Novel molecular designs unlock therapeutic potential of nicotine receptors

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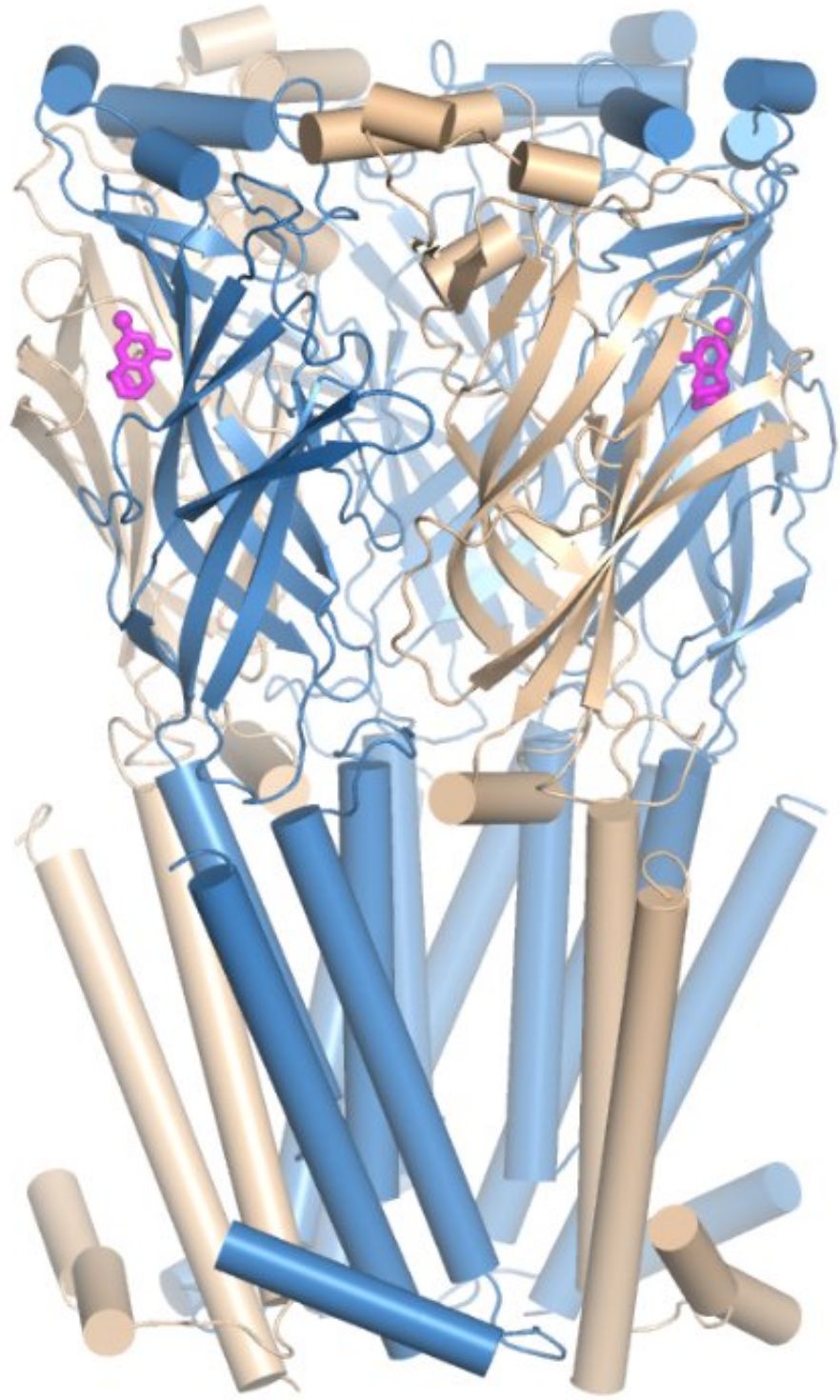

Modified cytisine molecules (fuchsia) bound to the brain's key nicotine receptor. Credit: Dr Sofia Oliveira, University of Bristol

Seven million people die each year from smoking related diseases, according to the World Health Organisation, with the annual death toll expected to rise to eight million by 2030.

Despite a WHO target to phase out tobacco usage by 2040, smoking remains one of the biggest global public health problems, with low to middle income countries accounting for around 80 per cent of the world's estimated 1.1 billion smokers.

To address this major health threat, there is a challenge to find smoking cessation therapies that are both low cost (and so widely-accessible) and that support smokers effectively to manage and then conquer their addiction.

Currently, there are two drugs which offer a related approach to smoking cessation. The first of these is cytisine, a natural product extracted from laburnum seeds and marketed as Tabex, that has been used for smoking cessation in central and eastern Europe for over 50 years. The other is varenicline (a chemical structure related to cytisine) that is available worldwide as Chantix or Champix. Both drugs work by selective stimulation of the brain's nicotine receptor in such a way that the smoker receives some but not all the reward of smoking so that, over time, they can manage withdrawal to eradicate their tobacco addiction.

However, both varenicline and cytisine activate other receptors in the brain that may be linked to various side effects. As a result, identifying more selective drugs that offer smokers an improved therapy would encourage greater end-user compliance and lead to increased quit rates.

Researchers from the University of Bristol, in partnership with colleagues from the universities of Bath, Oxford Brookes and Milan,

have been examining the chemistry and pharmacology of one of these drugs, namely cytisine (Tabex). Specifically, the team of synthetic and computational chemists, and pharmacologists and neuroscientists have looked at robust ways to target and modify specific parts of cytisine's chemical structure. They do this starting with cytisine itself, which offers a number of significant advantages, and this has led to new molecules that show higher selectivity for those key nicotine-activated receptors while still providing the necessary partial stimulation (reward) required by smokers to cope with cravings.

Using computational simulation methods developed with the aid of Bristol's high performance computing facilities, the researchers have also unpacked how the modified chemical structure determines the biological profiles of these new cytisine variants to provide the enhanced differentiation that they have observed. Longer term, and with further research, this work has the potential to produce a new smoking cessation therapy based on cytisine that, through better compliance, may lead to higher and more sustained quit rates.

Tim Gallagher, Professor of Organic Chemistry at the University of Bristol, said: "We had previously made some of these molecules by other routes but the poor efficiency of that chemistry seriously limited what we could do. We can now readily generate our molecules which offer more effective therapies, as well as biological probes that we and others will use to understand some of the fundamental questions associated with receptor activation."

Adrian Mulholland, Professor of Chemistry at the University of Bristol, said: "This work shows how computational simulation and experiment working together can identify potential new smoking cessation aids and can make a real difference. This also opens new ways of tackling these receptors very specifically, and understanding how they function."

Susan Wonnacott, Professor of Neuroscience at the University of Bath, added: "Manipulating the biological activity of ligands to give greater specificity for high affinity nicotine receptors is a key requirement for effective smoking cessation. Having the chemistry to achieve this, and the computational modelling to understand the mechanism, paves the way for the generation of novel therapeutics by rational drug design."

This research had additional support from Achieve Life Sciences (ALS), a pharmaceutical company specialising in cytisine as a smoking cessation aid.

"This is a first but very significant step towards targeted therapeutics and we have built a fantastic multidisciplinary team to pursue this problem," added Professor Gallagher. "We are now working on new and emerging aspects of this project, and that will include exploring, in partnership with ALS, the full potential of these ligands as therapeutic agents."

More information: Hugo Rego Campello et al. Unlocking Nicotinic Selectivity via Direct C–H Functionalization of (−)-Cytisine, *Chem* (2018). DOI: 10.1016/j.chempr.2018.05.007

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