Globally, smoking tobacco is one of the leading causes of preventable death. The World Health Organization estimates that more people die every year from tobacco use than HIV, tuberculosis, and malaria combined. Why do so many people struggle to stop smoking? The main reason is that smoking is highly addictive, but we do not know much about the mechanisms underlying this addiction. Through a series of studies, William N Green, Professor of Neurobiology at the University of Chicago, USA, and colleagues have significantly added to our comprehension of the biology of nicotine addiction and how smoking cessation drugs work. Their research paves the way for developing novel smoking cessation drugs.

Nicotine, tobacco’s addictive compound, binds to specific receptors on neurons in the brain called nicotinic acetylcholine receptors (nAChRs). These protein receptors are known as ‘ligand-gated ion channels’ because they open to allow ions to pass through the cell membrane in response to a ligand (a chemical messenger). In doing so, they transmit signals needed for cellular and brain function. These receptors consist of different subunits, most commonly the α4 and β2 subunits. The primary receptors implicated in nicotine addiction are α4β2Rs receptors. One effect of nicotine binding is the release of dopamine – the ‘feel-good hormone’ – from the reward centre of the brain. However, a person’s consistent exposure to nicotine makes the receptors less sensitive for it. To compensate for this change, the receptors are upregulated by modifications that increase their function and alter other receptor properties.

The rise and fall of nicotine

People smoke intermittently, meaning nicotine levels are not constant, first rising and then falling with each cigarette. However, over the course of a day, nicotine levels in the blood will consistently rise until they level out, as displayed in Figure 1, which shows the shape of this relationship to be much like a hill with a plateau at the top. Nicotine crossing the blood–brain barrier into the brain can access all nAChRs on neurons. The consistent level of nicotine causes functional changes in these nAChRs, with dopamine release likely increasing a person’s craving for nicotine.

When a person stops smoking for the day – usually before sleeping – blood nicotine levels drop rapidly, but α4β2Rs remain functionally upregulated longer than 24 hours. Subsequent decreases in dopamine are thought to amplify a person’s craving for nicotine.

Are Golgi satellites the key to understanding nicotine addiction?

Kicking a smoking habit is difficult, but why?

To answer this pressing question, Professor William N Green and fellow researchers at the University of Chicago and elsewhere in the USA focus on elucidating nicotine addiction and the working of smoking cessation drugs.

Their continued research has led them to single out organelles in our cells, called Golgi satellites.

The researchers have discovered the significant role of Golgi satellites in the upregulation of specific nicotinic receptors.

The progression of their research equips the scientific community to design new smoking cessation therapies.

This α4β2R upregulation is believed to be central to the mechanism of nicotine addiction.
feels of withdrawal. What causes the upregulation of these nicotinic receptors, and what are the underlying mechanisms at play? An understanding of the mechanisms of both nicotine addiction and smoking cessation drugs is needed for the design of new treatments.

Golgi satellites – the key organelles in nicotine addiction

Golgi satellites are cells’ ‘protein packaging factories’ that package proteins and lipids into vesicles that then travel to the cell membrane. The central Golgi apparatus forms part of a cell’s secretory pathway, an essential process that enables protein release from cells that is vital for normal cell function. Processing of proteins in this ‘factory’ converts the proteins’ sugars into more complex forms that generate the body’s supply of glycans. Such complex glycosylation is called sialylation, where a carbohydrate unit, sialic acid, is added to the other glycans attached to the protein.

The research team recently discovered that when neurons are stimulated, the Golgi apparatus appears to disperse into hundreds of smaller Golgi satellites. This occurs during high neuronal electrical activity as well as during exposure to nicotine. These miniature Golgi satellites emerge from another part of the secretory pathway, the endoplasmic reticulum, and associate nearby at membrane domains, especially synapses. They provide a glycosylation service for endoplasmic reticulum, and associate nearby at membrane domains, especially synapses. There, they provide a glycosylation service for endoplasmic reticulum, and associate nearby at membrane domains, especially synapses. Despite their abundance in active neurons, Golgi satellites have an affinity for α4β2Rs, meaning they bind to and interact with these receptors. Despite the success of varenicline, we do not know how the drug works in smoking cessation.

Varenicline’s immediate anti-nicotine effects are well understood, but in their most recent paper, the team have uncovered its long-term effects. In a breakthrough study, Green and colleagues used in vivo and in vitro imaging of mice brains to show how varenicline gets trapped inside acidic vesicles that also contain α4β2Rs. Nicotine is less acidic, and although it accumulates in vesicles, it does not get trapped, resulting in a brief lifetime in the brain of 1-2 hours. Ligand trapping of varenicline occurs because of its high acidity and affinity for α4β2Rs.

In fact, fluorescent imaging shows that this trapping occurs in the Golgi satellites. The findings show that varenicline is slowly released over time and well after nicotine has dissipated after smoking. Varenicline is most effective when released as smoking ends and targets the functional upregulated α4β2Rs.

This research significantly expands our knowledge of nicotine addiction. It could help us understand addiction to other drugs, such as opioids or cocaine, due to similar chemical properties that may make them susceptible to being trapped in vesicles. The discovery of the role of Golgi satellites in nicotine addiction and as a mechanism of smoking cessation drugs could be pivotal in developing new drugs. The researchers maintain that further studies will expand our knowledge of nicotine addiction and aid in the design, development, and testing of smoking cessation drugs. More effective therapies would help people quit smoking and prevent needless deaths.