NEUROSCIENCE

The smoke clears over diabetes

The discovery of a signalling axis that connects nicotine responses in the brain with glucose metabolism by the pancreas sheds light on why cigarette smoking increases the risk of diabetes. SEE ARTICLE P.372

GIUSEPPE BRUSCHETTA & SABRINA DIANO

One of the many dangers of smoking is an increased risk of diabetes, because nicotine uptake leads to altered glucose metabolism and increased blood sugar levels[1–4]. A group of neurons activated by nicotine is located in the brain's medial habenula (mHb) region; they are characterized by expression of nicotine acetylcholine receptor (nAChR) proteins[5]. These neurons promote aversive responses to nicotine, but until now, no one knew whether they also control the diabetes-associated effects of smoking — and if so, how. On page 372, Duncan *et al.*[6] identify a signalling pathway that links nAChR-expressing neurons and blood-glucose regulation by the pancreas. It involves a diabetes-associated transcription factor, TCF7L2.

TCF7L2 is part of a signalling pathway[7] that regulates the production and secretion of the hormone glucagon-like peptide 1 (GLP-1). GLP-1 promotes insulin release from the pancreas, and insulin promotes glucose uptake from the blood into tissues to be stored as fat. Thus, changes in TCF7L2 expression or activity can influence glucose metabolism. (Of note, the pathway is complex because activation of GLP-1 receptors by GLP-1 in turn leads to TCF7L2 activity, creating a signalling loop[7].)

Duncan *et al.* discovered that TCF7L2 is expressed in the mHb. Given the role of the mHb in the body's response to nicotine, the authors set out to investigate the possibility that TCF7L2 expression in this region is involved in nicotine-induced alterations in glucose metabolism. The researchers first generated two strains of mice — one in which the function of TCF7L2 was impaired in all tissues, and one in which the protein's expression could be inhibited in the mHb by introducing a virus carrying a short RNA sequence. They then provided the mice with a nicotine solution through a drip, rigged such that the animals could push a lever to receive an injection of nicotine at will. Both mice strains showed greater nicotine intake than did control animals.

Prolonged stimulation by nicotine causes nAChR-expressing neurons to become desensitized and stop responding to the molecule[8]. Further examination of the mutant animals indicated that TCF7L2 improves the ability of nAChR-expressing neurons to recover from this desensitization, presumably therefore promoting aversive responses to smoking. TCF7L2 seems to exert this effect by promoting signalling through cyclic AMP (ref. 9) — a molecule often involved in intracellular signal transduction.

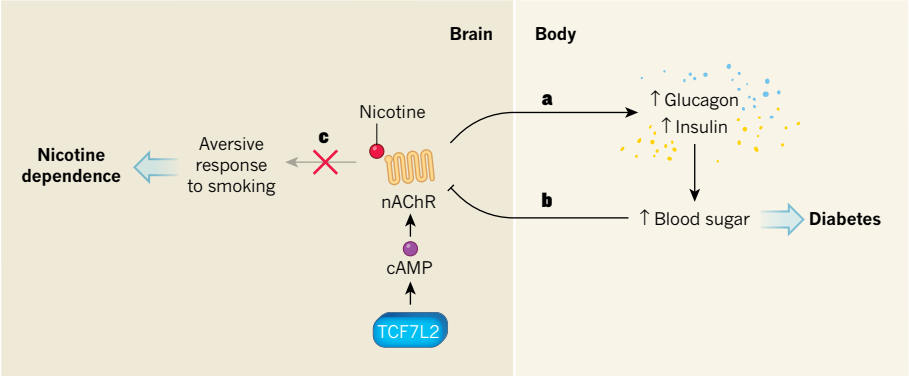

Figure 1 | A link between nicotine, diabetes and addiction. Nicotine activates nicotine acetylcholine receptor (nAChR) proteins in neurons. Activation of a population of nAChR- expressing neurons in the brain's medial habenula (mHb) region leads to aversive responses to nicotine. **a**, Duncan *et al.*[6] report that activation of these receptors in mice also leads to increases in the release of glucagon and insulin hormones from the pancreas. This leads to increased blood sugar levels — a change associated with an increased risk of diabetes in humans. **b**, The authors find that increased blood sugar levels in turn inhibit the activity of the nAChR-expressing neurons, establishing a feedback loop. **c**, As a result of this feedback, aversive responses to smoking are no longer triggered, resulting in nicotine dependence. The entire circuit is modulated by the protein TCF7L2 that, acting through a second messenger molecule called cAMP, mediates the sensitivity of nAChR-expressing neurons to nicotine.

Duncan *et al.* next demonstrated that TCF7L2 augments the ability of nicotine to increase blood-sugar levels: inhibition of TCF7L2 or GLP-1 receptors abolished this effect of nicotine, whereas a drug that stimulates GLP-1 receptors had the opposite effect. Furthermore, when the authors subjected wild-type mice to nicotine exposure and subsequent withdrawal, they observed increased levels of glucose, glucagon and insulin in the blood — indicative of an inability to properly regulate glucose metabolism. The effects were lessened in the mutant mice. Together, these analyses suggest that TCF7L2 activity decreases dependence on nicotine, but, conversely, hampers the body's ability to counteract the detrimental effect of nicotine on glucose metabolism.

To explore the neural circuits involved, Duncan and colleagues injected wild-type mice with a fluorescently labelled 'retrograde' virus, which travels along any neurons connected to an injection site. After injection in the pancreas, the authors found the virus in several areas of the brain, including the mHb, indicating the existence of a neuronal signalling axis from the mHb to the pancreas, by way of other brain regions. Thus nicotine, by stimulating mHb neurons in a TCF7L2-dependent manner, engages neuronal signalling to the pancreas and so alters blood glucose levels.

A 2011 report indicated that only around 6% of smokers quit successfully each year[10], and data indicate that people with diabetes find it harder to quit than do people without the condition[11]. In a final set of experiments, Duncan *et al.* gave mice sucrose every day for 6 weeks and showed that the subsequent increase in blood sugar led to reduced TCF7L2 levels and a decrease in nicotine-evoked activity in nAChR-expressing neurons. This observation suggests a feedback mechanism that could explain why it is harder for people with diabetes to give up smoking[11] (Fig. 1).

Duncan and colleagues' study sheds new light on the role of nicotine in the regulation of glucose metabolism. However, there are some caveats to consider. TCF7L2 is expressed not only in the mHb, but also in

other brain regions[12]. The pancreas, fat tissues and intestine — all of which are involved in glucose metabolism — also express TCF7L2. The possible contribution of these structures to nicotine-induced dysregulation of glucose metabolism needs to be considered and evaluated.

Furthermore, nicotine is a strong activator of the hypothalamus–pituitary–adrenal (HPA) axis — a network that promotes the release of stress hormones[13]. The function of the mHb is altered by stress, and stress hormones induce changes in blood glucose[13]. As such, it is conceivable that the some of the effects reported by the authors reflect not only the direct effect of nicotine on the mHb, but also an indirect effect through HPA-axis activation.

An interesting question is whether the effect of nicotine on the mHb–pancreas axis is different in males and females. In support of this idea, more men than women smoke, and the risk of female smokers developing diabetes is much greater than the risk for male smokers, compared with their non-smoking counterparts[4]. Furthermore, nicotine withdrawal induces greater weight gain in women than in men[14].

More broadly, further investigation is needed to confirm the role of the mHb–pancreas circuit in humans. Tobacco addiction in humans involves the interplay of pharmacological, genetic, social and environmental factors. Therefore, the full picture of nicotine's role in diabetes is likely to involve much more than a single regulatory circuit. Finally, this work raises the question of whether and how TCF7L2 could be targeted to combat tobacco dependency and diabetes. The feasibility of this tantalizing idea will require much more investigation in both mice and humans. ■

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CANCER

Brain tumours reset their clocks

The body's circadian clock ensures the rhythmic expression of some genes across the day. The catalogue of genes under circadian control changes in an aggressive brain cancer — a discovery that might open up a new avenue for treatment.

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All organisms have an internal circadian clock, which ensures that physiological functions occur at the right time of day — for instance, that the intestine, pancreas and liver are ready to metabolize food when you eat rather than when you are sleeping. Writing in *Cancer Discovery*, Dong *et al.*[1] report that the cells responsible for initiating a specific type of aggressive brain tumour, glioblastoma, rely on an altered circadian clock to grow. What's more, drug-based inhibition of the cells' molecular clock can kill them.

Glioblastomas are the most prevalent and aggressive tumour of the central nervous system. Fewer than 6% of patients survive for five years after diagnosis[2]. Cells in a glioblastoma often have varied gene-expression profiles. This, coupled with the fact that glioblastoma-initiating stem cells (GSCs) act to maintain the tumour, means that glioblastomas can rapidly develop resistance to conventional therapies[3]. New treatments are therefore urgently needed.

Disruption of the circadian clock, either because of lifestyle choices or because of mutations in core clock genes, is associated with a higher incidence of tumours[4]. In some tissues, clock genes can be co-opted to promote cancer (they are said to act as oncogenes), whereas in others they act as tumour suppressors[5–7]. The origin of such differences is an open question that, when answered, will help researchers to identify the mechanisms by which tumour cells hijack the molecular clock machinery to increase their chances of survival.

Dong and colleagues show that two key clock genes, *BMAL1* and *CLOCK*, are co-opted to act as oncogenes in glioblastoma. The authors first observed that the genes are essential for the survival and proliferation of GSCs *in vitro*. By contrast, neither differentiated glioblastoma cells nor normal neural stem cells (from which GSCs arise[8]) seem to depend on the genes in this way. The authors validated these findings by showing a strong correlation

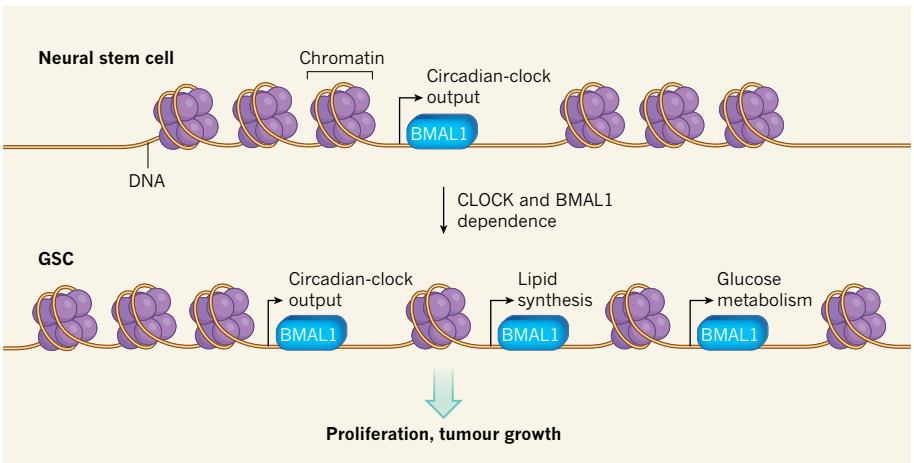

Figure 1 | Circadian reprogramming in cancer stem cells. The proteins BMAL1 and CLOCK are core components of the body's circadian clock. In neural stem cells, the proteins bind to specific regions of DNA (which is packaged around proteins as chromatin) to promote expression of the circadian-clock output — a collection of genes that are expressed in oscillating rhythms across the day (only BMAL1 is shown here). Dong *et al.*[1] report that, when neural stem cells become cancerous glioblastoma-initiating stem cells (GSCs), they become dependent on BMAL1 and CLOCK for survival. Changes in chromatin packaging enable BMAL1 and CLOCK to bind to more sites across DNA, promoting the expression of genes involved in lipid synthesis and glucose metabolism. Activation of these two metabolic pathways promotes GSC proliferation and so tumour growth.