Bright Ion Channels and Lipid Bilayers

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CONSPECTUS

If we look at a simple organism such as a zebrafish under a microscope, we would see many cells working in harmony. If we zoomed in, we would observe each unit performing its own tasks in a special aqueous environment isolated from the other units by a lipid bilayer approximately 5 nm thick. These confined units are social: they communicate with one another by sensing and responding to the chemical changes in their environment through receptors and ion channels. These channels control the highly specific and selective passage of ions from one side of the cell to the other and are embedded in lipid bilayers. The movement of ions through ion channels supports excitation and electrical signaling in the nervous system.

Ion channels have fascinated scientists not only because of their specificity and selectivity, but also for their functions, the serious consequences when they malfunction, and the other potential applications of these molecules. Light is a useful trigger to control and manipulate ion channels externally. With the many state-of-the-art optical technologies available, light offers a high degree of spatial and temporal control, millisecond precision, and noninvasive intervention and does not change the chemical environment of the system of interest.

In this Account, we discuss research toward the dynamic control of lipid bilayer assembly and channel function, particularly the transport across the lipid bilayer-ion channel barrier of cells using light. We first summarize the manipulation of ion channel activity with light to modulate the channel’s natural activity. Based on the type of photoswitch employed, we can achieve novel functionalities with these channels, and control neural activity. Then we discuss the recent developments in light-induced transport through lipid bilayers. We focus on three different approaches: the incorporation of photoswitchable copolymers into the lipids, the doping of the lipid bilayer with photosensitive amphiphiles and the preparation of the lipid bilayers solely from photoswitchable lipids.

These examples reflect the versatility of what we can achieve by manipulating biological systems with light, from triggering the permeability of a specific area of a lipid bilayer to controlling the behavior of a whole organism.

Photochromism and Molecular Photoswitches

Numerous biological processes, including the process of vision, are enabled by interactions of matter with light. Nature has developed advanced molecules, such as rhodopsin, which undergo isomerization upon absorbing a photon of a given energy; an event that is, for example, translated into sensual receptions. These intricate photoresponsive systems greatly stimulated the design of photochromic materials, in particular photochemically bistable molecules.

Nowadays, a plethora of synthetic molecules, called "molecular photoswitches", which change their structure and properties upon light irradiation, is available. These
compounds are often characterized by having two or more isomeric forms, which can be addressed in a reversible manner by illumination with light of a specific wavelength.

Molecular photoswitches have been used in the biological context, for example, in controlling the structure and properties of peptides and DNA, and channel protein function. The structures and photoinduced transformations of the photoswitches most relevant for this Account are summarized in Figure 1.

Small photocaged molecules (Figure 1A) undergo irreversible bond cleavage upon irradiation, which results in the triggered exposure of bioactive functionalities. UV-irradiation of azobenzene molecules (Figure 1B) promotes the trans–cis isomerization at the central double bond, resulting in a considerable change in geometry and polarity. This process is reversible both thermally and by irradiation with visible light. In spiropyrans (Figure 1C), the C<sub>spiro</sub>–O bond undergoes heterolytic cleavage upon UV-irradiation (360–370 nm) resulting in

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**FIGURE 1.** General types of molecular photoswitches used for the photoregulation of transport through lipid bilayers and ion channels.

**A** PHOTOCAGED SMALL MOLECULES

![Diagram](image1)

**B** AZOBENZENES

![Diagram](image2)

**C** SPIROPYRANES

![Diagram](image3)

**D** MALACHITE GREEN LEUCONITRILES

![Diagram](image4)
the formation of a polar, zwitterionic conjugated system, which is accompanied by a very large change in polarity. The ring-opening can be reversed both thermally and photochemically by irradiation with visible (>460 nm) light. Malachite Green derivatives (Figure 1D) undergo heterolytic cleavage of \( C-N \) bond, changing from a state of low polarity to a charged state of high polarity.

Transport Across Lipid Bilayers through Light-Modulated Ion Channels

Biological membranes that separate individual cells or subcellular functional units from their immediate external environment are composed of a mixture of lipid bilayers and proteins. While lipid bilayers do not allow the passage of polar or hydrophilic molecules across, protein-based ion channels form temporary pores in the lipid bilayer and allow the passage of specific ions after being excited by a variety of stimuli. The stimuli can be changes in the concentration of specific ligands or ions, fluctuations in temperature, changes in the membrane potential, membrane tension, or light intensity.\(^9\)

In the past few years, several strategies were developed to re-engineer ion channels and lipid bilayers. In the first part of this Account, we will focus on light as a tool for interference with ion channel functions.

**Ion Channels with Photocaged Small Molecules.** One of the earliest methods for manipulating transport across lipid bilayers was targeting ion channels and receptors with a channel modulator that has been made biologically inert by a photocleavable protecting group.\(^2\)

The caging technology has been applied to various neurotransmitters for controlling neuronal activity as discussed in a recent review.\(^6\) We explored the use of a caged light-switch to introduce light or pH-sensitivity to a mechanosensitive channel of large conductance (MscL), a membrane protein that is located in the cytoplasmic membrane of *Escherichia coli* (Figure 2A). In Nature, this channel senses the tension in the lipid bilayer upon a sudden hypoosmotic shock and functions as a safety valve to protect bacteria from lysing.\(^10\) Although the channel opens in response to tension, it can also gate spontaneously upon increase in the...
Bright Ion Channels and Lipid Bilayers

Szymański et al.

The hydrophilicity of its pore region (Figure 2B–D). This channel has been proposed by us as a remote-controlled release valve in liposomal drug delivery devices and sensory applications.

We designed synthetic compounds that undergo light-induced charge separation, localized buildup of charge, and opening of the channel (Figure 3A). The caged compound 1a (Figure 3B) comprises a cysteine-selective alkylating agent bearing a photocleavable protecting group. After its specific binding to the pore restriction of the engineered MscL channel, in which the 22nd amino acid is converted into a cysteine (G22C), the channel proteins (1b, Figure 3B) were reconstituted into artificial lipid bilayers and the ionic transport through a single channel was recorded by patch clamp measurements. There was no current flow observed through the channel in the dark (Figure 3C). However, when the proteoliposomes were exposed to UV light (>300 nm), the photolysis of the protecting group 1b liberated charged acetate 2 in the channel pore, which in return opened the channel spontaneously (Figure 3D).

Furthermore, we managed to render this channel pH-sensitive on command (Figure 4A). To this end, the amino group of a pH-modulator is coupled to a photolyzable group (Figure 1A) that can be removed by irradiation with UV light (366 nm) (Figure 4B). The functionality of the channels was tested in a fluorescence dequenching assay using synthetic liposomes with embedded MscL channels. In the dark, the channel modified with 3a (3b, Figure 4B) remains closed, irrespective of the environmental pH (Figure 4C, light gray bars). After removal of the protecting group at the amine moiety by UV irradiation (3c, Figure 4B), the channel becomes responsive to pH, which results in high release of the liposomal content at low pH due to the protonation of the amine group (3d) (Figure 4C, white bars).

Spiropyran-Modified Ion Channels. The light-induced conversion from the spiropyran to merocyanine form (Figure 1C) also causes a dramatic increase in surface wettability, that is, increase in the hydrophilicity of the pore lining. We applied this reversible change in wettability in the MscL mechanosensitive channel as a mean of reversible...
control over its gating in the absence of its native trigger, that is, tension.12 Compound 4a, based on a spiropyran core attached to a cysteine-selective iodoacetate moiety, was coupled to the amino acid 22 at the hydrophobic constriction of MscL to give 4b (Figure 5B). Upon irradiation at 366 nm, photochemical ring-opening takes place, resulting in a polar form and higher wettability allowing the passage of water and ions through the pore (4c, Figure 5B). Exposure to visible light (>460 nm) results in the reverse, ring-closing reaction, restoring the original, nonpolar state (4b, Figure 5B).

The modified channel was reconstituted into artificial lipid bilayers and its activity was monitored by patch clamp measurements. The channels conducted ions only after illumination with UV light. The channel closure could be obtained by exposure to visible light (Figure 5). Light-sensitive MscL channels were also tested for their ability to release a liposomal cargo in a fluorescence dequenching assay (Figure 6A). For both MscL 1b and MscL 4b the liposomal content could be released upon photoactivation of the channels (2 and 4c, respectively), whereas in the dark there was no release (Figure 6B). This system offers noninvasive control over drug release from liposomal delivery systems.

**Azobenzene-Modified Ion Channels.** nAChR is an ionotropic receptor at the neuromuscular junctions and member of a class of transmembrane ion channels that are opened or closed in response to the binding of a chemical messenger. Binding of acetylcholine results in structural changes of the nAChR and opens an internal pore (Figure 7A). Entrance of Na⁺ ions through this pore causes depolarization of muscle cells. In 1971, a noncovalent photoswitchable agonist, the symmetric meta-substituted azobenzene bearing two benzylc trimethylammonium ions, was shown to activate the receptor in *Electrophorus* electroplaques.15 The cis- and trans-azobenzene isomers activated the receptor to different degrees. Subsequently, nAChR was engineered by covalently attaching compound 5 (Figure 7) to an intrinsic cysteine in nAChR. Photoswitching the azobenzene unit between the two forms reversibly activated the nAChR channel.16,17

The strategy of converting a free photoswitchable ligand into a tethered one by adding a reactive group that attaches to the protein of interest has also been applied to Voltage-gated potassium channel.18 These channels play a crucial role in the nervous system of higher organisms as regulators of membrane potential during action potential propagation. Therefore, the ability to interfere with the functioning of these channels by light allows manipulating the electrical activity of neurons. Banghart and co-workers presented an azobenzene-modified photochemically controlled K⁺ channel SPARK (Synthetic Photo-isomerizable Azobenzene Regulated K⁺ channel).18 The switch molecule 6 (Figure 7) used in this study comprises an azobenzene, connected to a reactive maleimide, which allows attachment to a cysteine that is introduced into a Shaker channel. A quaternary ammonium group, which blocks the pore of K⁺ channels, was connected to the other end of the azobenzene. (Figure 7B). The system was designed so that the quaternary ammonium can reach the pore and block ion conduction when the azobenzene is in its elongated trans form but not in its bent cis form. As a consequence of UV-induced photosomerization of the azobenzene unit from trans to cis, it unblocks the channel (Figure 7B). Irradiation with visible light restores the blocked state by accelerating the reverse cis-to-trans conversion. Due to the thermal cis–trans isomerization, the reblocking also occurs spontaneously in the dark.18
The effect of compound 6 was tested on Shaker channels expressed in *Xenopus laevis* oocytes. When the photoswitch was tethered to the extracellular surface of the channels, ultraviolet light unblocked the channel, producing as much as 1 nA current, while visible light reblocked the channels almost completely. Both forward and backward isomerizations occur within 5 s under standard epifluorescence illumination (Figure 8).

This concept was extended to ionotropic glutamate receptors (iGluRs), which mediate the majority of the excitatory neurotransmission processes in the vertebrate central nervous system. The advantage of this system is that these channels are well characterized and their 3D structures of complexes with a number of agonists and antagonists are available. The X-ray structure of the ligand binding domain of iGluR6, complexed with agonist (2S,4R)-4-methyl glutamate, was used in the design of a tethered agonist 7 (Figure 7C). Covalent attachment to the clamshell-type ligand-binding domain of iGluR resulted in a light-activated channel, called “LiGluR”. Light-induced isomerization resulted in the bent cis configuration and directed the agonist to the binding site and activated the receptor (Figure 7C). With 500 nm light, the agonist was withdrawn and the receptor was deactivated. When LiGluR was expressed in HEK293 cells, whole-cell patch clamp experiments showed that LiGluR was activated both by free glutamate and by illumination.

Recent advances have enabled optogenetic studies on interference with the activity of live neurons with light, through genetically introducing light-sensitivity in ion channels present in cells. In the first azobenzene-based control of neuronal activity by light, 6-tethered K⁺ (SPARK) channels were used for silencing neuronal activity. The channels were first modified through genetic mutations in order to render the photoswitch the primary regulator of the channel gating. Subsequently, the modified SPARK channels were genetically expressed in rat hippocampal neurons. Neurons were incubated for 15 min with compound 6 before electrical measurements. Exposure to 390 nm light silenced spontaneous action potentials within 3 s, and exposure to 500 nm light restored activity. Activity could also be restored by leaving neurons in the dark after silencing. Light-sensitive action-potential firing was observed only with the neurons that were expressing Shaker channels (Figure 9).

In an attempt at controlling a function of a whole organism with light, Scott et al. interfered with the behavior of zebrafish by using LiGluR. LiGluR was selectively expressed...
in specific neurons of zebrafish that mediate the touch-evoked escape response. The neurons were numbed upon long illumination at 380 nm, followed by a period of darkness, and the zebrafish did not respond to a mechanical poke. However, a strong pulse of light focused along the spine could trigger a direct escape away from the optical poke (Figure 10).

Due to its biocompatibility and spatiotemporal resolution, light has been an excellent tool to manipulate transport across lipid bilayers by interfering with the functions of special ion channels not only at the single molecule level but also by control functioning of a whole organism. The spatiotemporal resolution intrinsic to optical technology matches well with the submicrometer and submillisecond cellular processes that underlie for instance neural activity. Genetic methods allow expressing light-sensitive proteins in cells and subcellular compartments or allows introduction of suitable anchoring groups to introduce synthetic photoswitches such as light-sensitive caged compounds, reversibly caged ligands, and photochromic
Bright Ion Channels and Lipid Bilayers

Szymański et al.

Three general strategies are used to establish photocontrol over the permeability of a lipid bilayer (Figure 11). The first one (Figure 11A) employs molecular photoswitches, usually in a form of copolymers, which are incorporated in the lipid bilayer. The second approach (Figure 11B) is based on photoswitchable lipids which are used as dopants in the membrane. Alternatively, the bilayer can be constructed completely from photochromic lipids (Figure 11C).

Incorporation of Photoswitchable Copolymers into Lipid Bilayers. The first method, pioneered recently by the group of Tribett, is based on the change in the polarity of azobenzene-bearing copolymer upon light-induced isomerization. Hydrophobically modified poly(acrylic acid) derivatives, such as 8, have the ability to bind to lipid bilayers through noncovalent, hydrophobic interactions. Upon coassembly into the lipid bilayer, they form transient nanochannels, retaining the integrity of the membrane. This process strongly depends on the hydrophobicity of HMPA, which can be affected by photosomerization of azobenzene residues incorporated in the copolymer structure (Figure 13A). In particular, the light-induced effect has been attributed to the deeper penetration of cis into the membrane.

This principle has been demonstrated by using 8 to control the translocation of molecules, peptides, and quantum dots through the membranes of GUVs and cells. An interesting example of an application in a highly biorelevant context was provided by incubation of mammalian CHO cells with biotynylated RL-9 peptide and either cis or trans (less polar). After incubation, the internalized RL-9 was visualized (Figure 13B) by conjugation with streptavidin-AlexaFluor488 (green), providing the proof of membrane permeabilization by compound selectively in its apolar, form.

This relatively new approach (Figure 11A) shows a great promise, due to little disruption to the membrane and proven compatibility with living cells, which is a unique achievement when compared to other methods (vide infra). What remains to be seen is the generality of the method with respect to the different architectures of lipid bilayers.

Doping the Lipid Bilayer with a Photoswitchable Amphiphile. This represents the most established approach, with its roots in the 1970s, when naturally occurring rhodopsin was used as dopant. Since then, a plethora of synthetic amphiphilic molecules was designed to play the role of photoactivating dopant (e.g., compounds 9–11, Figure 12).

Compound 9, introduced by the group of Yianni and Morgan and used extensively in a series of studies and became a “workhorse” for this type of research. It has found applications in the controlled fusion of liposomes, fast light-triggered solute delivery, and in stepwise, wavelength-programmed control of cargo release. Its action is believed to rely on the increased bulkiness of the photosomerized, cis-isomer, which interferes with the bilayer packing.

FIGURE 9. Expression of light-activated channels confers light sensitivity on hippocampal pyramidal neurons. (A) Spontaneous action potentials are silenced and revived by exposure to 390 and 500 nm light, respectively. (B) Summary of repetitive firing data. Number of spikes resulting from a suprathreshold depolarization to −15 mV is significantly modulated by light in the multiply mutated Shaker-transfected neurons treated with ligand (*P < 0.01). Neurons expressing the channel without treatment or treated with 6 without channel expression were unaffected by light. Adapted with permission from ref 18.

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FIGURE 10. Incorporation of photoswitchable copolymers into lipid bilayers. The first method, pioneered recently by the group of Tribett, is based on the change in the polarity of azobenzene-bearing copolymer upon light-induced isomerization. Hydrophobically modified poly(acrylic acid) derivatives, such as 8, have the ability to bind to lipid bilayers through noncovalent, hydrophobic interactions. Upon coassembly into the lipid bilayer, they form transient nanochannels, retaining the integrity of the membrane. This process strongly depends on the hydrophobicity of HMPA, which can be affected by photosomerization of azobenzene residues incorporated in the copolymer structure (Figure 13A). In particular, the light-induced effect has been attributed to the deeper penetration of cis into the membrane.
Bright Ion Channels and Lipid Bilayers

Szymański et al.

In the attempt to resolve the issue of destabilization of liposomes, which is often caused by doping with a photoswitchable amphiphile and which results in the spontaneous release of cargo,33 the group of Wang designed and applied a cholesterol-based, photoswitchable amphiphile 10.34 The spontaneous release of calcein from liposomes, formed from egg phosphatidylcholine with 20% 10, was studied, and it was reported that the addition of cholesterol greatly stabilizes the liposomes and helps to retain the cargo. Notably, the transport through the membrane could be reversibly photoregulated by alternating irradiation with UV and Visible light.

In a follow-up study, cholesterol derivative 11 was used for the preparation of vesicles aimed at stabilizing vitamin C (in the dark) and its release under the action of UV light, toward applications in sunscreen preparations.35 This constitutes a rare and noteworthy example of commercial application-driven research in the field covered by this Account.

A distinctly different approach to the design of photosensitizing dopant was presented recently by Kimura and co-workers.36 It relies on the use of lipophilic malachite green derivative 12, which upon irradiation with UV light undergoes a heterolytic cleavage of C–CN bond (vide supra), resulting in the formation of a positively charged amphiphile. A detailed

FIGURE 10. Light-control over zebrafish response to poking. (A) LiGluR remains activated (for tens of minutes) after brief exposure to 380 nm light. (B) A hippocampal neuron expressing LiGluR fires action potentials when illuminated at 374 nm for 5 ms and then continues to fire in the dark until 488 nm light restores native activity. (C) Zebrafish naturally respond to a mechanical poke in the side by making a directed C-turn to escape the stimulus. (D) Illumination at 380 nm, followed by a long period of darkness induces a numbing of the escape reflex, which is then restored after exposure to 500 nm light. (E) A focused optical poke with high-intensity 380 nm light prevents light from entering the eyes and induces the same C-turn escape maneuver as in panel (C). Adapted with permission from ref 21. Copyright 2007 Elsevier Inc.
study on the possible mechanism of UV-induced permeation of a lipid membrane doped with 12 (Figure 14A) suggests\textsuperscript{36} that at low concentrations of 12 (<2\%) the irradiation results in the change of the vesicle shape. Only when the concentration of 12 is above 2\%, the change in interactions of the amphiphile with the bilayer result in rupturing the vesicle structure. This assumption was supported by the study on the influence of the concentration of compound 12 on the photoinduced release of cargo from the vesicles (Figure 14B).

Low effective concentrations (<3\%) of dopant and important mechanistic insight render this approach a valuable addendum to the toolbox of methods aimed at externally controlling the transport through lipid bilayers.

Doping of lipid bilayers with photoswitchable amphiphiles (Figure 11B) has reached its adolescence as a method of photocontrolling the transport through membranes.

**FIGURE 11.** Strategies applied in the construction of lipid bilayers with photocontrolled permeability, including the doping of a bilayers with photochromic molecules (A) and photoswitchable amphiphiles (B), and construction of bilayers solely from photoswitchable amphiphiles (C). Dark and light blue: molecular photoswitchable structures in two different, photoisomeric forms.

**FIGURE 12.** Photoswitchable compounds employed in the preparation of lipid bilayers with photomodulated permeability. Photoswitchable moieties are highlighted in blue.

**FIGURE 13.** (A) Photocontrolled membrane permeabilization by compound 8. Apolar, trans-8 binds to the membrane via hydrophobic interactions and forms nanochannels. More polar cis-1 does not cause content release. Adapted with permission from ref 24. Copyright 2010 American Chemical Society. (B) Photocontrolled internalization of a peptide RL-9 into mammalian CHO cells. Reprinted with permission from ref 25. Copyright 2012 WILEY-VCH Verlag GmbH & Co. KGaA.
Initial hurdles, such as liposome destabilization and subsequent spontaneous cargo release seem to have been overcome, and the loadings of dopant can be decreased to <5%, bringing this approach closer to applications in biological systems.

**Preparation of Lipid Bilayers Solely from Photoswitchable Lipids.** This approach was used for the formation of cerasomes that release their cargo from their liposomal membrane in a photocontrolled manner.\(^3^7\) Liposomes were made from amphiphilic compound 13, which additionally incorporates in its structure both residues responsible for photoswitching (azobenzene) and formation of a porous silicate framework (Figure 15).

The light-responsive cerasomes showed expected photochemical properties, that is, reversible change in UV–vis absorption upon alternating irradiation with 365 nm (UV) and 450 nm (vis). Importantly, the controlled release of cargo (Nile Red dye) in aqueous environment could be achieved by irradiation at 365 nm, which results in the trans→cis isomerization of the azobenzene moiety, disruption of membrane packing, and, as a consequence, the increase of the bilayer permeability (Figure 15).\(^3^7\)

This novel approach to photocontrolling membrane transport (Figure 11C), although obviously limited to artificial systems, holds promise due to robustness and generality, which validate further research into the cargo compatibility and the use in biological environment.

In the context of hybrid, phototriggered delivery systems, we have recently reported\(^3^8\) the formation of rigid nanotubes, end-capped with lipid vesicles (Figure 16). Amphiphile 14 (Figure 16A), used for the construction of the nanotubes, incorporates in its structure a photoactive moiety which undergoes isomerization and cyclization upon irradiation with UV light. Compound 14 is able to self-assemble, probably via interdigitation of aliphatic chains (Figure 16B), forming 3 nm thick and highly stable bilayers that close into well-defined nanotubes. Importantly, when phospholipid 1,2-dioleoyl-sn-glycero-3-phosphate (DOPC) is added, phase separation between the amphiphile and DOPC results in a formation of unique nanotubes end-capped with lipid vesicles (Figure 16C). These end-caps can be removed and attached without affecting the nanotubes (Figure 16D).

Intriguing possibilities, which put our research in the context of smart delivery systems, are offered by the fact that the nanotubes can be disassembled photochemically. Irradiation with UV light causes cyclization of 14 followed by bursting and subsequent disassembly of the tubes, leading to small vesicles. Not only does this process take the advantage of the high spatiotemporal resolution using light, but its kinetics (rate of disassembly) can also be regulated by changing the wavelength and intensity of irradiation. It was
shown that the disassembly is complete in 25 s when the tubes are irradiated with higher intensity, 390 nm light (Figure 16E). On the other hand, irradiation with lower intensity, 365 nm light has to be carried out for 2 min before the tubes are degraded (Figure 16F).

Concluding Remarks
The precise control of transport across biological lipid membranes is a key event in sensing and cellular communication. With recent developments in optics, genetic, and molecular design, it has become possible to interfere in a noninvasive
manner with these transport processes by light with high spatial and temporal control.

Taking advantage of protein engineering techniques, synthetic photoswitches can be incorporated in, for example, channel proteins with high precision, allowing external control of channel function in vivo. Recently, fascinating opportunities arise from related in vivo approaches controlling neural functions of organisms by light. Alternatively, light-responsive amphiphiles allow direct control of bilayer organization and membrane permeability.

Based on these systems, novel approaches toward sensing, transport, and delivery systems emerge. In the broader context of optogenetics and synthetic biology and with the prospect of applications ranging from novel submicroscale delivery devices to external control of neuronal activity, we can look forward to a bright and exciting future for photoactive biohybrid systems.

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**FOOTNOTES**

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