Shedding light on photo-switchable analgesics for pain

Parisa Gazerani*

“Photo-pharmacology deals with a delicate process of design, synthesis and application of drugs that can be modulated with light. This approach offers a possibility to solve off-target side effects.”

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Photo-pharmacology [1] deals with photo-responsive agents that are compounds whose activity is controlled or regulated by light. Photo-responsiveness of these agents is achieved when a switch occurs between two (*cis-trans*) or more isoforms of photo-compounds in response to light. Hence, the biological functions can be controlled by these compounds that act on native receptors or acceptors [1–3]. Two types of synthetic photo-switches exist, those that are covalently attached to their target (photo-switchable tethered ligands) and those that are tightly bound through noncovalent interactions (photo-chromic ligands). Photo-switchable or photo-pharmaceutical terms are used to include both types. Targets for these compounds range from ion channels and G-protein-coupled receptors (GPCRs) to transporters, enzymes and lipids [2]. Photo-pharmacology principle holds an advantage of selectivity because light can be delivered with a high precision in terms of its intensity and wavelength for adjustable dosing [1–3]. The possibility to alter the activity of a drug by light offers several advantages, such as reducing

off-target, systemic side effects or even drug resistance [3]. Light-controlled drugs have been further studied in the field of cancer, diabetes, microbial infections and neurology [1–3]. In the latter concept, only few photo-switchable regulators of nociception have been described so far, which will be presented here briefly to stimulate curiosity for further research.

Photo-compounds for μ -opioid receptor

Photo-switchable opioids are compounds that can be reversibly switched on and off with light. Application of such compounds (potential photo-analgesics) can allow an optical control of μ -opioid receptors. The first compound was an azobenzene derivative of fentanyl (photofentanyl-2 or PF2) [4]. Fentanyl is a potent synthetic μ -opioid receptor agonist. The μ -opioid receptor is a member of GPCRs (family A) that also include adrenergic receptors, muscarinic acetylcholine receptors, dopamine, histamine and serotonin receptors.

The GPCR's photo-switchable compound PF2 was produced and tested in human

KEYWORDS

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*Department of Health Science & Technology, Faculty of Medicine, Aalborg University, Frederik Bajers Vej 7A2-A2-208, 9220 Aalborg East, Denmark; Tel.: +45 9940 2412; gazerani@hst.aau.dk

“Photo-pharmacological control of nociception pain is a rapidly growing field.”

μ -opioid receptor transfected into HEK293T cells with the G-protein-coupled inward rectifier channels (GIRK1 and GIRK2) [4]. The optimal photo-switching properties of PF2 were achieved at concentration of 25 μ M. *Trans*-PF2 is the isoform predominant in dark or in optical stimulation of 420–480 nm light. This isoform acted as an effective agonist for the μ -opioid receptor. However, *cis*-PF2, the predominant isomer at 360 nm was almost inactive. Hence, switching from 360 nm to blue light initiated a quick potassium influx via GIRK channels that was terminated by 360 nm light, which could abolish the activation of μ -receptors. Introduction of PF2 not only opened up a new road toward potential use of photo-analgesics in the future, but also to demonstrate that photo-switchable compounds can also be used to further investigate opioid receptors [3,4].

Photo-compounds for TRPV1 receptor

Photo-switchable compounds acting on TRPV1 have also been developed [5]. TRPV1 is a nonselective cation channel with a well-established role in nociception. A group of researchers initiated a breakthrough investigation of optical control of TRPV1 and developed several photo-switchable compounds [5]. This group also presented the first example of fusion of photo-pharmacology and lipid signaling with potential application in controlling protein–lipid interactions [5].

Capsaicin is a TRPV1 agonist. Azo derivatives of capsaicin were synthesized to investigate photo-switchable agonists of TRPV1. Isomeric (*cis* and *trans*) photo-switchable compounds were tested for their activity on TRPV1 channels. These compounds are inactive in dark or with blue light and active under UV-A light application. UV-switchable compounds have limited application for clinical use. Therefore, a lot of effort has been focused on synthesis of azo-benzenes that can be switched with visible light. One of the azologues of capsaicin (*cis*-AzCA4) was found to be the most effective in activating TRPV1. Photo-activation of TRPV1 with this compound was reversible and achieved in both HEK293T cells and C fibers. TRPV1-positive neurons of mice dorsal root ganglion selectively responded to *cis*-AzCA4. *In vivo* tests demonstrated a TRPV1-mediated hyperalgesia by this compound [3,5].

Photo-compounds for GABA_A receptors

GABA_A receptors are activated by GABA. GABA is an inhibitory neurotransmitter and following

its interaction with GABA_A receptors, chloride influx is promoted and the postsynaptic neuron is hyperpolarized. Hence, GABA_A receptors have been targeted for producing anesthetic, hypnotic and anticonvulsant properties.

Propofol acts on GABA_A and has long been used in systemic anesthesia. It is generally accepted that this lipophilic agent acts most likely through potentiation of GABA-induced currents and also through a direct activation of chloride channel when used at higher concentrations. GABA_A receptors are not sensitive to light. A group of researchers [6] produced photo-switchable agents based on propofol molecular structure that could be switched between an active and an inactive form by the application of light. Azo-benzene derivatives of propofol were synthesized as azo-propofols 1–16 (AP1–16). Among these azo-propofols, AP2 presented favorable characteristics. *Trans*-AP2 was found capable of activating GABA_A receptor subunit of $\alpha_1\beta_2\gamma_2$ in *Xenopus* oocytes. *Cis* isoform of this compound was found inactive. Whole-cell patch clamp method in HEK cells with *trans*-AP2 also showed that exposure to light leads to conversion of AP2 to its *cis* isoform and a decrease in current amplitude. Switching off the lights could reverse the diminished amplitude. An *in vivo* animal model in albino *Xenopus laevis* tadpoles was then applied to investigate AP2 anesthetic activity [6]. Inhibiting righting reflexes, a standard assay for studying anesthesia, was used and AP2 was shown to be capable of causing anesthesia. This study [6] demonstrated that azo-propofol AP2 potentiates GABA-induced chloride currents and can act as a light-dependent anesthetic agent, which is activated in dark and its activity is reversed by application of violet light [3,6]. It has been proposed that hyperpolarization-activated cation channels (HCN1) are also involved in propofol-induced anesthesia. AP2 might also be capable of modulating these targets, however, this is yet to be discovered [6].

Photo-compounds for voltage-gated channels

Quaternary ammonium-azobenzene-quaternary ammonium (QAQ) is a photo-switchable compound developed on the basis of lidocaine and its derivative QX-314, local anesthetics that block voltage-gated channels [7,8]. *Trans*-QAQ is capable of blocking ion channels, but the *cis* form is inactive. QAQ is selective for nociceptors and its inhibitory effect can be regulated by light.

QAQ has been used together with capsaicin to block TRPV1-expressing nociceptors selectively. Under prolonged pain conditions, QAQ inhibitory effect does not seem to need a co-targeting of TRPV1, due to the fact that active nociceptive neurons would allow its internalization [7,8]. An *in vivo* test was also performed by topical application of QAQ to rats' cornea, where von Frey hair evoked responses demonstrated that *trans*-QAQ could block blink sensitivity following irradiation of 380 nm light [8].

Fotocaine is another compound based on azologization of fomocaine, which is a local anesthetic. A group of researchers [9] have demonstrated that fotocaine is taken up by neurons in brain slices where neuronal action potential can be regulated by application of light. Neurophysiological application of this photo-switchable compound has opened up a possibility to test its application as a potential analgesic [9].

Perspectives

Photo-pharmacology deals with a delicate process of design, synthesis and application of drugs that can be modulated with light. This approach offers a possibility to solve off-target side effects. Photo-switchable compounds are bioactive molecules with moieties that change their structure by light and these changes regulate their therapeutic action. Photo-pharmacological control of nociception pain is a rapidly growing field. More photo-switchable compounds are in pipeline, for example, photo-switchable compounds for ionotropic glutamate receptors, kainate receptors, AMPA receptors, metabotropic glutamate receptors, adrenergic receptors, muscarinic acetylcholine receptors, dopamine, histamine, serotonin receptors, calcium and potassium channels and number of transporters and pumps [2,3]. Innovative photo-pharmaceutical candidates would not be achieved without combination of diverse expertise such as chemistry, biology,

physiology, pharmacology and medicine [2]. Suitable photo-switchable compounds and targets need to be chosen. Under ideal conditions, a photo-switchable compound is active as an agonist or antagonist in one molecular structure and fully inactive in other. A systematic classification of body organs has been proposed [3] to make it easier to understand how light can be delivered to them and this needs to be implemented for the compounds under developments. This classification has identified class 1 for easily accessible organs such as skin and eye. Class 2 compounds are those that can be accessed by endoscopy, for example, GI tract, intraoral cavity, sinuses, respiratory system, cervix and bladder. Class 3 includes those parts that are accessible through skin but without any incision, for example, thyroid, testicles, lymph nodes, muscles and tissues lying just under the skin. Class 4 would accommodate compounds that need a minor incision for accessibility, for example, pancreas, liver, ovaries, stomach, intestines, kidneys, spleen, prostate, some blood vessels, glands, lymph nodes, muscles and bones. Major incision or operative procedure would be needed for class 5, for example, to reach brain and bone marrow. Besides delivery, testing and ensuring efficacy and safety of developed compounds, economic aspects of development must also be taken into account for further development of realistic choices toward their clinical use [1–3].

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