



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

A remote control for switching

Citation for published version:

Vendrell, M 2018, 'A remote control for switching' Nature Chemical Biology, vol. 14, no. 8, pp. 749-750. DOI: 10.1038/s41589-018-0107-3

Digital Object Identifier (DOI):

[10.1038/s41589-018-0107-3](https://doi.org/10.1038/s41589-018-0107-3)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Nature Chemical Biology

Publisher Rights Statement:

Peer reviewed article as accepted for publication.

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



ION CHANNELS

A remote control for switching

Marc Vendrell

Calcium channels are crucial regulators of a broad range of biological processes. A photoswitchable chemical probe allows the opening and closing of these channels with unprecedented temporal resolution, providing new opportunities to study calcium-dependent signalling pathways in real time.

L-type calcium channels are essential gatekeepers that regulate how Ca^{2+} ions enter into cells, a process that is critical for many vital functions in our body, such as insulin secretion or cardiac pacing. The team led by Fehrentz, Klöcker and Trauner has developed a new chemical probe that, just with the use of light, controls whether L-type calcium channels are open or closed.¹ In their paper, the authors show that this small molecule works as a 'remote control' to switch on and off the influx of Ca^{2+} ions and, as a result, modulates how much insulin pancreatic cells release or how fast the heart can beat.

Photoswitches, i.e. chemical structures that change their conformation upon light irradiation, are very powerful tools to modulate chemical and biological processes.² The azobenzenes are a common type of molecular photoswitch, which can interchange between *cis* and *trans* isomers by exposure to light of different wavelengths. Since a report on the formation of *cis*-azobenzene upon exposure to light was first described,³ azobenzene photoswitches have been incorporated into numerous chemical scaffolds to generate molecules that are either active or inactive depending on the wavelength of the light they are exposed to. Using this approach, scientists have generated probes that optically control the activity of membrane receptors⁴ or the release of drugs in specific tissues to minimise side effects.⁵ However, the similarity between the main L-type calcium channels $\text{Ca}_v1.2$ and $\text{Ca}_v1.3$ and other voltage-gated ion channels, such as potassium channels K_v or sodium channels $\text{Na}_v1.5$, has hampered the design of photoswitchable probes that could reversibly regulate Ca^{2+} flux in a highly specific manner. Fehrentz, Klöcker and Trauner et al. have chemically modified the structure of the Ca^{2+} channel blocker diltiazem with a hydrophilic azobenzene to create a new photoswitchable probe, termed **FHU-779**. Under blue illumination (470 nm) or in the dark, **FHU-779** is preferentially present as the *trans* isomer and acts to block calcium channels. These channels are unblocked under UV irradiation (385 nm) when **FHU-779** is mainly present as the *cis* isomer (Figure 1). Importantly, the blockade of calcium channels by **FHU-779** is reversible, and therefore allows control over multiple cycles of channel switching and with full temporal resolution. This represents a significant advantage over photolytic dihydropyridine Ca^{2+} blockers, such as nifedipine, which can optically control Ca^{2+} influx but in a non-reversible manner.⁶ Furthermore, **FHU-779** proved useful for modulating Ca^{2+} -dependent functions of *ex vivo* tissues, including the release of insulin by pancreatic islets and the cardiac activity of intact hearts (Figure 1).

The activity of L-type calcium channels is associated with multiple tissues (e.g. brain, heart, smooth muscle, retina, pancreas) and biological processes beyond insulin secretion and heart pacing. Therefore, the possibility of regulating Ca^{2+} influx in a non-invasive and reversible

manner opens a whole range of exciting opportunities to design experimental models to understand the role(s) of Ca^{2+} movement through channels in healthy and disease states. Given the direct links to cardiovascular and metabolic diseases, this could be the first step towards photoresponsive biomaterials that might be combined with miniaturized implants⁷ as therapeutic or monitoring devices. In the near future, we will see this technology being applied not only to *ex vivo* tissues or organs, such as pancreatic islets or intact hearts, but also *in vivo* in whole intact organisms, where intercellular networks are maintained so that the broader implications of Ca^{2+} flux can be better understood. For instance, zebrafish, which are optically transparent organisms and therefore fully compatible with the use of visible light,⁸ could be excellent models to assess how photoactivatable chemical tools modulate cellular function *in vivo*.

Expanding the chemical toolbox to include longer wavelengths with deeper tissue penetration (or even better, towards a multi-colour palette of photoresponsive tools) may create avenues to remotely control multiple voltage-gated ion channels at the same time. To this end, recent chemical advances in molecular photoswitches that respond to light of different colours (including near-infrared light⁹) will pave the way for multiplexed systems where different signal transduction pathways may be turned on and off at will, with the precision of light. At the end of the day, there are few things easier to operate than a light switch.

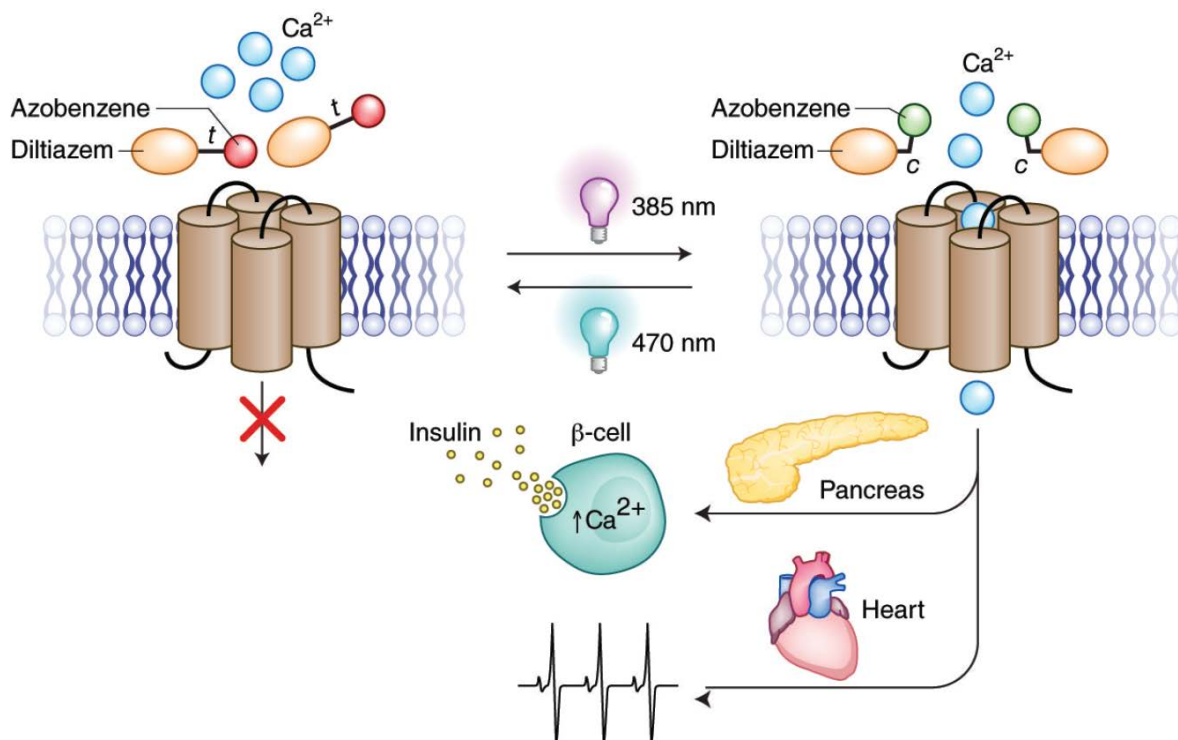


Figure 1. Optical control of calcium channels. The diltiazem-azobenzene photoswitchable probe allows L-type calcium channels to be opened and closed and thus regulate the Ca^{2+} flux into cells without affecting voltage-gated potassium or sodium channels. The downstream effects of modulating the Ca^{2+} flux were validated in intact tissues by optical control of insulin release in pancreatic islets and cardiac activity in *ex vivo* explanted hearts.

References

1. Fehrentz, F. et al. *Nat Chem Biol* **14**, xxx-yyy (2018).
2. Szymanski, W., Beierle, J.M., Kistemaker, H.A., Velema, W.A. & Feringa, B.L. *Chem Rev* **113**, 6114-6178 (2013).
3. Hartley, G. S. *Nature* **140**, 281 (1937).
4. Volgraf, M. et al. *Nat Chem Biol* **2**, 47-52 (2006).
5. Lerch, M.M., Hansen, M.J., van Dam, G.M., Szymanski, W. & Feringa, B.L. *Angew Chem Int Ed Engl* **55**, 10978-10999 (2016).
6. Morad, M., Goldman, Y.E. & Trentham, D.R. *Nature* **304**, 635-638 (1983).
7. Kang, S.K. et al. *Nature* **530**, 71-76 (2016).
8. Fernandez, A. et al. *ACS Cent Sci* **3**, 995-1005 (2017).
9. Klaue, K., Garmshausen, Y. & Hecht, S. *Angew Chem Int Ed Engl* **57**, 1414-1417 (2018).

Marc Vendrell is in the Medical Research Council Centre for Inflammation Research, The University of Edinburgh, Edinburgh, United Kingdom. e-mail: marc.vendrell@ed.ac.uk