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Review

Photons and neurons

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ABSTRACT

Methods to control neural activity by light have been introduced to the field of neuroscience. During the last decade, several techniques have been established, including optogenetics, thermogenetics, and infrared neural stimulation. The techniques allow investigators to turn-on or turn-off neural activity. This review is an attempt to show the importance of the techniques for the auditory field and provide insight in the similarities, overlap, and differences of the techniques. Discussing the mechanism of each of the techniques will shed light on the abilities and challenges for each of the techniques. The field has been grown tremendously and a review cannot be complete. However, efforts are made to summarize the important points and to refer the reader to excellent papers and reviews to specific topics.

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1. Introduction

Neural stimulation with photons is not a novel idea. Efforts to stimulate frog muscle tissue and nerve fibers with visible light were reported as early as 1891 (Arsonval, 1891). While the initial results were not convincing, recent developments showed that neural stimulation with light is possible and shaped the field of neurostimulation and neuromodulation. Fig. 1 shows typical radiation wavelengths that are used today for neural stimulation. Four different approaches can be distinguished, (1) direct stimulation of the target structure with infrared radiation (infrared neural stimulation or INS), (2) activation of ion channels expressed in neurons with visible light (optogenetics), (3) activation of temperature sensitive ion channels expressed in neurons with heat (thermogenetics), (4) and in the cochlea activation of neurons through mechanical events created by laser radiation. Hereby, the interactions between the photons and the tissue determine the mechanism by which stimulation occurs. Wavelength of the radiation, radiant energy, and temporal properties of energy delivery characterize the light source, while photon absorption, reflection, and scattering characterize the tissue properties (Jacques, 2013). Depending on the light source and the irradiated tissue one can distinguish among photothermal, photoacoustical, and photochemical effects. Photochemical effects come from endogenous or exogenous chromophores, which absorb the radiation and convert it into chemical energy. Heating of the target tissue after the absorption of the photon in the target tissue can lead to pressure waves and to photoacoustic effects. In addition to the information provided throughout the paper on the photon–tissue interaction, detailed descriptions and reviews on photon–tissue interactions have been published (for reviews see Jacques, 1992, 2013; Tuchin, 2000; Niemz, 2004; Welch and van Gemert, 2012).

Abbreviations: AAV, adeno-associated viral vectors; ABR, auditory brainstem response; oABR, optically evoked auditory brainstem response; AP, action potential; BSL, bio safety level; Ca^{2+}, calcium ion; CAP, compound action potential; ChR, channelrhodopsin; Cm, centimeter; CmAP, compound muscle action potential; cw, continuous wave; dB, decibel; DP-OCT, differential phase optical coherence tomography; *E*, fluence rate; eV, electron volt; FEL, free electron laser; *f*, repetition rate; fs, femto second; HEK293 cells, human embryonic kidney 293 cells; HeNe, helium–neon; Ho:YAG, holmium-doped yttrium aluminum garnet; *H*, radiant exposure; HR, halorhodopsin; Hz, Hertz = 1/s; ICC, central nucleus of the inferior colliculus; INS, infrared neural stimulation; J, Joule; LV, lentiviral vectors; Nd:YAG, neodymium-doped yttrium aluminum garnet; M, mole; NA, numerical aperture; m., musculus; mm, millimeter; ms, millisecond; nm, nanometer; ns, nanosecond; OHC, outer hair cell; Pa, Pascal; *P*, power; *Q*, radiant energy; s, seconds; SPL, sound pressure level (reference pressure is 20 μPa); TEM, transmission electron microscope; Ti:Sapphire, titanium–sapphire; TRP, transient receptor potential; TRPV, transient receptor potential vanilloid; W, Watt; Yb:glass, ytterbium-doped glasses; λ, wavelength; τ_p, pulse length; μm, micrometer; °C, degree celsius; Φ, fluence rate

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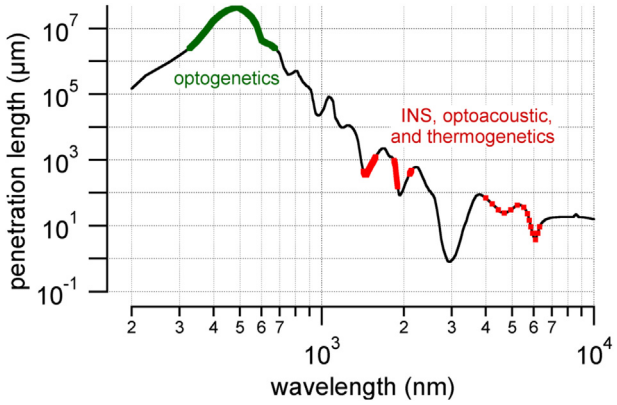

Fig. 1. The plot shows the penetration depth for radiation of different wavelength into water. The data were obtained from Hale and Querry (1973). Colored sections reflect the wavelength used for the different optical methods described. Green represents the range of radiation wavelengths used for optogenetics, red for thermogenetics, optoacoustics and INS. For the red dotted line it has been shown in the rat sciatic nerve that stimulation can be achieved. However, at present, it is not possible to deliver the radiation with optical fibers.

2. Early efforts to stimulate neurons with light

An overview of the efforts is given in Table 1. Subsequent to D'Arsonval's experiments, Arvanitaki and Chalazonitis (1961) demonstrated that inhibition and excitation can be triggered in unstained but pigmented nerve cells by irradiation with radiation of different wavelengths, ranging from the visible (λ = 400–700 nm) and infrared (λ = 750–4000 nm). They used several preparations for optical neural stimulation, such as Aplysia and Sepia giant axon. In response to the irradiation, most neurons were depolarized. However, some nerve cells in an Aplysia preparation decreased their neural activity during infrared irradiation. The hypothesized mechanism for both, excitation and inhibition, was the absorption of light by an undetermined cellular molecule.

To map intracellular connections of the abdominal ganglion of Aplysia californica, Fork (1971) irradiated its ganglion with continuous blue (λ = 488 nm), green (λ = 515 nm), or near infrared radiation (λ = 1060 nm) and evoked excitatory and inhibitory neural responses selectively and reversibly for 2–5 s. Stimulation of the neurons was possible without damaging the cells. He also examined possible mechanisms for the light-evoked stimulation of the cells by changing the ion content of the bathing solution and by applying different ion channel blockers. He concluded that the irradiation opens sodium-ion channels and may activate the sodium–potassium ion exchange pump. However, the persistence of residual responses in the presence of ouabain suggests a more complex mechanism.

For optical stimulation concurrent with electrical stimulation a variety of continuous and pulsed optical sources have been used to modulate electrically evoked neural activity. The effect of irradiation at wavelengths in the ultraviolet (λ < 370 nm; continuous wave (cw) irradiation for >2 min) on the excitability of myelinated nerve fibers has been studied (Booth et al., 1950). Irradiation of the node of Ranvier increased the electrical stimulation threshold and

Table 1
History of optical stimulation, optogenetics not included.

Wavelength (nm)	Light source	Mode	Tissue	Effect	Mechanism	Absorber	Literature
400–700	Broad band light source	Continuous	Aplysia californica, Sepia giant axon	Excit.	In Table 1 of their list possible molecules that likely absorb the radiation		Arvanitaki and Chalazonitis (1961)
750–4000	Broad band light source	Continuous		Excit./inhib.			
488, 515, 1060	Laser	Continuous	Aplysia californica	Excit./inhib.	Opens sodium channels; activates sodium potassium exchange pump	Not known	Fork (1971)
260, 265, 320, 370	Mercury vapor lamp	Continuous		Inhib.	Radiation destroys thiamin; neural damage	Thiamin	Booth et al. (1950)
694	Ruby laser	Pulsed (100 µs)	Cultured rat cerebellar tissue	Inhib.	Mitochondrial heating with subsequent damage	Mitochondria (?)	Olson et al. (1981a,b)
490, 685	Dye laser	Pulsed (1 µs)		Inhib.			
632	HeNe laser	Continuous	Snail ganglia	Increases rate of action potentials	Temperature increase	Water	Balaban et al. (1992)
434–600	Dye laser	Pulsed (15 ns)	Crayfish stretch receptor neurons	At 460 nm increases than decreases electrically evoked action potentials	Calcium release from mitochondria	Flavins	Uzdensky and Savransky (1997)
1064	Nd:YAG	Pulsed (8 ns)	Spinal card, dorsal roots, peripheral nerves	Decreases compound action potential amplitudes	Temperature increase		Wesselmann et al. (1991a,b)
1064	Nd:YAG	Pulsed (100 µs)	Nerve	Decreases compound action potential amplitudes	Temperature increase		Orchardson et al. (1997)
904	Gallium–Arsenide laser	Pulsed (220 ns)	Muscle and sciatic nerve	No effect on electrical evoked stimuli			Bagis et al. (2002)
980	GalnAs/GaAs laser diodes	Pulsed (4–400 ms)	Rat dorsal root ganglion cells	Induces inward current	Temperature increase		Greffrath et al. (2002)
532	Nd:YAG	Pulsed (10 ns)	Guinea pig cochlea	Cochlear compound action potential	Mechanically stimulate hair cells		Wenzel et al. (2009), Zhang et al. (2009)
420–2150	Optical parametric oscillator	Pulsed (3–5 ns)	guinea pig cochlea	Cochlear compound action potential	Mechanically stimulate hair cells	Water	Schultz et al. (2012a,b)