PANDORA'S BOX

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Are your smartphones and iPads messing with your health?

Our brains and bodies have adapted for thousands of years to cope with environmental changes. However, are they capable of adapting to the galloping technological developments we have adopted in recent years and made indispensable to our daily lives, some of which may cause harm as well as convenience?

Our internal clocks located in the suprachiasmatic nuclei in the hypothalamus have an independent, rhythm, which is entrained to the natural day/night cycle. The discovery of electricity caused us to adapt and entrain our internal clock to fit in with the introduction of artificial light. Our obsession with the use, at all times, of smartphones, tablets, laptops and other such sources of illumination challenges our circadian rhythms, to the detriment of our sleep and general health. However, as the ancient Greek Stoic philosophers said: «ουδέν κακόν αμιγές καλού», meaning, 'there is no bad without good'.

Researchers at the Salk Institute have been examining the mechanism via which repeated or prolonged illumination can influence the production of melanopsin by photosensitive retinal ganglion cells. Melanopsin suppresses the release of melatonin (a hormone synthesised by the pineal gland, which is closely linked to the internal clock), resulting in sleep disturbance. The researchers found that substances such as the β-arrestins regulate melanopsin production. Unravelling how β-arrestins regulate melanopsin photo responses may allow us to manipulate the production of melanopsin and enable us to influence our internal clocks. This could potentially be of major benefit in a variety of human conditions, such as sleep problems, jet lag, migraine and other circadian rhythm-related conditions, including the metabolic syndrome.

Mure L. S., Hatori M., Ruda K., *et al* (2018) Sustained melanopsin photo response is supported by specific roles of β-arrestin 1 and 2 in deactivation and regeneration of photo pigment. *Cell Reports*, **25** (9), 2497–2509.e4.

Genes and neurodevelopment – the link

A range of psychiatric diagnoses including schizophrenia, bipolar disorder, depression, autism and attention-deficit hyperactivity disorder (ADHD) are often observed within the same families as well as within individuals, and there is increasing evidence that these conditions may share genetic aetiology. However, the biological processes involved in this relationship are still to be unravelled.

Researchers from the mental health services with the University of Copenhagen and the Lundbeck Foundation's Initiative for Integrated Psychiatric Research Consortium attempt to shed light on this question by examining the genetic determinants of fetal neurodevelopment in relation to psychiatric disorders.

The comprehensive Danish national registers have for many years facilitated the production of important and wide-ranging studies, which require large numbers to demonstrate valid outcomes. In Denmark, almost every newborn has a heel prick blood sample taken for phenylketonuria (PKU) screening, which is kept in a worldwide unique PKU archive and made available for research. These archives/registers have been an invaluable source of data for this research. The investigators were able to correlate the DNA kept in the PKU archive with the Danish healthcare system's civil registration numbers, which contain anonymous information on the person's health, including any psychiatric diagnoses. Out of a total of one and a half million PKU samples taken between the years 1980 and 2005, 48,000 subjects had received at least one psychiatric diagnosis. Comparing the DNA of these subjects with the DNA of those who had not had a psychiatric diagnosis, they identified four novel genome-wide loci, encompassing variants which were predicted to regulate genes expressed in radial glia and interneurons in the developing neocortex during mid-gestation. They conclude, based on their findings, that 'dysregulation' of genes that direct neurodevelopment by common genetic variants may result in general liability for many later psychiatric outcomes.

Schork A. J., Won H., Appadurai V., *et al* (2019) A genome-wide association study of shared risk across psychiatric disorders implicates gene regulation during fetal neurodevelopment. *Nature Neuroscience*, **22**, 353–361.

Endocrine-disrupting chemicals (EDCs): a major health risk

Fetal neurodevelopment is vulnerable not only to our genes but also to our environment. For now at least, we are limited in our ability to influence our genetic makeup, but we can do a lot to improve our environment and reduce exposure to noxious agents.

Endocrinologists stress the vital role of thyroid hormone in fetal brain development and later neurocognitive ability. A recent thorough and extensive review of the literature on the subject of EDCs, from the University of Paris-Sorbonne, draws attention to epidemiological and experimental findings of the past decade, focusing on thyroid hormone-disrupting chemicals and their effects on brain development. They emphasise how maternal thyroid hormone signalling during early pregnancy affects offspring's IQ and risk of neurodevelopmental disease. They suggest a link between the increase in neurodevelopmental conditions such as autism and ADHD and exposure to thyroid hormone-disrupting chemicals during pregnancy.

The authors conclude that 'Many experts in the field consider that the current testing guidelines for thyroid-disrupting chemicals are not sufficiently sensitive, do not take into account recent findings and do not adequately consider risks to

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vulnerable populations, such as pregnant women'. They underline the need for a more targeted public health intervention strategy.

EDCs are found not only in pesticides, flame-retardants and perfluorinated compounds, but also in furniture, plastic and in the manufacture of drugs, cosmetics and other materials, and can get into our bodies through food, water, dust and inhalation of gases and air particles, as well as through the skin and via breast milk. EDCs could also modify oestrogen and androgen signalling, with adverse effects on reproductive function in men and women and other hormone-related functions. They are also suspected to be linked to the increased incidence of breast cancer and abnormal growth patterns, as well as changes in immune function. The World Health Organization responded to concerns at the third session of the International Conference on Chemicals Management in Nairobi in 2012, together with the United Nations Environment Programme, with a resolution to include EDCs as an emerging issue and raise public awareness. Seven years, later little progress seems to have been made!

Mughal B. B., Fini J.-B. and Demeneix B. (2018) Thyroid disrupting chemicals and brain development: an update. *Endocrine Connections*, **7**(4), R160–R186.

A mushroom a day keeps dementia at bay

Eating mushrooms is good for your brain! Researchers in Singapore claim that mushrooms contain bioactive compounds which can delay neurodegeneration. In a community-based study, they examined the cross-sectional association between mushroom consumption and mild cognitive impairment in 663 participants aged 60 and above using data from the 'Diet and Healthy Ageing' programme.

They found that those who consumed more than two portions (300[th]g) of mushrooms per week had significantly reduced odds of having mild cognitive impairment, compared with those who consumed mushrooms less than once per week. This association was independent of gender, age, education, smoking, alcohol consumption, physical and social activities, diabetes and cardiovascular disease. The researchers attribute the beneficial effects of mushrooms to various bioactive compounds such as ergothioneine, which has antioxidant and anti-inflammatory properties. Other mushroom compounds such as hericenones, erinacines, scabronines and dictyophorines may also contribute to the cognitive benefits of mushrooms by enhancing the production of nerve growth factors. Another possible brain-protective mechanism afforded by consuming mushrooms may be the inhibition of the production of beta amyloid and phosphorylated tau and also acetylcholinesterase.

Feng L., Cheah I. K., Ng M. M., *et al* (2019) The association between mushroom consumption and mild cognitive impairment: a community-based cross-sectional study in Singapore. *Journal of Alzheimer's Disease*, **68**(1), 197–203.

Sleep of mice and men

Do you suffer with insomnia? At the end of a hectic day you lie down looking forward to that very much needed and well-deserved sleep. You toss and turn, you count hundreds of sheep but alas you are still wide awake. Do you dream of being able to turn on sleep with the same ease and speed that you turn off the light switch? Dream on, as this may become a reality in the not so distant future.

In a recent study, in mice, researchers claim to have found a sleep switch in the hypothalamus, located in the galanin neurons in the ventral preoptic area. Lesions in this area are known to cause insomnia, and high-frequency stimulation can wake you up! However, they demonstrated that photostimulation of the ventrolateral preoptic galanin (VLPOGAL) neurons, with the right frequency (1–4Hz), promotes sleep – at least, it does so in mice. Higher frequencies of photostimulation, however, achieve the opposite by causing conduction block. There is further supportive evidence for this finding, namely that photogenetic and/or chemogenetic stimulation of VLPOGAL neurons promotes sleep. The sleep-inducing benefits of chemogenetic stimulation have also been demonstrated in animal models of insomnia.

Could an effective and safe method using photo- or chemostimulation of the human VLPGAL neurons be developed to deal with the widespread problem of insomnia?

Neuroscience News (2018) Out like a light: brain's sleep switch identified. *Neuroscience News*, 8 October.

Kroeger D., Absi G., Gagliardi C., *et al* (2018) Galanin neurons in the ventrolateral preoptic area promote sleep and heat loss in mice. *Nature Communications*, **9**(1), 4129.

Narcolepsy an autoimmune disease

Before you indulge in self-pity for your insomnia, spare a thought for those with narcolepsy. There are two types of narcolepsy. Type 1 (NT1) is the most common, and people affected by this lack the transmitter hypocretin, which regulates the waking state; in addition to uncontrolled sleep, they suffer with cataplexy, that is, episodic loss of muscle control. People with type 2 (NT2) narcolepsy have the same sleep problems as those with type 1, but without cataplexy.

Although for a long time narcolepsy has been suspected to be an autoimmune disorder, there has been no convincing evidence to support this view until a recent study from the University of Copenhagen. It is known that NT1 is characterised by the loss of hypocretin/orexin signalling in the brain; existing genetic, epidemiological and experimental evidence suggests the hypothesis that this condition is a cell-mediated autoimmune disease, which targets the hypocretin-producing

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neurons. In this study, the researchers detected CD8+ cytotoxic T cells, which targeted narcolepsy-relevant peptides in NT1-associated human leucocyte antigen (HLA) types.

The researchers examined blood samples of 20 people with narcolepsy and 52 healthy controls for the frequency of autoreactive CD8+ T cells. They found that the frequency of autoreactive CD8+ T cells was lower in healthy controls carrying the disease-predisposing HLA-DQB1*06:02 allele, compared with patients with narcolepsy but also with healthy controls who were HLA-DQB1*06:02 negative. They concluded that a critical level of CD8 + T cell reactivity is needed, together with HLA-DQB1*06:02 expression, for NT1 to develop. They recognise that the presence of autoreactive cells is not enough to cause narcolepsy and that something else is needed to trigger and activate autoreactivity, possibly a viral infection.

Pedersen N. W., Holm A., Kristensen N. P., *et al* (2019) CD8+ T cells from patients with narcolepsy and healthy controls recognize hypocretin neuron-specific antigens. *Nature Communications*, **10**(1), 837.

Global Echoes

BJPsych International would like to encourage submissions from medical students, foundation doctors and psychiatry trainees. Those who are beginning their careers in mental health are often involved in high-quality projects or have diverse training and clinical backgrounds that would be stimulating for our readers to discover. They represent a valuable source of knowledge that can help all professionals to keep abreast of what is happening in the field around the world. We would like to receive submissions in the following areas, with a focus on international mental health work: brief literature reviews on mental health policy or services; reports of elective projects in psychiatry or other experiences of working or volunteering abroad; reflective or descriptive pieces about work undertaken or experiences or challenges encountered in working around the world, or in carrying out research in challenging contexts. Submissions should be between 500 and 1500 words and original pieces. Email ip@rcpsych.ac.uk. Submissions will undergo peer review. See the online *BJPsych International* guidelines on format and style (https://www.cambridge.org/core/journals/bjpsych-international/information/instructions-contributors).

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