COMMENTARY

PDE and sGC hand in hand to see the light

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In PNAS, Sikka et al. (1) suggest that melanopsin, a non–image-forming opsin (opsin4, Opn4), may play a physiological role in the regulation of vascular tone by mediating photorelaxation. The authors conclude that the response to light is due to hyperpolarization of the vascular smooth muscle cells resulting from the activation of soluble guanylyl cyclase (sGC), but does not involve protein kinase G (PKG). This study not only provides an intriguing molecular explanation for a phenomenon (photorelaxation) that has puzzled vascular biologists for more than half a century (2), but also forces us to rethink the fate of the products generated by sGC.

The Tail Sees the Light

One can only be impressed by the data reported by Sikka et al. (1) and thus accept most of their interpretations, which are based on convincing studies with genetically modified animals, gene silencing, and pharmacological inhibitors. Thus, blood vessels contain melanopsin, which when activated by light of a defined wavelength (430–460 nm, known to stimulate opsin4 in other systems) induces relaxation of their vascular smooth muscle cells. The response is clearly eNOS-, NO-, and endothelium-independent, but—as pointed out by the authors—may involve other components of the blood vessel wall [in particular, adrenergic nerve endings and adventitial fat known to modulate local vascular tone (3, 4)], which under the conditions of their experiments would be exposed first to the light stimulus that they apply. The photorelaxation desensitizes rapidly, and this desensitization convincingly is attributed to β-adrenergic receptor kinase 1 (βARK 1 or GRK2), a conclusion that is in line with the G protein-coupled receptor nature of melanopsin. The photorelaxation is explained by hyperpolarization of the vascular smooth muscle cells, presumably a result of altered gating of (yet undefined) K^+-channels, to judge from its absence in preparations contracted by high K^+ depolarizing solution. In the aorta, in which most of the experiments were performed, as pointed out by Sikka et al. (1), the presence of melanopsin may be vestigial, as that blood vessel is not likely to be exposed to light except during surgical interventions. However, because photorelaxation is observed in the more superficial tail artery not only ex vivo but also in vivo, the phenomenon could indeed be of importance in the cutaneous regulation of blood flow on exposure to sunlight, although the authors may be a little overenthusiastic in their extrapolation of the potential therapeutic applications of their discovery, because external light might not reach most deep arteries involved in major vascular pathologies. So far, so good. . .

The brilliant study by Sikka et al. without doubt sheds a new light (pun intended) on the fascinating phenomenon of photorelaxation.

But Do the Authors?

Where things become a bit blurred is when Sikka et al. (1) consider the interactions between sGC, 3′,5′-cyclic monophosphate [cGMP] and phosphodiesterase 6 [PDE6]. The references that they cite [e.g., Bondarenko et al. (5)] indicate that it is the menbranaceous (particulate) form of gyanylyl cyclase that is involved in the response to activation of opsin4. However, the photorelaxation that they report is prevented by the prototypical sGC inhibitor 1H-[1,2,4] oxadiazolo [4,3-a]quinoxalin-1-one (ODQ), which they attribute to "promiscuity" of particulate and sGCs in vascular smooth muscle cells (1). It is not obvious what "promiscuity" signifies in pharmacological terms. In addition, Sikka et al.'s interpretation is hard to reconcile with the observation that in isolated arteries, ODQ does not prevent the relaxations and increases in cGMP effected by activators of particulate guanylyl cyclase (e.g., ref. 6). If light were to activate sGC in vascular smooth muscle, ODQ should reduce the content of cGMP. Unfortunately, Sikka et al. (1) do not provide measurements of cGMP levels upon exposure to light, nor do they demonstrate that in the presence of ODQ administration of exogenous cGMP (in the form of 8′-bromo-cGMP) reinstalls photorelaxation, which would demonstrate an obligatory role for this cyclic nucleotide. However, Sikka et al. intriguingly demonstrate that photorelaxation is not prevented by inhibitors of PKG, the canonical target of cGMP produced by sGC. In addition, Sikka et al. very convincingly demonstrate that PDE6 is present in their preparations and that inhibitors of that enzyme prevent their response, which adds to the mystery of the role played by cGMP itself versus one of its metabolites in their photorelaxation. In any case, from all we know, in vascular smooth muscle PDE inhibition should result in accumulation of cGMP, whether produced by particulate or sGCs. Additionally, I have found in the literature no indications that increases in cGMP can lead to vasoconstriction or abolition of dilatations, as observed by Sikka et al. (1), but ample evidence that PDE inhibitors facilitate (rather than prevent) relaxation of vascular smooth muscle cells. Thus, the similar effects on photorelaxation of sGC and PDE6 inhibitors (which should reduce and augment the levels of cGMP, respectively) are counterintuitive, at least in blood vessels. One cannot win both ways. We have, over the years, been confronted with other counterintuitive effects of sGC inhibitors, in that they prevent endothelium-dependent hypoxic vasoconstriction (7–9). We believe (9–11) that this can be explained by "biased" enzymatic activity of sGC, leading to the production of the noncanonical (12) vasoconstrictor cyclic nucleotide, inosine 3′,5′-cyclic monophosphate. These noncanonical cyclic nucleotides are also broken down by phosphodiesterases. Inhibitors of the latter enzymes [in particular zaprinast, also used by Sikka et al. (1)] facilitate hypoxic vasoconstrictions (7), whereas PKG inhibitors do not affect them (8).

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Could it be that, like hypoxia, blue light by activating melanopsin initiates the production of noncanonical cyclic nucleotides by sGC?

Tissues and rat tails do not lie, but authors interpret! Irrespective of matters of interpretation concerning the interactions between sGC, cGMP, and PDE6, the brilliant study by Sikka et al. (1), without doubt sheds a new light (pun intended) on the fascinating phenomenon of photorelaxation, and provides it with a potential physiological role.

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