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PHOTOPHARMACOLOGY

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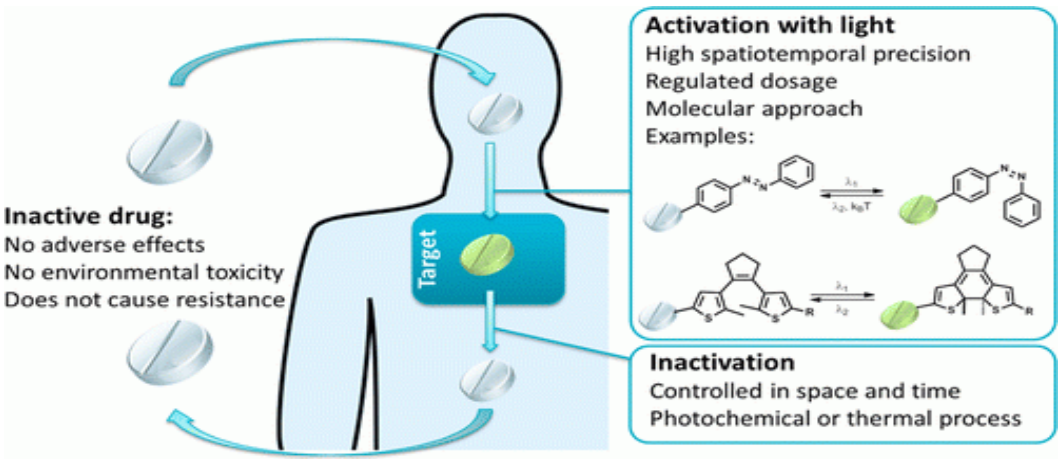
Photopharmacology means the use of light to precisely deliver the drug at the target site. Such a novel method of drug delivery system improve drug specificity by reducing off-target effects.[1] The energy of light is used to change the shape and chemical properties of the drug, resulting in different mechanism of action of the drug. This is done to eventually get control when and where the drugs are active in a reversible manner, to prevent side effects, adverse effects, and toxicity.[2] Selectivity to target site/organ can be increased by various strategies, and Photopharmacology is one such strategy. Photopharmacology provides us an external photo switch to control off-target site drug activity, and thus helps to attain selective biological activity and ameliorating off-target toxicity and resultant side effects.[3] Selectivity to target tissue/site is a problem with most of the drugs. Most of the sites of action of the drugs (receptors, enzymes, ion channels, and carrier molecules) are expressed in other sites/tissues/organs and the action in these sites leads to intolerable side effects, poor drug delivery, and then emergence of resistance.[4]

It aims to reduce systemic toxicity of the drug and the emergence of resistance, while attaining unprecedented correctness in treatment. By using small molecules, Photopharmacology provides a feasible alternative to optogenetics.[5] Whereas, serious indication of the different pharmacological targets in a wide range of organs and a survey of organ systems in the human body can be addressed in a non-invasive manner. The prospects for the target delivery of light to these organs and the exact necessities for light-activatable drugs. It also aims to illustrate the drug ability of medicinal targets with current findings and emphasizes where conceptually new approaches have to be explored to offer Photopharmacology with future prospects to bring "smart" molecular design eventually to the monarchy of clinical use.[6]

The principle of Photopharmacology consist of introduction of a reversibly Photoisomerizable unit into the molecular structure of bioactive compounds. Photoisomerizable drugs thus obtained can be used to treat localized diseases by light-activation of drugs precisely where and when they are required, leaving the rest of the treated organism unaffected, as schematically illustrated in figure 1.[6] Localized activation might reduce the toxicity burden imposed by the drugs on the patients. Moreover, the drugs can be "switched off" by light after the treatment to further minimize the side-toxicity and reduce the probability of the resistance to develop during the therapy.[7]



Photopharmacology is traditional pharmacology under control of light. Photo control can be either extrinsic (external light stimulus) or intrinsic (light from inside the body through *e.g.*, fluorescence activation at the site of action). Critical factors are: Light-delivery, target-selection, choice of photo responsive unit (photo switch) and drug-optimization.[8] Other definitions may include the use of biocompatible photo-removable drugs and generally light-responsive molecules. It is important, to mention that different approaches lead to various levels of control.[9] Photo switches offer the advantage of switching between different states reversibly. Thus allowing, for *e.g.*, local activation and deactivation. Also, further temporal deactivation can be controlled by suitable choice of thermal stabilities of the active and inactive isomer. Furthermore by various modality, selective action can be attained in special cases. Whereas, the various isomers of the photo switch show preferences for various pharmacological targets.[10]

Azobenzenes -The photoswitches

Previous researchers have observed a molecule that had two mirror image versions - or isomers - could be switched using light.[11]

The isomers required to have different shapes, so the switch was likely to alter the conformation of any attached drug and therefore the drug has the ability to reach its target site. In this way light could be used to switch drug activity on or off. The observable molecule was azobenzene ($C_{12}H_{10}N_2$), and is used extensively as a dye and food colourant. The molecule comprises two benzene rings linked by a nitrogen - nitrogen double bond.[12]

Azobenzenes, the little photo switches that could be used as very reliable little engines with which things could be driven." The more stable *trans* isomer has the benzene rings on opposite sides but, on irradiation with ultraviolet (UV) light, this switches to the *cis* confirmation, with the benzene rings sitting next to each other. In time, the molecule reverts to the more stable *transform.* Azobenzenes also benefit from a large pre-existing catalogue of toxicity data owing to their extensive industrial use.[13]

Restoring sight

The most advanced photopharmaceutical research and development being carried out by Photoswitch Biosciences is developing a light-responsive drug that could restore sight.

Principal cause of blindness is degeneration of photoreceptor cells in the developed world and is extremely irreversible. Actually there is a degenerative condition such as age-related macular degeneration (AMD), genetic diseases, such as retinitis pigmentosa.[14] The light-sensitive receptor proteins which are present in the eye called opsins, are mainly in-built photo switches which are present in membranes of retinal neurons. They work together with the light-sensitive vitamin A-based molecule retinal. A photon of light results in the photoisomerisation of retinal, which causes a conformational change in the opsin protein. This causes a cascade of cell signaling, that results in an electrical signal being sent to the brain.[15]

It was recently discovered that try to replace the function of opsins using a drug containing a switchable azobenzene molecule. The idea was to find a molecule that could directly block membranes of retinal cells through potassium ion channels & set off a signaling cascade similar to that created when photoreceptor proteins are working.[16]

Chemotherapy side effects

The novel synthesis of a photo switchable chemotherapy drug is based on combretastatin A-4(CA4). The molecule has the capability to stop cell division by inhibiting the production of microtubules (rigid, hollow rods of tubulin polymers that make up a cells cytoskeleton.)[17]

Drugs that inhibit the production of microtubules make up a major class of chemotherapies. However, as with many cancer drugs, their powerful effects lead to severe side effects, which can limit dosages.[18]

Photopharmacology may propose a new solution. "A new class of drugs that only hits microtubules". The original CA4 molecule has a trimethoxybenzene ring, giving *cis* and *trans* isomers of the drug. The *cis* isomer is more potent than the *trans* isomer. By substituting a carbon double bond with a nitrogen double bond and adding some extra functional groups, a new conventional compounds is formed named photostatins, whose drug activity can be controlled by blue light. The light causes a switch to the *cis* conformation, which is 250 times more toxic to cancer cells than the *trans* isomer. This method could be a novel treatment for skin cancers.[19]

Diabetes and beyond

Type 2 Diabetes Mellitus is commonly treated with drugs such as sulfonylurea, which stimulates insulin secretion by binding to receptors on pancreatic beta-cells. But therapy comes with some serious side effects such as blood glucose decreases and increases in cardiovascular disease etc. Limiting drug release to the pancreas might prevent these events by restricting the drug's actions to where it's needed, therefore reducing off-target physiological effects.[20]

Glimethoride is a third generation sulfonylurea drug, containing an azobenzene unit. The drug is activated after a meal, Most probably using an implanted blue LED: "The drug switches on very rapidly in milliseconds, and because it switches off within about two seconds it is able to get quite fine control.[21]

Photopharmacology could also be used to target antibiotic resistance. It has been at the forefront of

research in the field, has decades of experience in designing molecular switches for nanoelectronics and saw an opportunity to apply some of that experience to the problem of antibiotic resistance.[22]

If antibiotic activity could be switched off outside the human body, this would help to prevent developing a resistance. Recently, it has designed several switchable versions of a quinolone antibiotic containing an azobenzene unit. These could be switched on to their active state with UV light but switched off automatically within hours.[23]

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