrast, the protein was present in state A in healthy leaves of *Arabidopsis* (a non-thermogenic plant), whereas in thermogenic male cones of *Encephalartos ferox* it was present in state B. The purified protein exhibited discontinuous and reversible volume phase transitions in the presence of 1 pM SA. The protein stayed at each volume for ~4-5 min with a fast relaxation time between the 2 phases. The protein was self-assembled in aqueous solutions into micrometer sizes morphologies. The assembly produces a broad range of cyclic and linear morphologies that resemble micelles, rods, lamellar micelles, as well as vesicles. These assemblies suggest that the protein can be present as an oligomer inside the cell.

The existence of the protein in the human neuroblastoma cell line, SK-N-SH, and in mouse brain tissue has also been demonstrated. The charge state distribution of the human protein was identical to its plant counterpart from the *Sauromatum* appendix during heat-production (state B). Addition of 10 µM SA to the neuroblastoma cells caused a shift of the charge state distribution of the protein to higher *m/z* values. It implies that SA triggered a conformational change and the protein reached a more compact state. It suggests that the potential of the protein to respond to SA is conserved in humans.

These results may reveal the existence of a thermoregulation system that is evolutionarily conserved and is operating by conformational changes of NADP(H) reductase like proteins. This discovery may also represent an opportunity for a better understanding of some of the diverse functions of SA and ASA in plants and humans.

Conflicting interests

The authors have declared that no competing interests exist.

References

1. Raskin I, Skubatz H, Tang W, Meeuse BJD. Salicylic acid levels in thermogenic and non-thermogenic plants. Ann Bot 1990; 66:369-373.
2. Raskin I, Turner IM, Melander WR. Regulation of heat production in the inflorescence of an Arum lily by endogenous salicylic acid. Proc Nat Acad Sci USA 1989; 86:2214-2218.
3. Corina AV, Dempsey DA, Klessig DF. Salicylic acid, a multifaceted hormone to combat disease. Annu Rev Phytopathol 2009; 47:177-206.
4. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol 1971; 231:232-235.
5. Hennekens CH, Dyken ML, Fuster V. Aspirin as a therapeutic agent in cardiovascular disease. Circulation 1997; 96:2751-2753.
6. Paterson JR, Lawrence JR. Salicylic acid: a link between aspirin, diet and the prevention of colorectal cancer. Quart J Med 2001; 94:445-448.
7. Pugliese A, Beltramo T, Torre D. Reye's and Reye's-like syndromes. Cell Biochem Funct 2008; 26:741-746.
8. Meeuse BJD. The voodoo lily. Sci Am 1966; 218:80-88.
9. Meeuse, BJD. Thermogenic respiration in aroids. Ann Rev Plant Physiol 1975; 26:117-126.
10. Elthon TE, McIntosh L. Characterization ands of the alternative oxidase of Sauromatum guttatum mitochondria. Plant Physiol 1986; 82:1-6.
11. Vanlerberghe GC, McIntosh L. Alternative oxidase: From gene to function. Ann Rev Plant Physiol Plant Mol Biol 1997; 48: 703-734.
12. Horton ES. Introduction: An overview of the assessment and regulation of energy balance in humans. Am J Clin Nutr 1983; 38:972-977.

13. Hulbert AJ, Else PL. Basal metabolic rate: History, composition, regulation, and usefulness. Physiol Biochem Zool 2004; 77:869-876.
14. Gonzalez-Alonso J, Quistorff B, Krustrup P, Bangsbo J, Saltin B. Heat production in human skeletal muscle at the onset of intense dynamic exercise. J Physiol 2000; 524:603-615.
15. Westerterp KR**.** Diet induced thermogenesis. Nutr & Metab 2004; 1:5.
16. Clarke RJ, Catauro M, Rasmussen HH, Apell HJ. Quantitative calculation of the role of the Na^+, K^+-ATPase in thermogenesis. Biochim Biophys Acta 2013; 1827:1205-1212.
17. de Meis L. Ca^{2+}-ATPase Uncoupled ATPase activity and heat production by the sarcoplasmic reticulum Ca^{2+}-ATPase. Regulation by ADP. J Biol Chem 2001; 276:25078-25087.
18. Nedergaard J, Golozoubova V, Matthias A, Asadi A, Jacobsson A, Cannon B. UCP1: the only protein able to mediate adaptive non-shivering thermogenesis and metabolic inefficiency. Biochim Biophys Acta 2001; 1504:82-106.
19. Haman F. A physiological systems approach to human and mammalian thermoregulation. Shivering in the cold: from mechanisms of fuel selection to survival. J Appl Physiol 2006; 100:1702-1708.
20. Skubatz H, Kunkel DD, Patt J, Howald WN, Rothman T, Meeuse BJD. Pathway of terpene excretion by the appendix of Sauromatum guttatum. Proc Natl Acad Sci USA 1995; 92:10084-10088.
21. Skubatz H, Howald WN. Purification of a NAD(P) reductase-like protein from the thermogenic appendix of the Sauromatum guttatum inflorescence. Protein J 2013; 32:197-207.
22. Skubatz H, Howald WN. Two global Conformation states of a novel NAD(P) reductase like protein of the thermogenic appendix of the Sauromatum guttatum inflorescence. Protein J. 2013; 32:399-410.
23. Skubatz H, Orellana MV, Howald WN. A NAD(P) reductase like protein is the salicylic acid receptor in the appendix of the Sauromatum guttatum inflorescence. Intrins Disor Proteins 2013; 1:e26372.
24. Skubatz H, Howald WN. Human ortholog of a plant salicylic acid receptor found in SK-N-SH cell line. Protein J 2013; 32:641-648.