Pain Research Forum

Progress through collaboration

For Pain, Green Light Means Stop

Visual exposure to green light is analgesic in rats

by Stephani Sutherland on 6 Mar 2017

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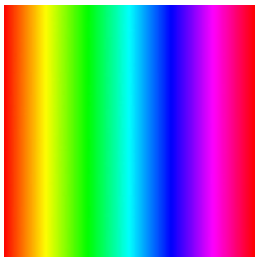

The next big wave in pain treatment might come in the form of light waves—green light, in particular. No, not from a high-tech optogenetic manipulation, but simply ambient green light.

According to new research, green light alleviated pain in naïve rats and in rats with spinal nerve ligation (SNL), a model of chronic neuropathic pain. Investigators determined that green light exerted its effects through the visual system and required the release of endogenous opioids in the central nervous system.

The work, a collaboration among researchers including Rajesh Khanna, Todd Vanderah and Frank Porreca, all at the University of Arizona, Tucson, US, was published February 1 in Pain.

“These experiments test an accessible, translatable hypothesis that supports further exploration of different spectral patterns of light to modulate pain in people with chronic pain,” said Andrew Ahn, a neurologist and translational neuroscientist at Eli Lilly and Company, Indianapolis, US, who recently studied pain-related photosensitivity and was not involved in the current work.

From green light to pain relief

To begin, first author Mohab Ibrahim tested the effects of various types of light on rats' responses to pain. Ibrahim placed light-emitting diodes (LEDs) on the outside of the rats' clear plastic cages and exposed the animals to light for eight hours per day for five days. (Aside from the colored LEDs, the room was dark.)

Rats exposed to normal ambient light (fluorescent lights and light from a window), white LEDs, or darkness did not show any change in paw withdrawal latency (PWL) from a hot surface. But green light (with a wavelength of 525 nm) had an unexpected effect.

"Much to my surprise, green light was anti-nociceptive in the rats," Ibrahim said.

PWL increased by about 25 percent, an effect that plateaued on the second day and remained steady for four days after the green light exposure ended. Blue light (472 nm) had a smaller but still statistically significant effect on PWL.

Skeptical of his results, Ibrahim told PRF, he ran the experiments several times. Once convinced the finding was real, Ibrahim tested different intensities of green light ranging from 4 to 110 lux and found that the lowest-intensity light was sufficient to increase PWL. Interestingly, exposure to 330 lux was less effective than lower intensities.

Importantly, green light also had an anti-nociceptive effect in the SNL rat model. Seven days following spinal injury, rats displayed thermal hypersensitivity and mechanical allodynia, as expected. Four days of green light exposure reversed the thermal hypersensitivity, an effect that lasted 10 days after the light was stopped. Mechanical allodynia was also reversed, which lasted four days beyond light treatment.

The finding that such a low-intensity light—only 4 lux—was capable of producing the analgesic effect is notable, Ahn told PRF. "Rodents are exquisitely sensitive to light," Ahn

said. “Had [the researchers] used a much higher level, I would wonder whether they were confounding the experiment with a noxious stimuli. So this is a strength of the study—that they are using an animal-appropriate level of illumination.”

Opioid release required

The authors traced the anti-nociceptive effect of green light to release of endogenous opioids in the central nervous system. After eight hours of green light exposure, rats were given the mu-opioid receptor (MOR) antagonist naloxone either subcutaneously or intrathecally. Both delivery methods reversed the light’s anti-nociceptive effect.

Neurons in the rostral ventromedial medulla (RVM) are a source of endogenous opioid release. Microinjection of the sodium channel blocker lidocaine in the RVM also reversed the pain-dampening effect of green light.

“The [analgesic] effect was blocked by naloxone and by block of RVM neuron activity, so that really suggests a central [nervous system] pathway,” said Susan Ingram, a pain physiologist at Oregon Health and Science University, Portland, US, who was not involved in the work. That’s important, she said, because “endogenous opioids are known to be released in chronic pain states, so [green light] could be useful to enhance that natural release.” Moreover, previous work has shown that a subset of neurons in the RVM was unexpectedly responsive to light (**Martenson et al., 2016**).

A survey of messenger RNA encoding endogenous opioids in the spinal cord suggested that the proenkephalin-A gene, but not other opioid genes, was upregulated in green light-exposed rats compared to controls, suggesting that endogenous enkephalins may mediate the anti-nociceptive effect.

Next, the researchers wanted to rule out the possibility that the green light was producing stress-induced analgesia via sympathetic nervous system activation. They delivered

pharmacological blockers of adrenergic receptors intraperitoneally immediately after light termination and tested PWL 20 minutes later. The antagonists did not prevent green light-induced analgesia, “which argues that the analgesia is not a stress response; it’s something else,” Ibrahim said.

Ingram said, however, that a better test would have been to block more specific receptors in the stress pathway in the CNS, such as corticotropin-releasing factor receptors or glucocorticoid receptors—and before the light treatment, to prevent any potential stress-induced analgesia from developing, rather than simply showing that green light-induced analgesia could not be blocked after treatment.

The rats did not display any signs of anxiety in several behavioral tests, and motor performance on a rotating rod test was unaffected by green light.

Light in the brain

Next, Ibrahim wanted to determine how green light influenced the nervous system—was it through the eyes, or the skin?

Albino and pigmented rats developed similar anti-nociception following green light exposure, suggesting a visual route of entry. To test that, Ibrahim wanted to block the animals’ vision. Fitting blinders on rats proved to be too difficult, so technician Kerry Gilbraith, whom Ibrahim called “amazing and extremely resourceful,” fabricated tiny plastic contact lenses for the rats. Black, opaque lenses completely blocked light from entering rats’ eyes—and the anti-nociceptive effect of green LEDs. Rats wearing clear lenses, in contrast, developed anti-nociception just as control rats without lenses did. Strikingly, analgesia was also evident in rats wearing green contact lenses—which allowed light only in the green wavelength to pass—and exposed to regular room light, confirming that the light’s pathway into the nervous system was through the eyes.

But when it comes to how the light exerts its effect in the brain, said Khanna, “we are just at the beginning of that journey.” Khanna says they will focus on studying the molecular underpinnings of this effect in the spinal cord and RVM, which perhaps involve glia or immune molecules. “Investigating those molecular mechanisms is our bag of tricks.” At this point, the pathway from the retina to the RVM, however, is “completely a mystery,” he said.

Ahn says that pathway may not depend on the classic visual system. “Light is perceived in the retina by rods and cones, which project through the classical thalamocortical pathway, allowing us to detect information about objects’ features and position, to read, and see.” But other photosensitive neurons in the retina, called retinal ganglion cells, project to non-thalamic centers in the brain. Ahn found that this population is activated by light in neonatal rats even before their eyes are open (**Delwig et al., 2012**).

“This is a very primitive light detection system that’s not associated with visual images. It influences circadian rhythms, and it also activates affective emotional circuits,” Ahn said. “The present work leaves many unanswered questions about whether non-thalamocortical pathways are involved, but they are a potential substrate for light’s modulation of pain.”

Light has long been recognized to affect emotional state and even pain: People with migraine headaches experience light as aversive and even painful, and bright white light therapy has been used to treat depression (e.g., see **Goadsby et al., 2017**; **Penders et al., 2016**). But no previous studies have investigated the effects of colored light on pain, particularly at low intensity.

Green light for people?

Will green light’s soothing effect translate to humans? Ibrahim and colleagues aim to find out: They are in the early stages of a clinical trial testing the effects of green light on pain in people with fibromyalgia. The preliminary results are promising, says Ibrahim, but forming any conclusions will take a while. Meanwhile, friends and

family are asking him how they can apply the technique. Self-treating with green light is probably premature, he said, “but this is not invasive, and there is no risk.”

And, said Ahn, “given that the current drug treatments for chronic pain are inadequate and leave people with serious unmet need, exploring non-pharmacological therapies is really important.” Nevertheless, Ahn added, the work might also suggest new opportunities for pharmacological enhancement of the light-induced effect.

Ingram said that further studies of green light-induced pain relief might reveal new details about pain-processing circuitry in the brain. “If green light is analgesic, that must mean that other components of light counteract the effect, all the time.” Investigating those pathways might one day present ways to further promote pain relief, she said.

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References:

Editors' Pick

Long-lasting antinociceptive effects of green light in acute and chronic pain in rats.
Ibrahim MM, Patwardhan A, Gilbraith KB, Moutal A, Yang X, Chew LA, Largent-Milnes T, Malan PT, Vanderah TW, Porreca F, Khanna R
Pain. 2017 Feb; 158(2):347-360.
PMID: 28092651.

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