Neurogenesis, networks and eating habits

Dr Mohammad K Hajhosseini is currently investigating the role of stem cells in the adult brain and their relevance to eating disorders such as obesity and anorexia. Here he discusses this research along with his earlier work on Apert syndrome.

What are fibroblast growth factor receptors and why are mutations which affect their expression involved in congenital craniosynostosis syndromes?

Cell-to-cell communication via fibroblast growth factors (FGFs) plays a very important role in controlling the rates of cell proliferation and differentiation processes that underlie morphogenesis and organogenesis during embryonic development. FGF receptors are expressed at the cell surface where they transduce FGF signals. Genetic mutations in FGF receptors can either abrogate or perturb the precise level of signalling that is required for normal development of tissues – as a result, mice or humans carrying such mutations show subtle defects in a wide variety of tissues. Visibly the most obvious of these are the craniofacial skeleton and limb abnormalities, as exemplified by Apert syndrome.

Does your development of an Apert syndrome mouse model provide hope for treating this condition in humans?

Fortunately Apert syndrome is a very rare disease, but from a biological perspective it presents an intriguing set of questions concerning multiple tissue types. We have already identified FGF10 as a key driver of abnormal FGF receptor function in this disease, and have shown that genetic knockdown of FGF10 in mutant mice reduces many of the abnormalities associated with this disease. The next challenge is to develop tools for reducing FGF10 function or correcting FGFR2 mutations in affected babies – either in utero or soon after birth – to respectively prevent or alleviate this syndrome.

There is a lot of attention among the public and media surrounding eating disorders – particularly the increasing prevalence of obesity. Does this have any influence on your work; perhaps making it easier to secure funding?

Obesity is not a mere physical inconvenience for the affected individual; it underlies life-threatening conditions such as diabetes and cardiovascular disease. As such, research into the cause, prevention and treatment of obesity is of highest priority for funding bodies worldwide. However, as with other diseases, the difficulty lies in convincing others that your approach in particular deserves support and attention.

Your current research examines the manipulation of the brain circuitry that controls appetite; can you explain the principles behind this?

Circuits controlling appetite are very complex, and though principally centred in the hypothalamus, are heavily influenced by activity in other brain areas. Indeed, recently an area close to the cerebellum was found to also influence appetite. Manipulating these circuits is our long-term goal. Our working hypothesis is built around the concept that for any brain function, collective functioning of a distinct number of neurons is important.

Has your work explored the genetic basis for differential development of hypothalamic cells?

Our work hasn’t explored this possibility, but it must certainly exist. We know that the level of adult neurogenesis in the hippocampus varies between different strains of mice. Differential development of the hypothalamus could therefore also be investigated in mice of different genetic backgrounds in a highly controlled fashion – although replicating such a piece of work would be very costly and laborious.

Do you envisage your work being applied to humans in the near future? What areas need to be developed further to allow this to happen?

In the long term, yes, and that is certainly our ultimate goal. There are strong anatomical and physiological similarities between rodents and humans and so our research using mouse models should be applicable to humans. Naturally, we must investigate whether human hypothalamic tanycytes are also capable of generating new cells, and with what dynamics. Recent advances in live imaging of whole organisms down to the single cell level should make it possible to address this question in humans. For now though, a great deal of intermediate questions still need to be addressed in rodents.

Drugs which are designed to modulate tanycyte activity could have the potential for unwanted side effects – how important will efficient drug delivery be when attempting to translate this research into novel therapies?

Focal and targeted delivery of drugs to hypothalamic tanycytes is challenging but surmountable. Fortunately, tanycytes are in close contact with both the cerebrospinal fluid and blood, so molecular targeting of chemicals to tanycytes through either of these routes could be possible. To achieve this, we need to know more about the cellular and molecular make-up of tanycytes, such as their membrane and cytoskeletal composition and their gene expression profile.
Eating disorders have become an increasingly serious problem with few satisfactory treatment options. Research from the University of East Anglia into a congenital developmental disorder has unexpectedly unearthed new insights into neurogenesis and appetite control in the brain, which could provide hope for truly effective solutions to these afflictions.

EATING DISORDERS ARE BECOMING INCREASINGLY COMMON IN THE DEVELOPED WORLD. In contrast to conditions such as anorexia and bulimia that can cause life-threatening weight loss, gross overeating can lead to obesity, which currently afflicts 26 per cent of adults in the UK and has equally severe health consequences. A wide range of illnesses have been associated with obesity, including cardiovascular disease, Type 2 diabetes, arthritis and some types of cancer. Obesity during pregnancy can predispose infants to diabetes and developmental disorders such as autism. The economic burden associated with obesity is therefore staggering; the estimated cost to the UK’s NHS totalled £4.2 billion in 2007 – a figure that is set to double over the next 30 years. From a clinical perspective, the options open to those affected are limited to significant changes in lifestyle; drugs with a range of side effects; or risky and laborious gastric band operations. Anorexia and obesity present qualitatively similar clinical problems that can potentially be tackled through better understanding of the biological basis for appetite, and by finding ways to manipulate it.

HOW IS APPETITE CONTROLLED? The control of appetite and energy expenditure is ultimately a function of the brain, involving complex interactions between clusters of neurons found in the hypothalamus and signals that emanate from other parts of the brain, as well as peripheral tissues such as the liver, stomach, gut, pancreas and fat cells. Key metabolic signals/hormones pertaining to the current state of the organism that participate in this process include glucose, insulin, ghrelin and leptin. These converge on two sets of appetite-promoting and appetite-suppressing neurons in the arcuate nucleus (ARC), and their net effect is then relayed to neurons in the paraventricular nucleus (PVN), resulting in altered eating behaviour and energy expenditure.

The vast majority of neurons found in the adult mammalian brain are produced in utero, suggesting that the adult brain has little capacity for regeneration and functional plasticity. However, the discovery of neural stem cells in two discrete niches of the adult brain – the hippocampus and subependymal lining of the lateral ventricles – has challenged this view. The discovery of a third neurogenic niche, by Dr Mohammad K Hajhosseini from the University of East Anglia, now suggests that neurogenesis may be more widespread in the adult brain than previously appreciated.

CLUES FROM APERT SYNDROME Progress in this field has come via the study of a seemingly unrelated disorder – Apert syndrome, a congenital disease characterised by malformations of the craniofacial skeleton and caused by mutations in the fibroblast growth factor receptor 2 (FGFR2) gene. Hajhosseini’s early work sought to elucidate the role of these receptors, but his unexpected findings have set the foundation for much of his current work: “Coincidentally, whilst developing transgenic mice that could allow targeted deletion of FGFR2, I generated an allele that mimicked the effect of Apert syndrome in mice,” Hajhosseini explains. Using this model he demonstrated that Apert syndrome also presents subtle phenotypes in non-skeletal tissues, including the lungs, salivary glands and brain. Further investigation revealed that knockdown of the Fgf10 gene in the Apert syndrome mouse model can rescue the mutant skeletal phenotypes, suggesting that Fgf10...
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plays a fundamental role in the malfunctioning
of FGFR2. To check whether Fgf10 was involved
in the brain defects, Hajihosseini's group also
examined the expression pattern of Fgf10 in
the developing and adult brain, only to discover
that Fgf10 is highly expressed in a population
of cells found in the floor of the third ventricles
called tanycytes.

RELEVANCE TO EATING DISORDERS
Tanycytes are best known for their supportive
function, transporting ions and metabolites
from the cerebrospinal fluid to hypothalamic
neurons, but it turns out that this is not their
only role. Hajihosseini's group has conducted
a variety of studies that suggest tanycytes are
in fact neural stem cells, capable of generating
neurons in the hypothalamus even during adult
life. The first clue lies in their morphology: they
are radially projecting bipolar cells similar to
the so-called radial glial stem cells found in the
embryonic brain and spinal cord. One way to
identify or classify cells is to look at the genes
that are expressed in them, and Hajihosseini's
group has found several neural stem cell marker
genes are expressed by tanycytes, including
BLBP, Nestin, Musashi1 and Sox2.

The team has also studied the behaviour of
these cells in vivo using a method known as
lineage tracing or fate mapping, which allows
the temporal and spatial observation of a cell
and all of its descendants. They did this by
activating heritable marker proteins in the
tanycytes of Fgf10-transgenic mice that have
been produced to allow this activation in
response to tamoxifen treatment. Observations
of the brains of these mice at regular intervals to
see if the fluorescently-labelled cells generated
any descendants demonstrated that tanycytes
behave like stem cells, proliferating in the
adult brain. Hajihosseini further explains: "This
work has established that tanycytes generate
new neurons in the postnatal and adult
hypothalamus, and interestingly most of these
find their way to areas of the hypothalamus that
are known to regulate appetite". Therefore, the
group's working hypothesis is that modulating
the behaviour of tanycytes will have an impact
on the neuronal circuits that regulate appetite,
either positive or negative.

FUTURE QUESTIONS
AND WIDER IMPLICATION
The finding that neurogenesis occurs in the
hypothalamus suggests that its appetite-
regulating circuitry is more adaptable than
previously thought, potentially responding to
environmental conditions through changes
in neurogenesis that in turn modulate eating
behaviour. This raises the possibility of helping
those who suffer from eating disorders by
targeting this endogenous population of stem
cells and controlling their proliferation in the adult
brain. By modulating the number of appetite-
suppressing neurons or appetite-promoting
neurons, it may be possible to intervene and
produce long lasting changes in appetite, eating
behaviour and energy expenditure.

There are, however, challenges to be overcome
before such treatments can be developed, and
these form the basis of Hajihosseini's plans
for future research. The first task is to better
understand the circuitry that regulates appetite,
as well as the role that tanycytes play in the
healthy adult – do they produce the desired cell
types and do these functionally integrate within
existing networks? Which genes are involved in
the regulation of their proliferation, cell survival
and migration? Only with answers to these
questions can effective drugs be developed to
manipulate tanycyte activity in a desirable way.
In any case this research presents a completely
different perspective on the problem of eating
disorders and provides a promising new avenue
for therapeutic intervention.