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Guest Editorial

Mitochondrial Mechanisms of Photobiomodulation in Context of New Data About Multiple Roles of ATP

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Various cellular responses to visible and IR-A radiation have been studied for decades in the context of molecular mechanisms of laser phototherapy [also called photobiomodulation, low-level light therapy (LLLT)]. LLLT uses monochromatic and quasimonochromatic light in the optical region of ~600–1,000 nm to treat in a nondestructive and nonthermal fashion various soft-tissue and neurologic conditions.[1] This modality also was recently used to reverse toxic effects of neurotoxins, to treat strokes and acute myocardial infarction, and to stimulate stem cell proliferation.[2] This multiplicity of conditions treated with photobiomodulation has persuaded many unbelievers of the value of such an universal method.[3]

It is generally accepted that the mitochondria are the initial site of light action in cells, and cytochrome *c* oxidase (the terminal enzyme of the mitochondrial respiratory chain) is the responsible molecule.[2–8] Mixed-valence copper components of cytochrome *c* oxidase, Cu_A and Cu_B, are believed to be the photoacceptors.[5,9,10] The same photoacceptor molecule for different cellular responses can explain, at least partly, the versatility of low-power laser effects.

The excitation of the photoacceptor molecule sets in motion cellular metabolism through cascades of reactions called cellular signaling[2,3] or retrograde mitochondrial signaling.[11] At least two reactions are starting points for monitoring cellular-signaling reactions after light action on the cytochrome *c* oxidase molecule. One of them is dissociation of NO from the catalytic center of cytochrome *c* oxidase.[12,13] Spectroscopic studies of irradiated cellular monolayer show that two charge-transfer channels putatively to $Cu_{A_{red}}$ and $Cu_{B_{oxid}}$, as well as two reaction channels putatively connected with d-d transition in $Cu_{B_{red}}$ and $Cu_{A_{oxid}}$ chromophores, are reorganized dependent on NO presence or absence.[9] It has been suggested that the dissociation of NO (a physiologic regulator of cytochrome *c* oxidase activity) rearranges downstream signaling effects.[14]

Another signaling pathway starting from the mitochondria is connected with ATP. The ATP extrasynthesis in isolated mitochondria and intact cells of various types, under irradiation with light of different wavelengths, is well documented.[2] ATP is a universal fuel inside living cells that drives all biologic reactions. It is known that even small changes in the ATP level can significantly alter cellular metabolism. Increasing the amount of this energy may improve the cellular metabolism, especially in suppressed or otherwise ill cells.[7,8]

In connection with the versatility of LLLT effects, I draw the readers' attention to a comparatively new aspect of the ATP molecule. A long series of discoveries has demonstrated that ATP is not only an energy currency inside cells, but it is also a critical signaling molecule that allows cells and tissues throughout the body to communicate with one another.[15] This new aspect of ATP as an intercellular signaling molecule allows broadening the understanding of universality phenomenon of LLLT as well. It is known now that neurons release ATP into muscle, gut, and bladder tissue as a messenger molecule. The specific receptors for ATP as the signaling molecule (P2 family) and for its final breakdown product, adenosine (P1 family), were found and identified.[15,16]

ATP activation of P2 receptors (subtypes P2X and P2Y) can produce different cellular effects. A recent article by Anders *et al*.[17] demonstrated that P2Y2 and P2Y11 receptors were expressed in the irradiated at $\lambda = 810$-nm normal human neural progenitor cells *in vitro*. It appeared that the irradiation could be used as a replacement for growth factors. This line of research opens a new understanding of the complicated mechanisms of LLLT. From the point of view of the topic of the present article, the role of ATP as a signaling molecule provides a new basis for explaining the versatility of LLLT effects.

The second important point in connection with multiple functions of ATP and P2X and P2Y receptors is the following. When bound by ATP, P2X receptors form a channel that allows sodium and calcium ions to enter the cells. ATP binding to the extracellular surface of P2Y receptors starts a cascade of molecular interactions inside cells, with those resulting in intracellular calcium stores being released.[16] The increase in intracellular Ca^{2+} ions ($[Ca^{2+}]_i$) due to the irradiation has been measured by many authors,[2] but the mechanism of the phenomenon of $[Ca^{2+}]_i$ increase in the irradiated cells has not been explained. Ca^{2+} is a global positive effector of mitochondrial function, and thus, any perturbation in mitochondrial or cytosolic Ca^{2+} homeostasis will have implications on mitochondrial functions. This concerns the regulation of $[Ca^{2+}]_i$ from outside by binding ATP to P2X receptors. It is important to remember that both Ca^{2+} uptake and efflux from mitochondria consume $\Delta\Psi_m$

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and, in this way, depend on mitochondrial activity (and therefore on ATP synthesis), which can be regulated by irradiation.

Understanding of the multiple role of ATP in cellular metabolism will also provide a better appreciation of the cellular and molecular mechanisms of LLLT. A recent review[16] indicates that laboratories worldwide are now racing to turn the data about ATP as a neurotransmitter into therapies. As a neurotransmitter, ATP is directly involved in brain function, sensory reception, and the neuron system control of muscles and organs. When released by nonneuronal cells, it often triggers protective responses, such as bone building and cell proliferation.[15,16] Even a very brief look at all the conditions in the human body in which ATP is now believed to play a role as the signaling molecule,[16] and comparison of these data with the data on the versatile clinical actions of LLLT[1] provides grounds for a new way of thinking.

First, chronic and neuropathic pains are the disorders treated successfully with LLLT for many years.[1,18] ATP signaling is believed to be involved into pain therapy.[19]

Second, it is proposed that acupuncture (mechanical deformation of the skin by needles and application of heat or electrical current) leads to release of large amounts of ATP from keratinocytes, fibroblasts, and other cells in the skin.[20] Recall that acupuncture by laser light is a well-known modality.[1]

Third, the tumor-killing action of the photobiomodulation technique has been documented[21] but met with skepticism.[1] A tumor-killing effect of ATP has been described.[22]

Perhaps it is now time to reconsider the skepticism about treating tumors with LLLT, taking into account that ATP signaling acts, in part, to promote the suicide of the tumor cells and, in part, to promote cell differentiation, which slows tumor cell proliferation.[22]

This offers grounds to hope that the new data about the multiple functions of ATP help to bring the LLLT method closer to mainstream medicine.

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