Fat Gut
or
Fat Brain
Everyone has already experienced a gut instinct. But what does it actually mean? What determines what you should eat - your brain or your gut? What is responsible for obesity in your body? In this issue, we will shed light on these and other questions. In 'The Fat Gut or the Fat Brain', we provide intriguing articles about the relationship between the brain and the gut and how it is associated with obesity. You can read about appetite regulation, neurogenesis, and the role of BDNF in controlling body weight and energy homeostasis. But this is not all: We give you an overview over the discovery of microbiota and what is known about it so far, how microbiota influences behavior, and what role they play in neurologic diseases. Last, but not least, we also offer solutions how to decrease your weight and fight obesity - drink more water and use Chinese medicine. Wouldn't that be easy?

Apart from that, we have many more articles you should have a look at, ranging from a report about this years' SfN conference to an article about why women leave academia. I would also like to introduce to you our newest member of the editorial staff: Laura Empl joined our team. Read her movie review about Super Size Me and her focus article 'Obesity and Inflammation'.

Finally, many thanks go to Katarzyna Winek and Charlotte Klein who contributed tremendously to this issue. Therefore, we decided that both will be the contest winners of this issue with a little reward of a voucher for Lehmanns bookstore. If you also have an idea, what the issues should be about, let us know!

Enjoy reading!

– Marietta
The Fat Brain or the Fat Gut
By Charlotte Klein and Katarzyna Winek, PhD Students Medical Neurosciences

Obesity - A Burden to Modern Society
Obesity has become one of the major challenges to human health worldwide, most markedly in industrialized countries. In Germany, about half of the adult population is classified as being overweight or obese, with a higher percentage in males (60%) than in females (44%) (GEDA, Robert Koch Institute, 2010). Overweight or obese individuals have a high risk of developing comorbidities, including type II diabetes, hypertension, and coronary heart disease, the most common cause of premature mortality in the obese population.

Body mass stability largely depends on the perfect coupling between caloric intake and energy expenditure [1]. Obesity is a state in which energy intake chronically exceeds energy expenditure. Even a subtle mismatch (less than 0.5%) in caloric intake over expenditure is sufficient to cause weight gain [2]. The rising prevalence of obesity is likely due to contemporaneous lifestyle factors, such as overconsumption of energy-dense food and reduced requirements for physical activity in comparison with the lifestyle of our hunter-gatherer ancestors.

Who is to Blame?
The Egg-or-Chicken Principle
The role of the hypothalamus in the regulation of feeding and energy balance was first highlighted by lesion studies in rodents [3, 4]). This brain area comprises specialized neurons that modulate food intake by acting to either stimulate or suppress appetite (see article by Charlotte Klein). Because of this, the hypothalamus has been determined as a key component in the regulation of metabolic homeostasis "integrating information regarding the body's internal environment and orchestrating a series of coordinated endocrine, autonomic, and behavioral responses that maintain metabolic homeostasis" [5]. However, while great efforts have been made to understand how the brain controls our desire to feed as well as the processes underlying the balancing of energy intake and expenditure, little is known about how the structure and organization of the hypothalamus are altered by obesity. The question still remains whether obesity is a consequence of hypothalamic dysfunction or if it even causes changes in the functionality of the hypothalamus, as has been observed in rodent studies of obesity.

The Role of the Intestinal Tract
Not only the brain, but also the gut takes part in the regulation of appetite and fat storage. There is a long list of factors that originate from the gastrointestinal system and play a role in the management of energy balance by regulating the satiety feeling and thereby, food intake. The main ones are ghrelin, cholecystokinin, peptide YY, pancreatic peptide, glucagon-like peptide 1, and oxyntomodulin (for reviews see [6] and [7]).

But these are not the only 'gut factors' controlling energy homeostasis of our organism. Recently, another key player was added to the regulators of our energetic well-being: the intestinal microbiota. These microorganisms, living in our gastrointestinal tract, have coevolved with their human hosts through ages, becoming important for many processes in the human body (see article by Sophie Schweizer). Actually, one could say, we are more microbes than man, because the number of bacterial cells in our intestines exceeds the number of the human cells in our body. Would you believe that the intestinal bacteria have an estimated mass of 1 to 2 kilogram? [9]

It has been shown in studies in mice and humans that the composition and function of microbiota may play a crucial role in the regulation of fat storage and lipid metabolism (more to be read in the article by Jana Foerster). Commensal microorganisms also seem to play a role in some obesity-related comorbidities, for example type II diabetes. Jens Nielsen, at the METAHIT conference in Paris in 2012, even stated that: "Gut microbiota species abundance is a more accurate predictor of type II diabetes than waist-to hip ratio"[10].

Very interesting data have been produced by studies using germ-free mice (animals raised with zero contact to bacteria, see also article by Katarzyna Winek). These mice are leaner than their wild-type littermates, who have about 40% more fat tissue. After colonization with bacteria from conventionally raised mice, the previously germ-free animals start to gain weight despite decreasing food consumption [10].

Then, is it the Microbiota Issue? Better Be Good to Your Commensal Bacteria!
It is good to take care of our microbial friends: A recently published Nature paper from the group of Martin Blaser describes how subtherapeutic doses of antibiotics can influence metabolism. They created an adiposity model by introducing antibiotic low-dose treatment. Investigated animals had changes in their microbiome composition and alterations in many metabolic pathways [11]. Another interesting study showed decreased diversity and overall number of gut microbiota in the populations with a high prevalence of severe obesity and its related diseases. Additionally, the most effective obesity treatment (a surgical intervention by gastric banding, sleeve gastrectomy or gastric by-pass, used only in the most severe cases) not only leads to improvement in the inflammatory and hormonal status, but also to changes in the gut microbiome. However, up to now only limited data have been produced [12].

We may say with certainty that we have not yet unraveled all the connections between the gut, the microbiota and the brain or their particular roles in the pathogenesis of obesity, but understanding this signaling in obesity and associated diseases is of huge importance. Recent discoveries and detailed characteristics of pathways involved in the pathogenesis may lead to more effective therapies with multiple targets. It is probably neither the brain nor the gut alone, but a complex interaction of both to blame for round shapes.

References
Bacteria: Friends or Foes?
By Sophie Schweizer, PhD Student Medical Neurosciences, AG Clinical Neuroscience

Nobel Prize winner, Joshua Lederberg, claims that we should overcome the "20th-century metaphor of war for describing the relationship between people and infectious agents" and use a "more ecologically informed metaphor" as "...microbes occupy all of our body surface..." and "...we are host to a poorly cataloged ensemble of symbionts to which we pay scant attention". (J. Lederberg, 2000)

The Early Days

As bacteria were the first forms of life to settle on young earth about 4 billion years ago, the history of mankind is inseparably linked to the existence of procaryotes. However, it took man a while to take notice of the sheer existence of his cohabitants. This process started in 1674 when Anton von Leeuwenhoek visualized bacteria for the first time. He found them while analyzing his own tooth plaque with the help of his newly developed microscope. Until today, the full scope of the various functions and abilities of this large domain is far from being fully revealed. Growing knowledge about these versatile microorganisms has slowly lead to a reevaluation of the relationship between bacteria and man.

In the mid-nineteenth century, due to revolutionary findings of scientists like Jenner, Semmelweis, Pasteur and Koch, the germ theory of disease was established. It proposed that microorganisms, including members of the domain bacteria, are the cause of many diseases. When the acceptance of the theory grew, a zealous hunt for drugs that would kill these disease-causing bacteria was opened. The devoted search for antibiotics began and it became common sense knowledge of evolution and ecology however, does not allow for the idea that bacteria were the 'bad guys' that had to be eradicated.

Obviously, an important step in this direction was Fleming's serendipitous discovery of penicillin in 1928. However, it was only applied as therapeutic agent in the 1940s. The first commercially available antibacterial was a sulfonamide, a synthetic red dye more popularly known by its trade name of Prontosil. The German biochemist Gerhard Domagk discovered it in 1935. At first, it was used as an industrial dye for wool and leather but Domagk noticed that the dye could stain bacterial cultures. The hypothesis was that if the dye entered the bacterial cells it might alter their growth or even kill them. Domagk tested it in cultures first, where the bacteria continued to grow. Yet, he continued with experiments in mice. He infected them with a lethal dose of Streptococcus and then some mice received Prontosil. Metabolic processes in the animal allowed for the active component (sulfanilamide) in the dye to be released and the treated group survived, while the whole control group was dead within two weeks. It was a promising result, but of course preventing an infection in mice doesn't necessarily mean curing it in humans. Domagk got his chance however, when his own daughter Hildegarde drove an embroidery needle into the palm of her hand when she fell. A few days later, the hand was swollen and the six-year-old girl developed a fever. As her condition deteriorated, the doctors recommended amputating her arm. Tests showed that Hildegarde was infected with Streptococcus and the chances of survival were little even after an amputation. Faced with his daughter's death, Domagk decided to give her Prontosil. Amazingly, Hildegarde recovered quickly and was completely cured a couple of days later.

Once his findings were published in 1935, doctors and researchers around the world began to develop derivatives. While common bacterial infections ran rampant in the 1920 and early 30s, effective treatments for meningitis, pneumonia and other bacterial diseases were then available through the new class of sulfa drugs which resulted in a sharp decline in mortality.

Antibiotics: Salvation and Curse

The discovery and mass production of antibiotics allowing for extensive clinical use and a successful fight against bacterial pathogens seemed like the way to salvation. In the 1960s, confidence about medicine's ability to fight infectious disease had grown to a degree that infectious microbes were portrayed as largely conquered. However, a couple of decades later the drawbacks have made themselves fiercely felt. Today, the fact that multi-resistant bacteria cause epidemics, especially in hospital wards, is widely acknowledged. Bacterial strains perform their part in the evolutionary race and improve their fitness by developing antibiotic resistant mechanisms. Currently, the most important resistance problems on a global scale are caused by methicillin-resistant Staphylococcus aureus (MRSA), and bacterial strains with plasmid-encoded extended-spectrum beta-lactamases (ESBL). There are now even bacteria resistant against 'drugs of last resort', like carbapenems. According to estimations of the Robert Koch Institute, Germany sees around four deaths every day as a result of infections acquired in hospitals. Key measures to combat this threat and prevent these epidemics are a prudent and more restrictive use of antibiotics together with improved diagnostics and a better infection control. Our actual knowledge of evolution and ecology however, does not allow for the idea of a complete eradication of bacterial pathogens anymore. In the case of multi-resistant bacteria in hospitals, a system implemented in Dutch hospitals could serve as a successful model: Every at-risk patient is first placed in quarantine until the results of a nasal swab test indicate that she or he is MRSA-free. Carriers of the dangerous bacterium are kept in isolation and treated until pathogen detection is no longer possible.

Yet, the development of multi-resistant bacteria is not the only difficulty arising from an excessive use of antibiotics. The use of antibacterial drugs can also perturb the intestinal bacteria living in our gut as commensals. And how important they really are, has only been started to be acknowledged recently.
The Gut Microbiota - Another Organ of the Human Body?

The human body is actually inhabited by at least 10 times more bacteria than the number of human cells in the body. The majority of those bacteria are found in the human gastrointestinal tract. Throughout the history of microbiology, the study focus lay on pathogens while fewer studies have examined the benefits of the resident bacteria. In 2001, Joshua Lederberg suggested the concept of the human microbiome, defining it as “the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space”. He encouraged and supported the growing understanding that a simple black-and-white view of ‘we good – they evil’ was no longer suitable. More and more recent experiments show that a proper balance of gut microbiota communities is crucial not only for the degradation of essential substrates of a modern diet, but also for the development and functional equilibrium of the immune system. It is now known that dysregulation of immune responses both in the gut and in distal effector immune sites such as the central nervous system may be referred to alterations of the gut microbiome. The microbiota is often called ‘the forgotten organ of the human body’, its metabolic capacities are compared to those of the human liver: Commensal bacteria produce vitamins that we cannot synthesize alone, they take part in detoxification processes, regulate the gut movements and help to form the gut-barrier. They even produce antibacterial substances that can prevent the growth of pathogens. Obviously, antibiotic intake has an effect on the resident communities and impacts this equilibrium. Once a patient’s intestinal microbiota is seriously perturbed, for example after prolonged antibiotic treatment, the “friendly” bacteria leave space for pathogenic species, like e.g. *Clostridium difficile* - the causative agent of pseudomembranous colitis, a condition that can be life-threatening. The main symptoms of the *Clostridium difficile* infection (CDI) causing this type of colitis are diarrhea, abdominal pain and fever. The main problem - getting rid of *Clostridium difficile* is not an easy task. However, new troubles lead to new solutions...

Fecal Transplantation (yuck!!)

A new interesting therapy against CDI, if standard treatments fail, is fecal transplantation also called intestinal microbiota transplantation (IMT). The procedure was first documented in humans in 1958. In animals, it has been performed for more than 100 years. For example, veterinarians treat horses with diarrhea by infusing stool from healthy horses into the rectum of the sick animals. Nowadays, approximately 450 cases of fecal transplantation as a treatment for CDI in humans have been reported worldwide. Small samples of donor stool in a saline solution are delivered into the patient’s colon. The result is amazing. According to reports, diarrhea vanishes within days and analysis of the gut microbiota shows a re-colonization of functional communities. A systematic summary of the literature on IMT determines a resolution for 92% of CDI patients in case of fecal transplantation (89% after a single treatment). So far, protocols among studies still vary but randomized controlled trials are currently underway to test the efficacy of this procedure. Further, it is also applied in other diseases believed to be causally related to intestinal microbiota disruption, such as inflammatory bowel disease and irritable bowel syndrome. An advantage of the IMT procedure is the relatively low risk it poses. An impediment, however, seems to be the 'yuck' factor that, according to polls, appears to be more common in physicians than in patients. Instead of the crude transplant practitioners hope for the development of a microbe containing pill - a fecal transplant in a capsule, so to speak. We will see what the future holds.

A growing awareness of the relevance of the microbiome is definitely detectable. In 2007, the human microbiome project was founded with the aim to compare the human microbiome between individuals and to assess how changes correlate with respect to human diseases. More fascinating insight - apart from spectacular new therapeutic methods like fecal transplant - are to be expected.

A recent publication, for example, gives us an idea about adaptation to local diet.

While Japanese people might have a problem with the metabolism of alcohol it has recently been shown that they have developed an advantage over their Caucasian brothers and sisters in the digestion of sushi!

What Do Bacteria Have to Do With Sushi?

A paper published in *Nature* in 2010 compares microbiomes of Japanese and North American subjects and makes an astonishing discovery: By acquisition of novel genes, resident gut microbiota makes an adaptation to local diet possible. Strains of *Bacteroides plebeius* found in several Japanese subjects harbor a gene acquired from marine bacteria, which encodes for an enzyme that is necessary to degrade porphyranin edible seaweed, like porphyra nori, the red algae that is the crucial ingredient of sushi. Marine algae contain these unique polymers that are absent in terrestrial plants and certain marine bacteria used these polysaccharides as a carbon source. As the study shows this carbon source is no longer a privilege of marine bacteria but also to Japanese whose daily intake of seaweed is around 14.2 g per person per day.

The necessary gene is not detectable in the microbiome of North American subjects, where microbial enzymes targeting polysaccharides from terrestrial plants that dominated diet throughout human evolution are predominant.

It will be quite interesting to track the worldwide development of the gut microbiome as a considerably rise of sushi consumption in non-Japanese cultures makes itself felt. Will *Bacteroides plebeius* be true to its name and one day settle in the gut of common folk all over the world instead of just a privileged Asian group of people?

Further Reading

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The Brain-Gut Axis

By Katarzyna Winek, PhD Student Medical Neurosciences, AG Clinical Neuroscience

Everyone has experienced a gut feeling. But have you ever thought what it could actually mean? The intestinal nervous system is more complicated than it would seem at first. The number of neurons in the Enteric Nervous System (ENS) is comparable to the number of neurons in the spinal cord [1]. The ENS is therefore often called the second or the little brain of our body. The innervation of the intestinal wall consists of the submucosal (Meissner’s) and myenteric (Auerbach’s) plexus. The Meissner’s plexus lies between the circular and longitudinal muscle layers and regulates the epithelial cells and submucosal vessel function. The Auerbach’s plexus is located in the submucosa and takes part in controlling gut motility. There are many interconnections between these two systems, which is the reason why the intestine is able to react fast to changes in the environment. The ENS was first described in 1921 by Dr. Langley, a British physician, as the third part of the autonomous nervous system.

Although the intestine is able to function – to some extent – independently, it is of course controlled by the central nervous system, mainly through the sympathetic and parasympathetic nerve networks. The efferent connection is realized via sympathetic nerves from the nerve roots Th1 to L3 and parasympathetic fibers through the vagus, splanchnic, and pelvic nerves from S2 to S4 (responsible for the modulation of gut motility and sensivity). Information delivered back to the brain mainly flows through the vagus nerve to the nodose ganglion in the brainstem, but also through afferent sympathetic fibers that originate in the gut and the brain. In this way, a new concept has been introduced: the brain-gut-microbiota axis. It functions bidirectionally - on the one hand, the brain is able to change the intestinal parameters, and on the other, the microbiota can influence some processes in the central nervous system. The brain can regulate intestinal physiological functions, automatically introducing changes in the environment of the microbiota by regulating gastrointestinal motility, secretion, and mucin production, as well as by the release of neurotransmitters. Intriguingly, some microbes can directly respond to catecholamines (just think about the norepinephrine transmission in the sympathetic nervous system). When I tell you that microorganisms are able to communicate with each other, you will probably not be surprised. They certainly do. For this purpose, they use hormone-like signals in a process named quorum sensing (QS). However, this system seems to not only be restricted to these prokaryotic organisms. Norepinephrine has been shown to induce growth of some bacterial strains, for example the commensal and pathogenic strains of Escherichia coli [4, 5]. Moreover, presence of catecholamines is linked with the expression of virulence-associated factors such as fimbriae and toxins in the pathogenic strains of this bacterium [6].

It has also been shown that some bacterial strains are able to synthesize GABA. Thus, finding a common language with microorganisms does not seem to be difficult [7].

Living in the Bacterial Matrix? Microorganisms are Able to Control Behavior!

Possible ways of influencing the central nervous system by microorganism include interactions with the enteric nervous system, the immune system, the production of several metabolites and the release of bacterial components. Intestinal bacteria remain in close contact with the gut surface and create signaling pathways with intestinal cells. Very interesting data come from experiments in germ-free (GF) animals.

Several groups have shown that GF mice have an altered behavioral pattern when compared to normally colonized Specific Pathogen Free (SPF) mice. The most characteristic features are decreased anxiety, increased exploratory behavior, and increased locomotion. Moreover, behavioral changes are followed by biochemical changes in the central nervous system (altered BDNF levels, although results reported are contradictory). GF mice...
also lack some memory functions when compared to SPF animals. The group of Professor Collins from McMaster University in Canada went one step further and proved that even the behavioral phenotypes characteristic of different mouse strains can be transmitted via the microbiota (for a review see [7]).

Additionally, microorganisms seem to play a role in the development and programming of the central nervous system. Sudo and colleagues observed increased ACTH and corticosteroids levels in young GF mice (compared with SPF mice) after mild stress. This effect was ameliorated by the colonization with Bacteroides infantis, but only partially reversed when GF mice were colonized with intestinal flora from SPF mice. This indicates that commensal gut microorganisms are involved in the suppression and amplification of the HPA-axis stress response. Normalization was possible when mice were colonized at early stage of development, but not when colonization occurred at a later stage [10]. In another study, commensal bacteria were shown to affect the serotonergic system in the brain. GF animals showed elevated levels of 5-HT and its main metabolite. These biochemical changes in the CNS were irreversible when the colonization occurred post-weaning [11].

In studies using probiotics, the effect of potentially beneficial bacteria on the central nervous system was examined. For example, Bravo and colleagues showed that long-term treatment with Lactobacillus rhamnosus led to region-specific alterations in GABA receptor expression, reduction of stress induced corticosterone response as well as anxiety- and depression-related behavior. None of these effects could be found in vagotomized mice [12]. Here, it should be mentioned that the communication route might be dependent on the bacterial strain used because in other studies some probiotic effects were found to be independent from the vagal nerve.

**Good or bad bacteria?**

Many experiments have focused on the role of commensal bacteria in pathogenesis of diseases of the host. There is a long list of disorders linked to disturbances in the microbiota or where the link is suspected. In obesity, diabetes type I and II, gastrointestinal malignancies, allergies, inflammatory bowel diseases, and irritable bowel syndrome, but also in autism or experimental autoimmune encephalitis (EAE) - a mouse model of multiple sclerosis - the connection is already fairly well documented [8]. It is hoped that advances in microbiota research and our understanding of its connections with physiological and pathological processes in the host (including their role in the communication with the central nervous system) will help to find new solutions and therapies.

Maybe Hippocrates was right claiming "the bad digestion is the root of all evil"?

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**Did you know...?** In the mouth alone there are between 500 and 1,000 bacterial species. Each tooth – and even each side of each tooth – has a different combination of species!
Feeding and energy expenditure are controlled by complex neural networks distributed throughout the forebrain and brainstem. Homeostatic feeding behavior is integrated within the hypothalamus. Key peripheral signals of energy status such as gut hormones and adipokines either signal to the hypothalamus directly or indirectly via the brainstem and vagal afferent fibers. Adiposity signals such as insulin and leptin are involved in the long-term energy homeostasis, and gut hormones such as ghrelin are implicated in the short-term regulation of meal ingestion [1-3]. The Hypothalamus comprises various nuclei, of which the arcuate nucleus (ARC), the paraventricular nucleus (PVN), the ventromedial nucleus (VMN), the dorsomedial nucleus (DMN), and the lateral hypothalamic area (LHA) play a role in energy homeostasis.

Hypothalamic Orexigenic and Anorexigenic Neuropeptides

The ARC, known as the infundibular nucleus in man, is situated at the base of the hypothalamus. It contacts the peripheral circulation through semi-permeable capillaries in the underlying median eminence and is thus in an ideal position to integrate hormonal signals for energy homeostasis. In the ARC, there are two important discrete neuronal populations: Neurons coexpressing neuropeptide Y (NPY) and agouti-related peptide (AgRP) stimulate food intake, whereas neurons coexpressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) suppress food intake. Both subpopulations project to the LHA and PVN, where they control the function of second-order neurons. In the PVN, two distinct subpopulations of neurons produce the anorexigenic (appetite-suppressing) neurotransmitters thyrotropin-releasing hormone, and corticotropin-releasing hormone. In contrast to this, in the LHA, two other subpopulations produce the orexigenic (appetite-stimulating) neurotransmitter orexin (hypocretin) and melanin-concentrating hormone (for review see [4, 5]).

Peripheral Hormones and Peptides Regulating Appetite

Leptin, predominantly synthesized in adipose tissue, inhibits NPY/AgRP neurons and stimulates POMC/CART neurons. Circulating leptin levels are directly proportional to adiposity in animals and humans. Insulin, which is produced in the β cells of the pancreas and rapidly secreted after a meal, binds to insulin receptors on the surface of POMC/CART neurons and activates them. The rise in circulating insulin in response to a glucose load is proportional to fat mass. Ghrelin, a hormone from the stomach, exerts a stimulating effect when binding at growth hormone secretagogue receptors on NPY/AgRP neurons. Circulating ghrelin decreases in response to chronic overfeeding and increases in response to chronic negative energy balance associated with exercise or anorexia nervosa. Whereas obese people usually have high plasma leptin, they have low plasma ghrelin (for review see [6]).

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Did you know...? Babies come from a germ-free environment into the world. Vaginally born babies are coated with microbes from their mothers’ birth canals. Babies born by Cesarean section are covered in microbes typically found on the skin of adults.

January 25th, 2013: Neuroscience Colloquium Talk
Emeran Mayer from the Department of Physiology, David Geffen School of Medicine at UCLA, Los Angeles (http://bit.ly/Q6CAal) will give a talk entitled "Communication between gut microbiota and the brain" in the Neuroscience Colloquium on January 25th, 2013. Don't miss it!
Neurogenesis in the Hypothalamus

By Charlotte Klein, PhD Student Medical Neurosciences, AG Neural Regeneration and Plasticity

In the adult mammalian brain, there are two main neurogenic regions: the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus in the hippocampal formation. They have been considerably documented and are still intensively studied (for more information see CNS Newsletter Volume 5, Issue 3, p. 6-8). However, generation of new neurons throughout adulthood has also been reported in various other brain areas including the hypothalamus.

Evidence for Cell Proliferation and Differentiation

The hypothalamus is a source of adult cell proliferation in a variety of rodent species. Hypothalamic cell proliferation occurs constitutively without apparent influence from external cues [1-3], regardless of the mode of administration and the dose of the cell proliferation marker (mostly BrdU) used. Discrepancies in the location and abundance of proliferated cells reported in different studies may be explained by the mode of administration of the proliferation marker as BrdU-positive cells in the parenchyma of the hypothalamus are significantly more abundant after intracerebroventricular administration than after intraperitoneal injection (3.5-fold increase) [1].

The use of specific cell markers for neurons, non-differentiated glial cells, astrocytes, and oligodendrocytes for colocalization with proliferation markers has demonstrated the generation of new neurons, oligodendrocytes and astrocytes in the periventricular zone as well as in the parenchyma of rodents [1, 2, 4-7]. However, the proportion of new neurons arising from newborn cells is much lower in the hypothalamus (1-37%) [8] than in the hippocampus or olfactory bulb (70-100%) [9].

A Neurogenic Niche

Recent studies have identified a progenitor population within a dedicated hypothalamic neurogenic zone [10]. The so-called tanycytes are specialized radial glia-like cells composing the ventral hypothalamic ventricular zone. Tanycytes are divided into four distinct subclasses based on: the position of their cell bodies along the ependymal wall, the projection of their basal processes, and their gene expression pattern, of which the β2 tanycytes have been directly shown to proliferate substantially at the base of the third ventricle within the median eminence (ME) giving rise to newborn neurons. Hence, the tanycytes function as neural progenitors at significant levels in the ME, but not in other regions of the hypothalamus in vivo. In contrast, BrdU-labeled neurons found in the hypothalamic parenchyma, many at considerable distance from the ventricles, may be generated from a yet uncharacterized neural progenitor population.

Modulations of Hypothalamic Neurogenesis

Just as in the hippocampus and the olfactory bulb, hypothalamic neurogenesis is a dynamic process that can be modulated by external factors. Growth factors such as brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF) significantly contribute to proliferation. In rats, intracerebroventricular administration of BDNF increased the number of new neurons in the hypothalamus [4]. Kokoeva and colleagues have found that central administration of CNTF enhanced cell proliferation in the arcuate, ventromedial, and dorsomedial nucleus of the mouse hypothalamus, with newly formed cells expressing early neuronal markers [7]. Environmental, hormonal, and behavioural signals may also regulate adult hypothalamic neurogenesis. Hippocampal neurogenesis can be altered by various hormones, social behaviour, enriched environment, exercise, and stress; all of which engage hypothalamic neural circuitry.

Functional Implications?

The functional significance of adult hypothalamic neurogenesis in the mammalian brain is largely unknown due to its relatively recent discovery. Findings from studies addressing this question suggest that adult-born hypothalamic neurons appear to play a role in the regulation of metabolism, weight, and energy balance. Co-administration of CNTF and the anti-mitotic drug AraC into the lateral ventricles blocked cell proliferation in the hypothalamus and reversed CNTF-induced weight loss suggesting a role for hypothalamic neurogenesis in weight regulation [7]. Focal irradiation targeted to the hypothalamic proliferative zone, which selectively inhibited adult neurogenesis in the ME of animals fed with a high-fat diet, resulted in significant attenuation in weight gain and higher levels of activity as well as basal metabolism relative to controls [10]. This suggests that ME neurogenesis induced by overfeeding acts to reduce baseline energy consumption and promotes energy storage in the form of fat.

A key step for future studies would be to extend the demonstration of the existence of hypothalamic neurogenesis to non-human primates as well as to humans.

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www.medical-neurosciences.de
The Role of BDNF in the Regulation of Body Weight and Energy Homeostasis: an Overview

By Charlotte Klein, PhD Student Medical Neurosciences, AG Neural Regeneration and Plasticity

Brain-derived neurotrophic factor (BDNF) has been shown to play a crucial role in the regulation of neuronal development including survival, differentiation, and growth of existing and new neurons [1]. However, BDNF has also been identified as a key component of the hypothalamic pathway that controls body weight and energy homeostasis [2]. In the hypothalamus, BDNF mRNA is found in most of its functional units, i.e. paraventricular, arcuate, ventromedial and dorsomedial nuclei as well as the lateral hypothalamic area and the median eminence. Together with the hippocampus, the hypothalamus is the brain structure that contains the highest BDNF mRNA and protein levels. BDNF is largely coexpressed with its tyrosine kinase receptor trkB, suggesting that autocrine or paracrine mechanisms account for the general modality of BDNF action in the CNS (reviewed in [3]).

It has been shown that BDNF levels are low in obese people [4]. Interestingly, on the contrary, it has been found that serum levels of BDNF are significantly increased in obese women and significantly reduced in female patients with anorexia nervosa or bulimia nervosa compared to age-matched normal control subjects. Since BDNF has been described to exert a satiating effect, this may represent a long-term adaptation to counteract decreased caloric ingestion in anorexic and bulimic individuals or the increased one in obese subjects [5-7]. In humans, obesity and obesity-related symptoms have been associated with functional loss of one copy of the BDNF gene [8] and with a de novo mutation in the BDNF receptor Ntrk2 gene [9].

In animal studies, obese phenotypes are found in Bdnf-heterozygous mice associated with hyperphagia, hyperactivity, hyperleptinemia, hyperinsulinemia, and hyperglycemia [10, 11]. Both central and peripheral administration of BDNF decreases food intake, increases energy expenditure, and leads to weight loss [12, 13]. A recent study suggests that gene transfer of BDNF has a therapeutic efficacy in a mouse model of obesity and diabetes, leading to marked weight loss and alleviation of obesity-associated insulin resistance [14]. Knowledge of the exact molecular mechanisms of how BDNF regulates body weight and energy homeostasis is sparse and must be further elucidated.

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Intestinal Microbiota and Obesity

By Jana Foerster, PhD Student, German Institute of Human Nutrition Potsdam-Rehbruecke

The intestinal microbiota – a collection of more than 10^14 cells – plays a crucial role in human health and disease, particularly in the development of obesity. There is convincing evidence that individuals with distinct microbiota composition have different abilities to extract energy from diet and by this means their risks of gaining weight vary [1]. Studies in both animals and humans show that the composition of the intestinal microbiota is different in obese and normal weight individuals [2, 3]. Different hypotheses have been suggested through which an altered microbiota may trigger obesity: (a) by increasing the energy harvest from diet; (b) by influencing the host's inflammatory response and (c) by affecting the brain-gut-axis and by this means control food intake. Higher energy extraction from diet by microbiota can partly be explained by an enhancement of genes that are involved in the degradation of dietary polysaccharides in obese individuals [4]. Furthermore, gut bacteria have the ability to digest primarily indigestible food compounds, e.g. polysaccharides from dietary fiber, and thereby, provide new energy sources, e.g. short chain fatty acids, to the host metabolism. The chronic state of low-level inflammation, which is meant to be a shared characteristic in the development of obesity and other metabolic disorders, is also associated with gut microbiota composition. Intestinal bacteria can control systemic inflammation processes by mechanisms including glucagon-like peptide 2 (GLP-2) and cytokine production [5]. In addition, mechanisms inducing an increase in intestinal permeability and thereby promoting low-grade inflammation are also related to gut microbiota composition. Studies in mice have revealed that gut microbiota composition plays a crucial role in brain development and subsequent adult behavior [6]. Possible mechanisms include neural, endocrine, and immunological pathways [7] each of which may have the potential to influence nutritional behavior through, for example, hormonal satiety signals.

References
Obesity and Inflammation

By Natalia Denisova, MSc Student Medical Neurosciences

The prevalence of obesity (defined as a Body Mass Index equal to or greater than 30) is increasing around the world. Medical doctors and investigators have long wondered if there is a link between obesity and brain disorders. Interesting observations were made regarding the age of obesity onset. Higher fetal and postnatal levels of adiposity contribute to better brain development. However, obesity in mid-life - at ages 40-55 - and during late-life - at age 70+ - increases risk for dementia, independent of education, IQ or other factors.

But what are the mechanisms by which obesity influences the brain and cognitive function? Adipose tissue may contribute to cognitive decline in a variety of ways. This may happen indirectly because obesity can cause diabetes or hypertension, leading to cardio- and cerebrovascular diseases that are able to impair cognitive function.

A more direct link is via adipokines. They can cross the blood-brain barrier and cause structural abnormalities, such as increased amounts of white matter. Leptin, produced mainly by adipose tissue, has remarkable effects on neurogenesis, neuroprotection, and regulation of beta-amyloid levels. Hereby, it is able to improve cognition, delay age changes, and optimize learning and memory processes. However, patients with common obesity can not benefit from elevated leptin levels because they show increased leptin resistance. A number of mechanisms, including the leptin-stimulated phosphorylation of Tyr(985) on LRB and the suppressor of cytokine signaling 3, attenuate leptin signaling and promote a cellular leptin resistance in obesity [1].

Another important multifunctional hormone is ghrelin. It is produced in a wide variety of tissues associated with the progression of obesity and metabolic syndrome. Acyl-ghrelin may modulate specific molecular intermediates involved in memory acquisition and consolidation through promotion of synaptic plasticity. In patients with Alzheimer's disease, the ghrelin autocrine/paracrine loop in the temporal lobe was found to be dramatically disrupted [2].

Furthermore, the brain can be susceptible to higher adiposity due to basic underlying differences in the structure and function of the nervous system. Studies using MRI have identified a number of brain regions potentially related to adult human obesity. These are mostly prefrontal areas which are different in gray matter density in obese and lean individuals. Higher BMI has also been related to a higher rate of brain atrophy using serial MRI [3].

It looks like exercise and maintaining a healthy weight are necessary not only to keep ourselves fit, but also to keep our brains functioning well.

References

Obesity and Inflammation

Today, obesity has become a regular term in our media. In order to raise awareness for the new epidemic that is sweeping our globe, scientists plead for a healthier lifestyle and advise us to leave our sedentary ways and high-caloric eating habits behind. Unsurprisingly, current research has identified our high-fat diet as one of the main culprits, responsible for obesity and its many associated illnesses such as type II diabetes, cardiovascular disorders and osteoarthritis.

In this respect, experiments in animal models of diet-induced obesity have uncovered a possible link between obesity and inflammation in our brain. In more detail, animals who were exposed to a high fat diet, displayed an immune cell-mediated tissue inflammation of the hypothalamus, a key structure for the control of energy homeostasis and body weight. Many support that it is the excess intake of nutrients that leads to the activation of microglia, and can in turn cause cell damage or further amplification of the inflammatory cascade. In response to the tissue inflammation, many additional events have been proposed to occur and among others include the upregulation of certain signaling pathways and endoplasmatic reticulum stress. These mechanisms can then directly or indirectly interfere with the receptor signaling of the hormone leptin. As a consequence our brain and body develop a resistance to it. Leptin, a hormone that is secreted by adipocytes and the hypothalamus itself, serves as a marker describing the current energy levels of the body. Hence, if leptin can no longer bind to its receptors, as it is inhibited by the inflammatory processes and the activated pathways, the hypothalamus can no longer fully establish metabolic homeostasis and predisposes the organism towards obesity.

Luckily however, these findings identifying diet-induced inflammation in the hypothalamus as a contributor to the pathogenesis of obesity open up a whole new world for novel treatment targets. Indeed pharmacological and genetic approaches, which target the pathways inhibiting the hypothalamus from working correctly, may become effective treatment methods. Lastly, it seems that the scientists (and our parents) encouraging us to “go play outside” instead of sitting around all day might be right after all. In fact, exercise, a common remedy to maintain weight and counteract obesity, has recently been shown to reverse the hypothalamic inflammation in a genetic mouse model for the metabolic syndrome. Yup, after eating all those early Christmas cookies I think it’s time for a jog. (De)

References
Obesity: New Perspectives for Pharmacological Intervention

By Anna Sofia Norton, MSc Student Medical Neurosciences

In my home country, the United States, obesity is the leading cause of preventable deaths, and its prevalence, along with the billions of dollars that are spent every year to treat diseases associated with it, continues to rise. I have always believed that behavioral interventions, such as increased exercise and decreased calorie intake, are the best ways to combat obesity. While it is true that some cases are primarily due to largely uncontrollable factors, such as genetics, increases in recent years can mostly be attributed to a sedentary lifestyle, increased reliance on fast food, and the like.

Nonetheless, the demand for pharmacological interventions is high, and many have joined the rat race to try to identify anti-obesity drugs that are both safe and effective. This has proved to be a very difficult task. Most scientists have tried developing drugs that target satiety pathways. The hypothalamus is known to play a fundamental role in the regulation of hunger and satiety. It contains two critical subsets of neurons: the NPY/AgRP/GABA neurons, which, when activated owing to decreasing glucose and leptin levels, promote appetite, in part by suppressing the activity of neighboring POMC neurons. The activation of POMC neurons, which release e-MSH, the agonist for melanocortin receptors, leads to satiety. Therefore, these neurons are one of the main targets for clinical trials.

However, the non-specificity of many of the developed therapies has proven dangerous in practice. Serious side effects such as an increased risk of heart attack and suicide have lead to withdrawal of several medications. But, even if a more specific drug could be produced, it might be destined to fail. The problem with sustained satiety is that it promotes glucose utilization in the periphery. This results in the production of reactive oxygen species (ROS), which can be detrimental for tissue integrity and survival. Many drugs aim to increase the release of serotonin and catecholamines in the brain in the hope that this will activate POMC in the hypothalamus. While that has been shown to be true, these monoamines have many other functions in the nervous system. They have the power to alter cognition, hormonal secretion and sleep in patients.

In their recent review, Dietrich and Horvath suggest some new directions for future therapies. The first would be to develop drugs that inhibit NPY/AgRP/GABA neurons, which preferentially use free fatty acids as a main source of fuel to sustain firing, resulting in low levels of ROS production. They also suggest to pharmacologically promote the molecular pathways involved in the effects of regular exercises. Personally, I would advise people to avoid taking such medications unless it is a last resort.

Herbal Fight Against Obesity

By Tian Zhang, PhD Student Medical Neurosciences, AG Clinical Neuroscience

The increasing prevalence of obesity has rendered it a major health hazard world widely. Besides regaining body weight after cessation of treatment, diverse side effects, including mood changes and gastrointestinal complications, have limited the usage of western anti-obesity drugs. On the contrary, traditional Chinese medicine (TCM), especially Chinese herbal medicine (CHM), has been studied as an alternative therapy for this health challenge.

As early as in the Han dynasty (BC202-220), TCM doctors have reported symptoms and risk factors of obesity and prescribed CHM to reduce body weight [1]. The theory of TCM emphasizes on restoring internal balance. Traditional doctors have no idea about gut microbiota, but they think that the gut is the foundation for human health. As the importance of gut microbiota for modulating energy homeostasis has been recognized in recent years, many groups have started to investigate if and how Chinese herbs can control body weight through regulating gut microbiota.

Zhao Liping, a biomedical professor of Shanghai Jiao Tong University, is one of them [2]. He was inspired to combine TCM and gut microbes to understand and fight obesity, when he managed to lose 20 kg in 2 years by combining Chinese yam and bitter melon with a diet on whole grains. He believes that eating these fermented foods has changed the growth of bacteria in his digestive system, since Faecalibacterium prausnitzii - an anti-inflammatory bacterium - increased from an undetectable level to 14.5 % of his total gut bacteria.

Further, confirmation that Zhao was heading on the right track was provided when Gordon's paper [3] supplied the first evidence that gut microbiota can indeed regulate host genes. In his recent study [4], Zhao and colleagues administered berberine, a major pharmacological component of Chinese herb Coptis chinensis, to high-fat diet (HFD)-fed rats. They observed that food intake of HFD-fed rats significantly decreased and that the effect of berberine is partially mediated by structural modulation of the gut microbiota.

Zhao's results are encouraging. However, when TCM meets western reductionist science, obstacles are obviously encountered. On the one hand, substances used in TCM are not yet accepted as food or medicines in Europe and North America, which slows down the process to get permission for clinical trials. On the other hand, more studies using international standards are indispensable for dissecting the mechanistic pathways of functional ingredients in CHM. Nevertheless, due to its lower intolerability, TCM still has the incomparable appeal to be considered as a future treatment for obesity.

References

The Possible Role of Water Consumption in Weight Management

By Dr. Rebecca Muckelbauer, Berlin School of Public Health

Drinking plenty of water is often recommended and applied as a dietary means for weight management. Although no evidence-based recommendation for increased water consumption exists, a nationwide survey in the US showed that about 30% of adults who tried to lose weight stated that they drank a lot of water for losing weight [1]. Among a sample of female college students, even one third reported using water as an appetite suppressant [2].

Up until now, the role of water consumption in weight management has been investigated in only two interventional [3, 4] and one observational longitudinal study [5]. The results of these studies point toward a beneficial, weight reducing effect of water consumption in addition to a weight loss or weight maintenance program [3-5]. There are several dietary and physiological mechanisms suggested that could mediate this effect. Increased water consumption could prevent weight gain by replacing the sugar-containing beverages such as soft drinks and fruit juices, which are linked to weight gain and obesity [6]. Short-term effects of pre-meal water consumption that may be beneficial for weight management include an increased satiety and reduced feeling of hunger [7], which could lead to reduced energy intake. In fact, two reviews showed that pre-meal water consumption reduces the energy intake during the subsequent meal, but only in older-aged subjects [7, 8]. Another potential mechanism of water consumption on body weight is the so called thermogenic, energy-consuming effect of ingested water. Boschmann and colleagues demonstrated in two experimental studies that the consumption of 0.5 l of water increased the metabolic rate resulting in excess energy expenditure by about 100 kJ in normal and 95 kJ in overweight adults [9, 10].

Despite the fact that drinking water is widely promoted as a means to assist in weight management, the evidence to support this claim is currently scarce and of low quality. Experimental studies are needed to confirm the suggested pathways of increased water consumption on dietary behavior and weight development. The beneficial effect of drinking water in programs for weight management has to be tested in longer-term randomized controlled trials.

References
[4] Dennis et al., Obesity (Silver Spring), 2010
[5] Stookey et al., Obesity (Silver Spring), 2008
[7] Dennis et al., Eat Behav, 2009
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Gut Instinct

As many of us have experienced, many of our emotional states, especially stress, are reflected in terms of the gut physiology and symptoms. This is one example of the role played by the brain-gut axis. Another one is monitoring of the gut function involving nerves, hormones, and other molecules such as cytokines.

The term dysbiosis describes a state of imbalance between beneficial and potentially harmful microbiota in the microflora in the body. It has come to light that it is important to study the link between the gut microbiota and the brain because it has been shown that several psychiatric disorders, for example autism and depression, as well as behavioral changes such as anxiety, are connected with changes in the gastrointestinal tract.

In a mouse model of antibiotic-manipulated intestinal flora, altered exploratory behavior has been observed, accompanied by changes in levels of brain-derived neurotrophic factor (BDNF). These behavioral changes have also been shown to be independent of immune activation or vagal activity and could not be attributed to malaise. Further support for the hypothesis that the intestinal microbiota plays a role in changing behavior is lent by the observation that an intestinal microbiota transfer between two mouse strains with opposite behavioral phenotypes (one calm and shy, the other gregarious and explorative) resulted in the recipient strain adopting a similar behavior to that of the donor. This series of experiments lead to the important conclusion that the gut microbiota is one of the factors determining the behavioral phenotype of a species. The interpretation of this data lead to two hypotheses concerning the mechanism by which the gut microbiota might induce physiological changes in brain accompanied with alterations in the behavior: 1. By direct action of bacterial products on the host's brain; or 2. by the interaction of bacterial products with host's metabolites and the interaction of these with neurotransactive molecules.

Taking a look at the phenomenon from a different perspective, stress itself induces alterations in microbiota. Apart from this, stress induces changes in gut motility, epithelial and immune function as well as in neurotransmitter release. Taken together, these factors change the gut environment and the habitat for the gastrointestinal flora, bacterial content, and activity. A deceasing amount of Lactobacilli was observed in Rhesus monkeys upon maternal separation.

This interconnection plays an important role in inflammatory bowel disorders, as dysbiosis may be associated with behavioral changes present in these conditions; and in primary psychiatric disorders where intestinal microbiota should be further analyzed. (II)

Reference

Did you know...? In 1996, NASA scientists find bacteria-like fossils in rocks from Mars.

www.medical-neurosciences.de
Super Size Me

Super Size Me, a documentary that hit theaters back in 2004, begins with the epigram of Ray Kroc, the founder of the McDonald's restaurants: "Look after the customer and the business will take care of itself". Oh the irony, you think, even eight years after its release.

Written and directed by Morgan Spurlock, this movie goes on a mission to unravel the American way of eating, its consequences on health, and the tactics of the food industry to promote food, which is considered extremely unhealthy.

In essence, Spurlock lives 'every eight years old dream' by going on a 30-day fast food binge, following a few simple rules: He can only eat food sold over McDonalds counters, has to have a meal three times a day and if asked by the cashier, has to get the super-sized portion of his order.

At first, you get to know the protagonist as a well-trained man praised by his doctors for his excellent health status. By the end of the experiment, however, even his 'good genes' cannot save him from the inevitable (and also predictable): A gain in weight of over 11 kg, a severe increase of cholesterol, an inflamed liver, fatigue, mood swings, and even signs of addiction, all showing the possible detrimental effect of daily fast food intake.

Alongside his personal journey (complete with seeing him vomit and getting humiliated by his girlfriend for calling him out on his sexual performance during the experiment), Spurlock also interviews professors, doctors, authors, pupils, and by-passers to shed light on the link between the rise of obesity and the increased rate of fast food intake and availability in the U.S. In addition, he explores some facets of the fast food advertising industry, specifically targeting young children and priming them to their products and wrong eating habits at a very young age, as well as the faulty supply of junk-food free meals in American schools.

Viewers are oddly reminded of a Michael Moore documentary, as Spurlock presents his evidence with the help of colorful images, info-graphics, and a dash of reality-tv-like voyeurism along the way. In contrast to Michael Moore, however, who has been criticized of being overly one-sided, Spurlock manages to portray a more complete picture and allows his audience to decide whether they will convert to total fast-food abstinence or not. The bottom line is everybody should know by now that fast food isn't the best fuel for your body, but it's never bad to get a thought-provoking, yet entertaining reminder of what we eat and what social issues can go along with it.

Picture: Artist "spqr"

Intracranial Self-Stimulation in Rats – A Most Rewarding Experience

AG Experimental Psychiatry (Christine Winter)

I started the Master's with a plan to do one of my lab rotations with cells, one working with human subjects, and one with animals. That process took me to some interesting places, including Christine Winter's Experimental Psychiatry lab, where I did my third placement last summer. I worked with Timo, a fellow MedNeuro student (graduated 2011) on his thesis investigating the dopaminergic reward system in a rat model of obsessive compulsive disorder. We implanted electrodes directly into the main reward pathway of the brain, trained the animals on an intracranial self-stimulation (ICSS) paradigm and then looked at how different dopaminergic drugs change hedonic responses. ICSS is, in my opinion at least, the coolest way of investigating the reward system that there is. Unlike other rewarding stimuli, there is no concept of satiety (as there is for food rewards, for example) or tolerance (as seen when utilising drugs of abuse). Studies have revealed that a rat will chose brain stimulation reward over anything else, neglecting to eat, drink or sleep and rejecting sex etc. to keep on pressing the lever.

I decided to do my Master's thesis in the Winter lab and was pleased to learn that there was another ICSS project on offer. The group works with various other animal models of different psychiatric disorders and focuses on deep brain stimulation (DBS) as an experimental tool and potential treatment as well as conducting behavioral and immunohistochemical investigations. My project explores the effects of medial prefrontal cortex DBS on hedonic responses in a rat model of depression, using ICSS as a key measure. As anhedonia (the inability to experience pleasure) is a key symptom in depression, it is interesting to examine reward in models of the disorder, but the real aim was to investigate whether DBS – a potential treatment for depression – has any effect on reward-seeking behavior. The project has been challenging at times, but working with such a lovely group and receiving exactly the right ratio of support to independence has made it entirely worthwhile. If it sounds like your sort of thing then I'd thoroughly recommend getting in touch with Christine!
The PhD – a First Step into an Academic Career or the First Step Out?

Why Universities Should Worry about PhD Programs
By Odilo Engel, PhD Student Medical Neurosciences, AG Clinical Neuroscience

Despite the high number of female undergraduate and PhD students, most higher positions in academia, namely professorships, are given to men. A recent study in the field of Chemistry aimed to enlighten the underlying reasons [1].

First, it is important to look at the pool of applicants from which universities recruit their top staff. In a prior study, PhD students were asked about their career plans at different stages of their PhD [2]. At the beginning, obviously, both men and women are enthusiastic about pursuing a career as researcher, both in academia and industry: This intention is expressed by 61% or 72% of first-year male and female PhD students, respectively. However, in the third year of their PhD, women changed their mind dramatically. Whereas 59% of men still see research as a career option, only 37% of women do so.

If one separates between a career intention in industry and in academia, only 12% of women and 21% of men see their future in academia. In other words, 88% of female PhD students and 79% of their male fellows don’t want a career in academia. Curt Rice describes this as an alarming result for universities, as they may no longer be capable of attracting the best and the brightest minds [3].

Both genders, but especially women, regarded an academic career as all-consuming and competitive. First of all, the short-term nature of most post-doctoral positions implies frequent relocation and a lack of security about future employment. The level of competitiveness to achieve a permanent position is seen as very fierce and the impression of young scientists is that it has become harder to get a first foothold on the ladder, especially under the circumstance of a constant hunt for funding [1].

However, there are several issues that affect only women keeping them away from academic careers: There is a lack of positive examples, as most women feel that female professors often show a quite masculine behavior and are, in many cases, childless. They do not want to sacrifice their personality and their plans for a family, to an academic career. Whereas both male and female PhD students report poor supervision, frustrating experiences in the research process, and problems within the research group, women feel more affected and restricted by this and are more likely to see this as a personal failure. A relevant number of women also report that they were told that their gender might be a problem for a future academic career [1].

Although these studies were focused on Chemistry, it seems to be likely that it is not much different in other subjects. Obviously, the pool from which universities can recruit their lecturers and professors shrinks, and especially women are not attracted by an academic career. Universities should ask themselves if the working conditions and career paths they offer are suitable to encourage talented young researchers staying in academia. Without young and innovative researchers, cutting-edge research at universities is endangered. But considering recent headlines about the German Max Planck Society and its practice to cut PhD students from social security system [4], a fundamental rethink has not yet begun.

References

Open Positions for Master Students in Neuroscience Research in Berlin

Type: Lab Rotation/Master/PhD Thesis
Title: Elucidate the localization and binding function of the blood-brain barrier protein tricellulin (Tric)
Field of Research: Role of tight junctions in modulating blood-brain barrier function
Starting Date: Immediately
Research Group: Molecular Cell Physiology, AG Blasig, Leibniz Institut für Molekulare Pharmakologie (FMP)
Contact: PD Dr. Ingolf E. Blasig, IBLASIG@fmp-berlin.de, tel: 030/94793244

Type: Lab Rotation/Master/PhD Thesis
Title: Resolve the structure and function of the extracellular loops (ECL) of claudins involved in the blood-brain barrier
Field of Research: Role of tight junctions in modulating blood-brain barrier function
Starting Date: Immediately
Research Group: Molecular Cell Physiology, AG Blasig, Leibniz Institut für Molekulare Pharmakologie (FMP)
Contact: PD Dr. Ingolf E. Blasig, IBLASIG@fmp-berlin.de, tel: 030/94793244
The Largest Annual Neuroscience Gathering
The Society for Neuroscience Meeting in New Orleans in October 2012
By Christine Römer, PhD Student Medical Neuroscience, AG Clinical Neuroscience

The biggest annually held neuroscience conference is also a challenge to the brain of any neuroscientist who attends it. Twenty-eight thousand researchers from all over the world came together to attend the 5-day core meeting with dozens of satellite symposia and themed social gatherings, hundreds of lectures, and thousands of poster presentations. Luckily, a modern scientist owns a memory outside the body: tablet PCs and smartphones everywhere you look.

The latest technology met cutting-edge research in various fields of neuroscience which was presented in fresh and interesting ways, with 'outside the box' thinking. In the age of virtual social networks, the investigations of structures and circuits of the 'social brain' came just at the right time. Other lectures addressed how early-childhood trauma shapes the brain, which brain regions are important in altruistic motives and behavior, or which neurological components influence dietary disorders. Advances in the early diagnosis of Alzheimer's disease as well as innovative treatments for stroke and spinal cord injury were highlighted in the daily lecture marathon.

The evenings were reserved for the overcrowded, yet magnificent presidential special lectures starring the who is who of the neuroscience society. The cover story was "From human genome and development to plasticity".

Language-related Genes Identified
Simon E Fisher, director of the Max Planck Institute for Psycholinguistics and Professor of Language and Genetics at the Donders Institute for Brain, Cognition and Behaviour in Nijmegen, reported about advances in identification of language-related genes. Fisher was among the first researchers to find that mutations in the FOXP2 gene lead to problems in coordinated mouth movements necessary for fluent speech. A regulatory protein translated from the FOXP2 gene modulates the expression of other genes which have been implicated in language delays in autistic children.

Learning Language Before Birth
Language is made up from multiple levels of interacting rules and requires biological preparedness. Here, the prenatal period is of major importance. Janet F Werker, the University of British Columbia faculty member and chair in Psychology, showed how the level of interaction between mother and fetus determines the normal development of language skills. At birth, an infant has connections in place supporting language acquisition and is able to learn any of the world's languages.

How Neural Circuits Keep Going
James E Rothman, the founder of the SNARE system, Professor of Chemistry and Cell Biology at Yale University, described the molecular mechanisms of synchronous neurotransmitter release, which enables neural circuits to keep pace. Membrane fusion at nerve terminals is mediated by SNARE proteins between the vesicle and the plasma membrane. Only recently, it became evident that just two additional synapse-specific proteins, synaptotagmin and complexin, are needed to synchronize the release by SNAREs and add calcium dependence.

Brain Plasticity: Stop and Go During Developmental Critical Periods
Carla Shatz, Professor of Biology and Neurobiology at Stanford University and a former president of the Society for Neuroscience, gave an exciting talk about the critical role of immunological molecules in brain plasticity during developmental critical periods. Synaptic remodeling, e.g. in visual perception, is mediated by MHC molecules which localize at synapses and bind to PirB innate immune receptors in the central nervous system. This family of molecules, previously thought to only function in immunity, plays a role as a 'brake' in synaptic plasticity.

If you wanted to get an insight into all the different neuroscience research areas, if you wanted to see innovations, exchange with fellow researchers, and get dazzling lots of ideas, or if you just wanted to get a lifetime reward for your work, then you should have been in New Orleans this year.

Brecht Keller
If you want to have your hearty German meal in peace after a hard day of pipetting, march down to the more secluded and quiet restaurant "Brecht Keller" at the Brecht Haus (do not confuse this with the restaurant Brechts on the Spree - way different in terms of ambiance and price range). The house is preserved as a museum for the renown playwright Bertold Brecht, who took his last residency in this very building.

The restaurant is actually in the cellar. The atmosphere is cozy, with its cute raw brick walls, dark wooden tables and family style food choices. The menu is usually quite small, meaning that they probably do what they serve very well. I've only ever been once, but I would definitely go back for a bigger family style gathering. Typical German dishes, very generous portions and a proper wine and beer selection. Low key, relatively budget-friendly, and friendly staff! The garden area is also open for dinners in the summer.

Reservations preferred, but only after 6 pm each day. (ge)

http://www.brechtkeller.de/
Chausseestrasse 125
10115 Berlin, Germany
Phone: 030-282-38-43

Did you know...? The human gut microbiota as a whole encodes 150 times more genes in their collective metagenome than are present in the human host genome.
**Chocolate...**

Also, the consumption of dark chocolate can be healthy! It is capable of lowering blood pressure and is a potent antioxidant. A study performed at the University of Calgary added a further beneficial aspect, as they found an increase in cognitive performance when exposing their research snails to a flavonoid of dark chocolate. Lymnaea stagnalis normally breathe via their skin. However, if the surrounding water is too low in oxygen, they extend a tube with a respiration hole on the tip and thereby breathe air from above the water surface. By gently tapping the respiration holes, Fruson and Lukowiak conditioned the mollusks to keep them closed even in hypooxygenated water. After a 30 minute training session, the animals remembered to keep it shut for three hours, but forgot it the next day. Only when the researcher added the flavonoid epicatechin to the water, the conditioning lasted for 24 hours. Now, it remains open how and what the flavonoid effects are within the nervous system, a question Fruson and colleagues will focus on in the future. (jr)


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**...and Chains of Omega-3 Fatty Acids**

Chains of omega-3 fatty acids have been linked to reducing the risk of coronary heart disease, which has been known for a while now. The effect on stroke, however, remained unclear until Dr. Chowdhury from Cambridge University and Professor Franco from Erasmus MC Rotterdam looked at the results of 38 studies including about 800,000 participants in 15 countries. In the studies, the consumption of fish, omega-3 fatty acids, and fish oil supplements was assessed as well as the level of omega-3 fats in the blood. Individuals eating 5 or more servings fish per week had 12% lower risk of cerebrovascular diseases; those having two to four servings had a decreased risk of 6% compared to those who ate less fish. Supplements of fish oil did not have any risk-reducing effects. Interestingly, the blood level of omega-3 fats did not correlate with the reduced risk. This might be an indicator that other factors are contributing to lower the risk for such cerebrovascular diseases. For instance, an increased fish intake might lead to a reduced intake of red meat, which is associated with vascular problems. Furthermore, eating a good amount of fish might be a sign of a generally healthier diet and higher socioeconomic status. It still seems to be reasonable to advise having fish at least once or twice a week. And maybe go for some dark chocolate as dessert. Bon appétit! (jr)

Neuroscience in Your Everyday Life

Why is it Again that we Dream?

Dreams have been fascinating mankind since the dawns of history and as such, many theories on why we dream have evolved. Are they bottom-up, meaning that in order to dream we need to have sensory input, which is then interpreted by higher order areas, or is it top-down: imagination or memories that are then enriched with sensory aspects? Lesion studies point more to the latter option: dreaming requires an intact tempo-parieto-occipital junction. Not only dreaming is effected when lesioning this area, but also ‘imaginative skills’ are disturbed in wakefulness. Lesion studies have also given us insight into the neural correlates of dreams. They have shown that in order to dream we need the forebrain and not brainstem structures that are important for REM sleep.

Sometimes, it is hard to distinguish a dream from being awake, but why is this so? When comparing being awake to REM sleep by EEG or measurement of brain metabolism by positron-emission tomography (PET), both cases show an activation of high-order occipital-temporal visual cortex. Interestingly, deficits in wakefulness are also reflected in dreams. Subjects suffering from impaired face perception will not see faces in a dream. Yet, there are undeniably many differences between wakefulness and dreaming, with the latter having no perception of environmental cues (even when eyes are taped open) and reduced self-awareness as well as altered reflected thought (flying on a pink elephant over the Mount Everest). This is due to the deactivation of various cortical regions (posterior cingulate cortex, orbitofrontal cortex, dorsolateral prefrontal cortex, inferior parietal cortex). We also have a high degree of emotional involvement coming from highly activated limbic and paralimbic structures, the insula, and the anterior cingulate cortex.

Zooming into the molecular level, we can also see that the activation of certain brain areas is reflected in neurotransmitters levels. During REM sleep, acetylcholine alone is maintaining brain activation, whereas monoaminergic systems are silent. As cholinergic innervation is predominant in limbic structures and not high in the dorsolateral prefrontal cortex, we have differentially active brain regions as mentioned above.

Did that really happen or was it all a dream?

All information is taken from Nir and Toni, 2009 which I can highly recommend as an overview for dreams and neurophysiology.

Do you also sometimes wonder about the simple neuroscience questions in everyday life, but don’t really feel like looking them up right away? For questions like this, just mail us your question (cns-newsletter@charite.de) and Dr. Harebrained will give us his explanation in the next issue! Our next issue’s question: Why is it again that we only use 10% of our brain? (vl)

Reference
Nir and Tononi, Trends Cogn Sci, 2010

Open Positions for Master Students in Neuroscience Research in Berlin

Type: Master thesis
Title: Regulation, axonal transport and translation of mRNA for opioid receptors and TRPV1 in inflammatory pain
Field of research: Pain research
Starting date: As soon as possible, latest January 2013
Deadline for application: December 15th, 2012
Research group: Anesthesiology, Campus Benjamin Franklin
Contact: Dr. Morgane Rouault, morgane.rouault@charite.de, tel: 030/84452131

Type: Lab Rotation/Master Thesis
Title: Behavioural and neurochemical effects of Deep Brain Stimulation in animal models of psychiatric disorders (applied methods: surgery, behavioural testing incl. intracranical Self-stimulation, immunohistochemistry)
Field of research: Deep Brain Stimulation as a potential treatment for therapy-resistant psychiatric disorders
Starting date: Immediately
Research group: Experimental Psychiatry, AG Christine Winter
Contact: Julia Rummel, julia.rummel@charite.de, tel: 030/450525016

Type: Master thesis
Project Title: The role of Notch3 in adult hippocampal neurogenesis
Field of Research: Neuroregeneration and neuroplasticity in models for neurodegenerative disorders
Possible starting date: Immediately
Research Group: Neural regeneration and plasticity
Contact: Barbara Steiner, barbara.steiner@charite.de
Neurosciences in Berlin – International PhD Fellowships

The NeuroCure Excellence Cluster invites applications for its PhD program starting in 2013

NeuroCure is an inter-institutional research network based at the Charité – Universitätsmedizin Berlin, the Humboldt-Universität zu Berlin and the Freie Universität Berlin, with its partners, the Max Delbrück Center for Molecular Medicine Berlin-Buch (MDC), the Leibniz-Institut für Molekulare Pharmakologie (FMP) and the Deutsche Rheuma-Forschungszentrum Berlin (DRFZ).

With over 45 internationally recognized research groups, NeuroCure offers outstanding interdisciplinary training and research opportunities for national and international scientists from a wide range of academic backgrounds.

Fellowships are available in the following subject areas:

- Molecular mechanisms of nervous system development and function
- Mechanisms of neural damage and cellular age
- Endogenous brain protection
- Nervous system regeneration
- Crosstalk between nervous and immune system
- Developmental disturbances
- Synaptic plasticity

For more details on subject areas and participating research groups go to: http://www.neurocure.de/en

How to apply: Send a full CV, two academic references and a personal statement of your interest in this program to neurocure-phd@charite.de.

Closing date for applications is 7 January 2013. Short-listed applicants will be invited to a Skype interview in February; the final interview will take place in March 2013. Queries should be emailed to benedikt.salmen@charite.de or britta.eickholt@charite.de.
Experimental Design: The First 'New' Module
The module 'Experimental Design' will prepare you for your Master thesis, focusing on how to design your experimental setup. You are to learn the most important method(s) necessary to successfully work within your thesis project. Working from preliminary data you have obtained, you will develop a realistic plan for your Master thesis. The intention of this module is not scientific inquiry as such, instead emphasizing the experimental method(s) you will use to approach your thesis project. To this end, the essay assignment (5 to 10 pages long) should focus on the design of the experiments, the rationale that governs your choice of methods and the answers you hope to reveal in your experimental setting. You should also expect to explain established methods and common or potential pitfalls. The report must follow a similar format to a lab report. Contact Benedikt (benedikt.salmen@charite.de) for details.

Individual Focus: Online Courses
From now on, we will approve certified online courses (e.g., those offered by coursera) for your individual focus. Before taking these, however, you have to make sure that the course is acknowledged by the program office. It also goes without saying that the course has to be certified by the course provider. Secondly, copies of home assignments and other assessed tasks have to be handed in to the program office. Master students can gain up to two credit points from such courses, PhD students up to six. No credit points will be granted without certification of successful completion. Contact Benedikt (benedikt.salmen@charite.de) or Ralf (ralf.ansorg@charite.de) for details.

Person in Charge of PhD Students
As Chen left the program in August this year, Ralf will be in charge of the PhD admissions and administrative matters from now on. We would like to thank Chen for his dedication to the program and wish him all the best for his future. Please contact Ralf (ralf.ansorg@charite.de or 2093-4585), if you want to make an appointment.

Help Us Streamline Our Services: PhD Credit Points
The program office kindly asks PhD students to hand in course documentation on time, i.e. (at the very latest) around the time you officially file your PhD Thesis at the Promotionsbüro. To speed up the production of academic records (e.g., spreadsheet, transcript, etc.) with your estimate of credit points according to the regulations. Please contact Ralf (ralf.ansorg@charite.de or 2093-4585), if you have any related questions.

Good Start: New MSc Students Settled
Having overcome unprecedentedly tough competition, 15 of roughly 150 applicants finally succeeded it to be admitted to our Master's program this year. In addition, a new group of Erasmus students (Erasmus Mundus) students have joined our program, both as 1st and 2nd year students. Furthermore, two Erasmus students from Amsterdam have enrolled to the first semester of our program as well. Please join us in giving them a warm welcome to the Medical Neurosciences Program in Berlin.