January 2013

Kopf Carrier #76

KOPF CARRIER

PUBLISHED BY DAVID KOPF INSTRUMENTS ■ TUJUNGA, CALIFORNIA

Brain Reviews: Of Guts and Brains

Edlira Yzeiraj, Emily Forbes, Kelly Nahum, Brian H. Hallas, Joerg R. Leheste, German Torres*
Department of Biomedical Sciences, New York Institute of Technology College of Osteopathic Medicine, Old Westbury, New York 11568, USA

*Corresponding Author: German Torres, Ph.D.
Associate Professor, Department of Biomedical Sciences NYIT/COM
PO Box 8000, Old Westbury, New York
Telephone: 516-686-3806
Fax: 516-686-1454
E-mail: torresg@nyit.edu

Introduction

The adult human gastrointestinal (GI) tract is home to trillions of bacterial microbes that far exceed the combined number of cells in the body, with their non-redundant genes, vastly outnumbering our own *Homo sapiens* genes by approximately 100-fold. Together, these microbes function as another organ embedded within a host body shaping an intimate interconnection between two different organismic physiologies. This pervasive interconnection obviously not only affects the concept of who we are in terms of our sense of "cell individuality" and "self DNA" but it also makes us wonder how these archaic genes and their encoded inhabitants affect our general health and behavior. This brief essay discusses the impact gut microbiota exerts on systems physiology, and the implications of this impact for the host brain.

Table 1. Biological Functions Attributed to Gut Microbiota
Carbohydrate Fermentation and Absorption
Repression of Pathogenic Microbial Growth
Trophic Effects - Lymphoid tissue growth - Changes in expression of cell surface proteins (e.g., sodium/glucose transporters)
Metabolic Functions: - Vitamin synthesis (e.g., biotin, folate) - Absorption of ions (e.g., magnesium, calcium and iron) - Metabolizing dietary carcinogens, microcomponents and macrocomponents
Preventing Inflammatory Bowel Disease
Gut flora have continuous and dynamic effects on host's gut and systemic immune systems

Basic Concepts

Before proceeding, see the attached Glossary for definitions of microbiota and other terms used in this essay. The average human gut predominantly houses bacterial organisms from both the *Bacteroidetes* and *Firmicutes* phyla (Backhed et al., 2005; Turnbaugh et al., 2009). By-and-large, sub-species from these phyla assist us with the breakdown of otherwise indigestible polysaccharides, plant-derived cellulose, resistant starches and other dietary substances (Backhed et al., 2005). Additional biological functions attributed to gut bacteria are shown in Table 1.

Besides bacteria, small numbers of archaea and eukaryote microorganisms also reside in the GI tract making the underlying epithelium of the gut a patched ecosystem for all three domains of terrestrial life (Fig. 1). Further, distal extensions of the GI tract (e.g., skin, mouth, throat and nostrils) as well as the six major divisions of the human colon (i.e., cecum, ascending and descending colon, transverse colon, sigmoid colon and rectum) and the vagina (i.e., posterior fornix) also teem with thousands of bacterial species along with fungi and viruses (Gevers et al., 2012 and Li et al., 2012).

This community landscape is pervasive: Almost every organ in our body is seeded with single microbial species or defined species mixtures that are critical for host physiology. Despite millions of years of co-evolution, however, the host-microbiota relationship can sometimes go awry. This thread of breach with ensuing pathologies is particularly apparent in the relationship between the microbiota, the immune system and metabolic signaling pathways.

Interactions Between the Immune and Metabolic Signaling Pathways

Despite the symbiotic nature of the host-gut relationship, opportunistic invasion of host tissue by resident microorganisms or broad-spectrum antibiotics that can directly modify the physiology of microbes, may lead to immune deficits in ways that predispose to disease. For example, there is circumstantial evidence that children with asthma not only harbor different bacteria, including *Staphylococcus aureus*, but are also home to a less diverse mix of microbes than those who are healthy (Bisgaard et al., 2007).

The risk of immune-mediated diseases such as inflammatory bowel disease (IBD) and asthma is also seen in infants delivered at birth by cesarean section or in children treated with high doses of antibiotics. Cesarean section infants display lower densities or frequencies of *Bacteroidetes* in their guts relative to

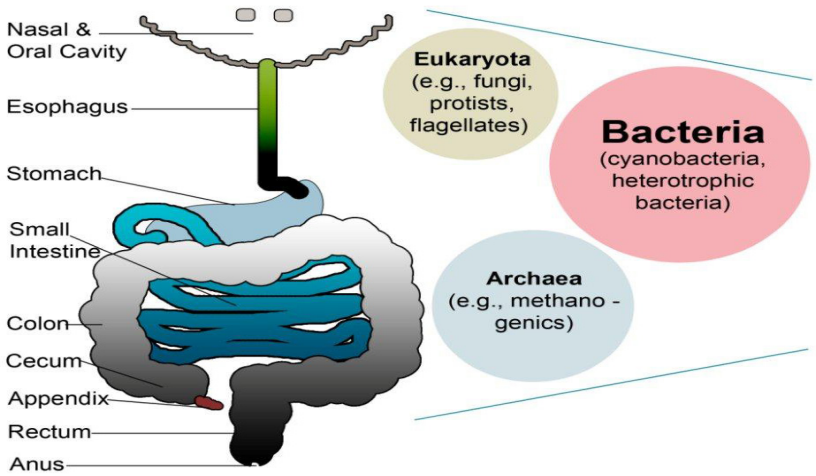

Fig. 1. A complex ecosystem resides in the human gastrointestinal tract. Along its entire length, the human GI system (left) is home to representatives of all three domains of terrestrial life (right). This ecosystem of approximate 100 trillion microorganisms is highly enriched in the large intestine (cecum to anus) and is mostly colonized by bacteria (red circle). The acquisition of GI microbiota during the postnatal period of life is vital for maintaining epithelial and immunity homeostasis. Composition and diversity of this ecosystem can be modified by diet as well as health status.

cohorts born by vaginal delivery (Bennet and Nord, 1987; Penders et al., 2006). Shifts in the composition of bacterial species in the gut or lungs at delivery might reflect opportunistic invasions by better-adapted microorganisms that increase the risk of allergic asthma. The influence of bacterial diversity and population makeup also extends to cystic fibrosis (CF) where lungs of these patients harbor a different microbial profile, including less diversity of species from the phyla *Bacteroidetes* and a greater number of Actinobacteria, than the lungs of healthy individuals which are primarily inhabited by *Bacteroidetes* and *Firmicutes* (Costello et al., 2012). It is therefore conceivable that a less diverse mix of bacteria might increase the severity of pulmonary inflammation in CF patients and asthmatics as well. The same might be true for frequent antibiotic use, with antibiotics disturbing the host-microbe interaction thus contributing to intestinal inflammation and increasing the risk for lung malignancy (Costello et al., 2012). Together, these findings suggest that commensal bacteria have a significant impact on immune signaling cascades that extends well beyond mucosal tissues, and that substantial variation in both the diversity and composition of microbial colonies is critical for healthy humans.

The microbial landscape is also shaped by diet and food intake and it is conceivable that disruption of the gut microbiota (dysbiosis) by antibiotic therapy might promote obesity-related metabolic abnormalities that increase the risk of developing type 2 diabetes and cardiovascular disease. Indeed, this possibility is supported by human and animal-based studies that show a strong interaction between the immune system, gut microbes and signaling pathways involved in energy and lipid metabolism at peripheral sites. For example, longitudinal studies conducted in children indicate that early exposure to antibiotics disrupts the composition of gut microbiota leading to changes in food metabolism and body mass later in life (Trasande et al., 2012).

Along the same lines, obese individuals exhibit a different and a less varied bacterial profile than that of lean persons, with a lower prevalence of *Bacteroidetes* and a higher incidence of *Firmicutes* (Turnbaugh et al., 2009). These differences in bacterial composition may result in obese individuals being more efficient in extracting energy from food with subsequent increased levels of lipogenesis in their intestines, low-grade inflammation and insulin resistance (Turnbaugh et al., 2006). Susceptibility to obesity is also seen in mice with defects in Toll-like receptors that are expressed in certain immune and intestinal cells (Vijay-Kumar et al., 2010). Absence of these membrane-anchored receptors alters the gut microbiota leading to increased food intake, insulin resistance and other characteristics (e.g., hyperlipidemia, hypertension and substantial adiposity) of metabolic syndromes. Finally, mice reared in germ-free environments are more susceptible to weight gain, when they are colonized by microbes derived from obese rather than lean mouse donors (Backhed et al., 2007; Turnbaugh et al., 2008). These results support the emerging view that resident bacteria can influence host immune system development and ensuing immune response.

Of Guts and Brains

There is no doubt that changes in microbe diversity and composition can have profound consequences for host health. The question that remains unanswered is whether gut bacteria can also shape the biochemistry of the human brain to ultimately change emotional behavior. Here we review the current knowledge on three issues relevant to gut microbes and brains: (1) is there an extended communication network between the microflora and the host brain, (2) might the gut microbiota be aiding the onset of certain psychiatric disorders and (3) is there a therapeutic approach to use beneficial bacteria or probiotics to treat behavioral phenomena?

The notion that a communication system that provides a signaling route between the gut and the brain has at least two clear precedents: First, the observation that the brain has the ability to influence the GI tract in terms of motility, permeability and secretion modalities (Collins et al., 2012) and second, that emotional experiences such as stress and anxiety can exacerbate pre-existing conditions such as chronic inflammatory bowel disease (IBD), including Crohn's disease, ulcerative colitis and gastro-esophageal reflux disease (Mawdsley and Rampton, 2005; Mayer and Tillisch, 2011). Against this background, it is proposed that a cross-talk between the gut and the brain involves the secretion of gut hormones such as neuropeptide Y, peptide YY, pancreatic polypeptide, cholecystokinin and ghrelin all of which have been linked to the regulation of energy balance, anxiety and depression-related phenomena (Holzer et al., 2012; Manco, 2012). These biologically active peptides might change the microbial composition and activity of microbiota which would indirectly influence a broad-spectrum of behavioral traits, including emotion, satiation and stress.

At the level of the brain, hormonal output from the hypothalamus and the pituitary, including corticotropin-releasing factor (CRF) and adrenocorticotropin hormone (ACTH) respectively, and secretion of cortisol from the adrenal glands might affect the microbial composition of the gut to enhance the risk of developing visceral obesity (Manco, 2012). In addition to the aforementioned entero-endocrine pathways, a cross-talk between the gut and the brain might involve efferent neural pathways such as those constructed by the vagus nerve (cranial nerve X) in the central nervous system (Bercik et al., 2012). Alternatively, it is conceivable that gut microbiota might influence behavior via the synthesis of epinephrine, serotonin, dopamine, γ-aminobutyric acid (GABA) and acetylcholine molecules, which are the same neurotransmitters that the brain recruits for synaptic transmission in both healthy and pathological states (Collins et al., 2012; Cryan and Dinan, 2012). In addition, neuroactive bacterial metabolites such as short-chain fatty acids, lactic acid and propionic acid might also activate trans-membrane receptors to indirectly influence synaptic-based processes involved in learning, memory, mood and pain perception (Cryan and Dinan, 2012; Schellenkens et al., 2012).

It is thought that these bacterial-based neurotransmitters and circulating metabolites would gain entrance to the brain via the bloodstream and area postrema to induce a transient shift in behavior with disease risks. Collectively, these data suggest that neural, immunological, endocrine and metabolic

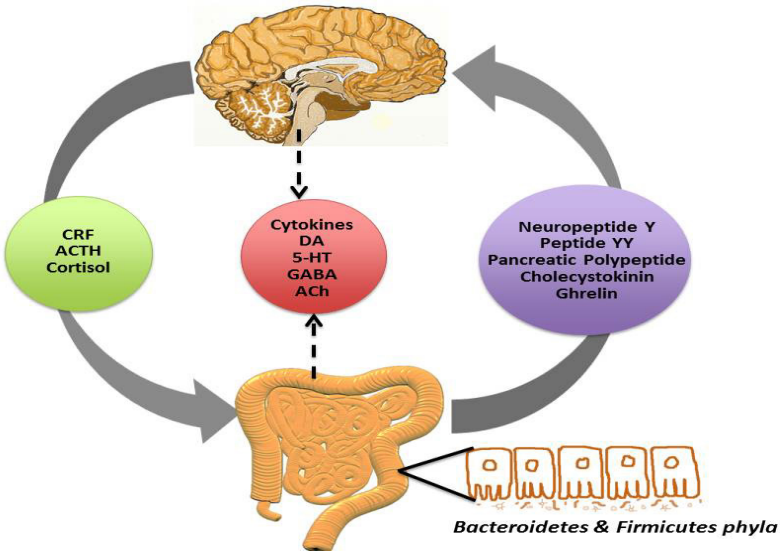

Fig. 2. A bidirectional communication exists between the gastrointestinal tract and the brain. Specific phyla, classes or species of bacteria reside in the gut and interact with the brain via neural, immune, endocrine and metabolic cues. Changes in brain chemistry and subsequent changes in emotional behavior appear to be influenced by microbial composition and activity of the gut microbiota.

cues are widely used by the gut and brain to cross-talk and that changes in brain chemistry and corresponding changes in emotional behavior are influenced by the human's internal bacterial ecosystem (Fig. 2). Of note, most of the information listed above is derived from mouse studies; however, these findings are likely to hold up in humans as well.

Thus, on the basis of results from animal studies, it is tempting to speculate that changes in gut microbiota might influence human disease outcome during development or adulthood. Indeed, patients with hepatic encephalopathy, a severe liver disease, exhibit significant shifts in their gut bacteria relative to those of healthy controls (Bajaj et al., 2012) and interestingly, oral administration of antibiotics can reverse some of the clinical symptoms of encephalopathy (Schiano, 2010).

These results strongly suggest that the brain is exquisitely sensitive to single-celled products and metabolites, their strain composition, their numerical levels and their physiological modulation (Fig. 3). Indeed, epidemiological studies, particularly association studies in humans show putative links between neurodevelopmental disorders such as autism spectrum disorders, schizophrenia, depression and anxiety and microbial pathogen infections during infancy, and perhaps even during the perinatal period (Mittal et al., 2008; Finegold et al., 2010). In general, information listed in Fig. 3 suggests that bacteria translocation or pathogenic bacterial strains are capable of modulating the stress response and stress-related behaviors that are relevant to psychiatric disorders.

There also appears to be a role for segmented filamentous bacteria in the development of autoimmune experimental encephalomyelitis in transgenic mice (Lee et al., 2011). If this is substantiated in humans, it would be reasonable to view multiple sclerosis and other chronic inflammatory autoimmune disorders as pathologies driven in part by microbial infection (Berer et al., 2011; Berer and Krishnamoorthy, 2012). This would not be surprising as pro-inflammatory cytokines, including interleukin-4 and interferon-γ, have been implicated not only in autoimmune diseases but also in clinical depression and other stress-related syndromes (Desbonnet et al., 2010). In this regard, alterations in gut

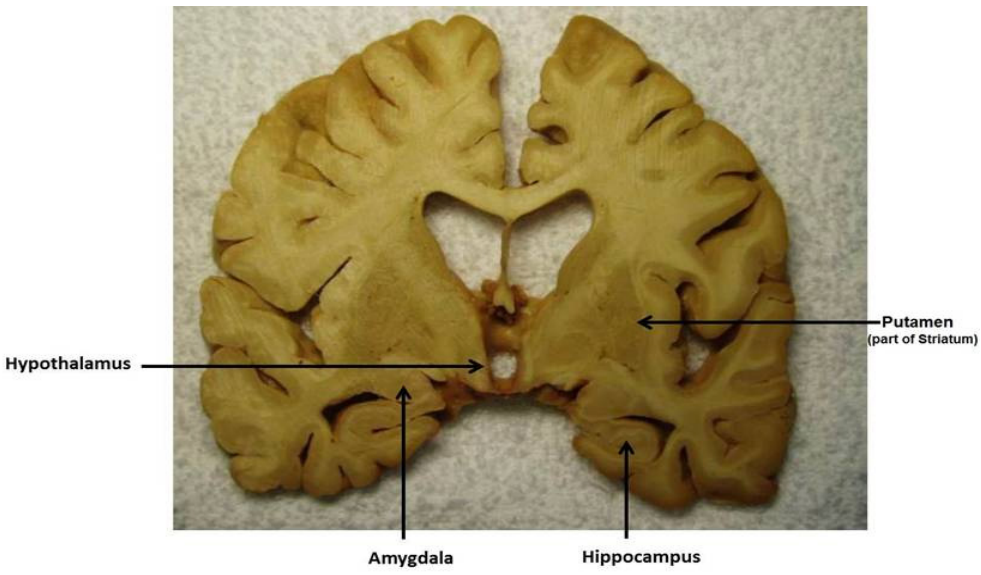

Fig. 3. The brain sends and receives chemical signals from the gut microbiota. Certain brain regions in particular the hypothalamus, striatum, amygdala and hippocampus are implicated in stress-related psychiatric disorders such as major depression. It should be noted that major depression, autism spectrum disorders and schizophrenia, among others, are neurodevelopmental disorders thought to be associated with microbial pathogen infections during the perinatal period. Perhaps burden of infection might affect the synthesis and release of neurotransmitters to produce deficits in cognitive behavior.

microbial composition are known to influence systemic cytokine levels and the innate mucosal immune system in particular, is crucial for normal T lymphocyte development (Collins et al., 2012). It is difficult to avoid the inference therefore that at least one of the ways in which the brain may become diseased is through changes in one's own gut microbial composition.

The above clinical and pre-clinical findings also point to some practical ways to improve human health. For instance, it is not far-fetched to start thinking about how to manipulate gut bacteria to promote or restore brain health and mental well-being. The first step to take in this direction would be to identify previously unrecognized irregularities in the physiology of microbial communities and to link them with disease onset and disease progression in the host brain (i.e., to establish cause and effect between the microbiome and health). Second, if certain bacterial populations are identified to be deleterious to the brain, the idea would be to eradicate such pathogenic populations from the gut and replace them with appropriate levels of beneficial microorganisms.

Perhaps, future therapies might target the microbes rather than specific brain disorders. For instance, it might be possible to design drugs that mimic the chemicals synthesized by intestinal bacteria and use them to minimize clinical symptoms of depression and anxiety, or to inhibit the metabolites that might lead to psychological despair and other stress-related phenomena. Also, as most brain pathologies listed in Fig. 3 are neurodevelopmental disorders, perhaps the strongest direction would be to pre-empt such diseases with healthy diets of microbes during critical stages of brain development.

These strategies are already undergoing clinical trials for IBD and other chronic inflammatory disorders (Rook and Lowry, 2012). Lastly, a novel and unconventional therapy is fecal transplantation or human probiotic infusion which is currently used for clinical conditions such as refractory *Clostridium difficile*, a particular toxic strain of bacteria that inhabits hospitals and affects thousands of patients across the U.S.A (Collins et al., 2012).

The basic idea for this particular type of therapy is to re-colonize, via colonoscopic injections, a patient's GI tract with bacteria derived from healthy donors (Damman, 2012). Fecal transplantation is also being tested in Parkinson's disease patients to determine whether such treatment might improve their severe constipation. Regardless of mode of therapy, what is clear is that the actions of the microbiome extend far beyond the GI tract. It appears that human brain chemistry, for instance, is dependent on the integrity of microorganisms to generate healthy and pathologic behavior.

References

Bäckhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. 2005. Host-bacterial mutualism in the human intestine. Science.307(5717):1915-20. Review.

Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. 2007. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc Natl Acad Sci U S A. 104(3):979-84.

Bajaj JS, Hylemon PB, Ridlon JM, Heuman DM, Daita K, White MB, Monteith P, Noble NA, Sikaroodi M, Gillevet PM. 2012. Colonic mucosal microbiome differs from stool microbiome in cirrhosis and hepatic encephalopathy and is linked to cognition and inflammation. Am J Physiol Gastrointest Liver Physiol. 303(6):G675-85. doi: 10.1152/ajpgi.00152.2012.

Bajaj JS, Ridlon JM, Hylemon PB, Thacker LR, Heuman DM, Smith S, Sikaroodi M, Gillevet PM. 2012. Linkage of gut microbiome with cognition in hepatic encephalopathy. Am J Physiol Gastrointest Liver Physiol. 302(1):G168-75.

Bennet R, Nord CE. 1987. Development of the faecal anaerobic microflora after caesarean section and treatment with antibiotics in newborn infants. Infection. 15(5):332-6.

Bercik P, Park AJ, Sinclair D, Khoshdel A, Lu J, Huang X, Deng Y, Blennerhassett PA, Fahnestock M, Moine D, Berger B, Huizinga JD, Kunze W, McLean PG, Bergonzelli GE, Collins SM, Verdu EF. 2011. The anxiolytic effect of Bifidobacterium longum NCC3001 involves vagal pathways for gut-brain communication. Neurogastroenterol Motil. 23(12):1132-9. doi: 10.1111/j.1365-2982.2011.01796.x.

Berer K, Mues M, Koutrolos M, Rasbi ZA, Boziki M, Johner C, Wekerle H, Krishnamoorthy G. 2011. Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination. Nature. 479(7374):538-41. doi: 10.1038/nature10554.

Berer K, Krishnamoorthy G. 2012. Commensal gut flora and brain autoimmunity: a love or hate affair? Acta Neuropathol. 123(5):639-51.

Bisgaard H, Hermansen MN, Buchvald F, Loland L, Halkjaer LB, Bønnelykke K, Brasholt M, Heltberg A, Vissing NH, Thorsen SV, Stage M, Pipper CB. 2007. Childhood asthma after bacterial colonization of the airway in neonates. N Engl J Med. 357(15):1487-95.

Collins SM, Surette M, Bercik P. 2012. The interplay between the intestinal microbiota and the brain. Nat Rev Microbiol. 10(11):735-42. doi: 10.1038/nrmicro2876.

Costello EK, Stagaman K, Dethlefsen L, Bohannan BJ, Relman DA. 2012. The application of ecological theory toward an understanding of the human microbiome. Science. 336(6086):1255-62.

Cryan JF, Dinan TG. 2012. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 13(10):701-12. doi: 10.1038/nrn3346.

Damman CJ, Miller SI, Surawicz CM, Zisman TL. 2012. The microbiome and inflammatory bowel disease: is there a therapeutic role for fecal microbiota transplantation? Am J Gastroenterol. 107(10):1452-9. doi: 10.1038/ajg.2012.93.

Desbonnet L, Garrett L, Clarke G, Kiely B, Cryan JF, Dinan TG. 2010. Effects of the probiotic Bifidobacterium infantis in the maternal separation model of depression. Neuroscience. 170(4):1179-88.

Dinan TG, Cryan JF. 2012. Regulation of the stress response by the gut microbiota: implications for psychoneuroendocrinology. Psychoneuroendocrinology. 37(9):1369-78.

Finegold SM, Dowd SE, Gontcharova V, Liu C, Henley KE, Wolcott RD, Youn E, Summanen PH, Granpeesheh D, Dixon D, Liu M, Molitoris DR, Green JA 3rd. 2010. Pyrosequencing study of fecal microflora of autistic and control children. Anaerobe. 16(4):444-53.

Gevers D, Knight R, Petrosino JF, Huang K, McGuire AL, Birren BW, Nelson KE, White O, Methé BA, Huttenhower C. 2012. The human microbiome project: a community resource for the healthy human microbiome. PLoS Biol. 10(8):e1001377. doi: 10.1371/journal.pbio.1001377.

Holzer P, Reichmann F, Farzi A. 2012. Neuropeptide Y, peptide YY and pancreatic polypeptide in the gut-brain axis. Neuropeptides. S0143-4179(12)00079-0. doi: 10.1016/j.npep.

Lee YK, Menezes JS, Umesaki Y, Mazmanian SK. 2011. Proinflammatory T-cell responses to gut microbiota promote experi-

mental autoimmune encephalomyelitis. Proc Natl Acad Sci U S A. 108 Suppl 1:4615-22.

Li K, Bihan M, Yooseph S, Methé BA. 2012. Analyses of the microbial diversity across the human microbiome. PLoS One. 7(6):e32118.

Manco M. 2012. Gut microbiota and developmental programming of the brain: from evidence in behavioral endophenotypes to novel perspective in obesity. Front Cell Infect Microbiol. 2:109.

Mawdsley JE, Rampton DS. 2005. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. Gut. 54(10):1481-91.

Mayer EA, Tillisch K. 2011. The brain-gut axis in abdominal pain syndromes. Annu Rev Med. 62:381-96.

Mittal VA, Ellman LM, Cannon TD. 2008. Gene-environment interaction and covariation in schizophrenia: the role of obstetric complications. Schizophr Bull. 34(6):1083-94.

Penders J, Thijs C, Vink C, Stelma FF, Snijders B, Kummeling I, van den Brandt PA, Stobberingh EE. 2006. Factors influencing the composition of the intestinal microbiota in early infancy. Pediatrics.118(2):511-21.

Rook GA, Raison CL, Lowry CA. 2012. Can we vaccinate against depression? Drug Discov Today. 17(9-10):451-8.

Schellekens H, Finger BC, Dinan TG, Cryan JF. 2012. Ghrelin signalling and obesity: at the interface of stress, mood and food reward. Pharmacol Ther. 135(3):316-26.

Schiano TD. 2010. Treatment options for hepatic encephalopathy. Pharmacotherapy. 30(5 Pt 2):16S-21S.

Trasande L, Blustein J, Liu M, Corwin E, Cox LM, Blaser MJ. 2012. Infant antibiotic exposures and early-life body mass. Int J Obes (Lond). doi: 10.1038/ijo.2012.132.

Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 444(7122):1027-31.

Turnbaugh PJ, Bäckhed F, Fulton L, Gordon JI. 2008. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe. 3(4):213-23.

Turnbaugh PJ, Gordon JI. 2009. The core gut microbiome, energy balance and obesity.J Physiol. 587(Pt 17):4153-8.

Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI. 2009. A core gut microbiome in obese and lean twins. Nature. 457(7228):480-4.

Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. 2009. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Sci Transl Med.1(6):6ra14.

Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, Sitaraman SV, Knight R, Ley RE, Gewirtz AT. 2010. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science. 328(5975):228-31.

Glossary

Acetylcholine (Ach): transmitter found in central and peripheral nervous systems. It plays a role in skeletal muscle movement and in the regulation of smooth muscle and cardiac muscle and it's believed to be involved in learning, memory and mood.

Adrenocorticotropic hormone (ACTH): hormone produced and secreted by the anterior pituitary gland in response to stress. Its principal effects are to increased production and secretion of corticosteroids.

Amygdala: nucleus located deep within the medial temporal lobes. Part of the limbic system, whose primary role is to process memory and emotional behaviors.

Corticotropin-releasing factor (CRF): hormone produced and secreted by the hypothalamus in response to stress.

Crohn's disease: an inflammatory bowel disease that causes inflammation of the lining of the digestive tract which leads to abdominal pain, severe diarrhea and malnutrition.

Dopamine (DA): neurotransmitter produced in several areas of the brain, including the substantia nigra and ventral tegmental area.

γ-aminobutyric acid (GABA): an inhibitory neurotransmitter of the central nervous system.

Hippocampus: located in the medial temporal lobe, plays a major role in formation and consolidation of memory.

Hypothalamus: area of the brain that produces hormones that control body temperature, hunger, sex drive, sleep and thirst.

Microbiota: microbial flora harbored by normal, healthy individuals.

5-Hydroxytryptamine (5-HT): or serotonin, a hormone and transmitter found in the brain, platelets, and gastric mucous membranes. Its functions include vasoconstriction, stimulation of smooth muscle and transmission of impulses between nerve cells.

Toll-like receptor: A receptor protein integral to the digestive system and the innate immune system. This receptor contains structurally- conserved molecules derived from microbes.

Area postrema: located in the medulla oblongata area of the brain. The area postrema is a chemoreceptor trigger zone responsible for vomiting.

Cytokines: peptides or glycoproteins that modulate the cellular and humoral responses of the immune system.

Bibliographies

Edlira Yzeiraj (eyzeiraj@nyit.edu) OMS III, received her B.A in Political Science at Queens College, City University of New York (CUNY). She subsequently taught and worked as a research assistant in a molecular genetics laboratory at Queens College, CUNY. She is currently enrolled at the New York Institute of Technology College of Osteopathic Medicine (NYIT COM) receiving a dual D.O./M.A. degree.

Emily Forbes (eforbe01@nyit.edu) OMS III, received her B.A in Biology at New York University in 2007. She subsequently worked in a molecular genetics laboratory at Massachusetts General Hospital. She is currently enrolled at the New York Institute of Technology College of Osteopathic Medicine (NYIT COM) receiving a dual D.O./M.A. degree.

Kelly Nahum (knahum@nyit.edu) OMSII, received her B.A. from University of Wisconsin-Madison in May 2009. She then received her Master's in Biomedical Sciences from University of Medicine and Dentistry of New Jersey (UMDNJ-SOM). She is currently enrolled at the New York Institute of Technology College of Osteopathic Medicine (NYIT COM) and will graduate in May 2015.

Dr. Brian H. Hallas (bhallas@nyit.edu) received his Ph.D. in neurobiology from Purdue University in 1979. He also holds an M.S. in biology from Purdue University, a B.A. in Psychology, and a B.S. in Biology from University of Hartford. He has been awarded numerous research grants and has authored many articles in scientific journals. He is the recipient of various honors and awards, most recently the prestigious Presidential Service Award from New York Institute of Technology in 2007. In 2004, he was awarded a fellowship by the Heritage Foundation Health Policy for Research in Health Policy based on stem cell research. From 2003 to 2007, he was Associate Dean of Research at the New York Institute of Technology College of Osteopathic Medicine, where he is currently Professor in the Department of Biomedical Sciences. He has published over 70 peer reviewed articles, several book chapters and 225 abstracts.

Dr. Joerg Leheste (jleheste@nyit.edu) received his Ph.D. in Molecular Biology from the Humboldt University, Berlin/Germany in 2001. He also holds an M.S. in Biology with focus on Molecular Genetics and a B.S. in Biology from Philipps University, Marburg/Germany. Dr. Leheste is currently employed as an Assistant Professor in the Department of Biomedical Sciences at the New York Institute of Technology College of Osteopathic Medicine. His specific research interest focuses on age-related disease of the central nervous system. Dr. Joerg Leheste has published numerous articles in peer reviewed journals and is supported by grants from the New York Institute of Technology College of Osteopathic Medicine.

Dr. German Torres (torresg@nyit.edu) received a Ph.D. in Neuroscience from the University of California at Santa Barbara and is currently an Associate Professor in the Department of Biomedical Sciences at the New York Institute of Technology College of Osteopathic Medicine. His specific research interests are centered on the biological basis of brain disorders.

Contact Information: New York Institute of Technology College of Osteopathic Medicine, Northern Blvd., Old Westbury, NY 11568; (516) 686-3806.

Editor's Column

It is the Holiday Season here in Florida (and elsewhere, of course) as I write this column. We are having trouble getting too excited because the weather is a balmy 80° F with lots of sun. We did have a good bit of beach erosion when hurricane Sandy passed by (then hit the New Jersey shore so badly) and now 2 of the 4 lanes of the beach highway, A1A are closed because part of the beach washed out, undermining the roadway there. However, most of the Ft. Lauderdale beach is just fine. Alas, tomorrow, we will be able to get more excited about the season as we are heading to Dublin, Ohio for a month in our condominium there. It is a good bit cooler there. We will have our family Christmas there in mid-December, then travel to Detroit to spend actual Christmas with our oldest son, Shane and his family. We may come back to Dublin shortly after new years, then back to Florida mid-January. We are really looking forward to seeing the grandchildren again and spending as much time as possible with them.

This 76th edition of the Kopf *Carrier*, is the second in the series of Brain Reviews organized by Brian Hallas, Ph.D., Joerg Leheste, Ph.D. and German Torres, Ph.D. They enlisted three osteopathic medical students from their institution as co-authors. The article is a very interesting synthesis of an area that is undergoing increasing scrutiny in biomedical science. For a number of years it has been evident that there is more than a one-way communication between the gut and the brain. Several substances that are now known to be neurotransmitters were first in fact discovered in the gut. The remarkable diversity of flora and fauna found in the human gastrointestinal and other systems is truly amazing. In their article these authors point out that there may be far more interaction between the brain and the gut then we ever realized. In fact what goes on in the gut may well predispose or even cause behavioral and psychological disorders. They cite new evidence suggesting that alterations in the gut bacterial populations made directly predispose or cause such things as changes in mood and behavior. If this relationship is borne out in further studies, it would suggest ways of altering the gut bacterial populations to ameliorate these conditions. This article truly presents much food for thought about the tremendous and complex interactions in our bodies. And once again it reminds us that as scientists we need to keep in mind that there is much to be discovered in our universe. Many thanks to these authors for this wonderful contribution. We look forward to seeing more in this interesting series.

Neuroscience meetings this year were held in New Orleans. It was really great to be back in that wonderful city and see the tremendous recovery that has been undertaken since hurricane Katrina. That disaster in 2005 literally destroyed most of the city. However the city is once again a vibrant and exciting place to visit. The attendance at this years neuroscience meetings was down a bit, perhaps due to people still not being confident in the city's recovery, but the meeting itself was, as usual, an exciting event. Once again David Kopf instruments sponsored the Kopf Neuroethics lecture that this year was given by Barbara Sahakian, Ph.D. from the University of Cambridge. Her topic was "The Impact of Neuroscience on Society – The Neuroethics of "Smart Drugs"'. She gave much for us to think about in terms of the effects of various drugs that alter mood and behavior and their impact on society. I also attended the annual meeting of the international Neuoethics Society that was held in conjunction with the neuroscience meeting. While still a relatively small group, the International Neuroethics Society is an extraordinarily vibrant and meaningful organization. The topic of neuroethics is becoming increasingly important in the study

of brain and behavior. As neuroscientists we must become more aware of the ethics of what we do and how we can influence the use of our data to the good of society. If we are not actively engaged in this dialogue we run the risk of our data and knowledge being misused. I would encourage all of you to consider joining the International Neuroethics Society and attending their annual meeting. Information about the group and how to join can be found at www.neuroethicssociaty.org.

I wish all of you a very happy holiday season and a great new year. I also invite you to consider writing an article for the *Carrier*. An honorarium is paid for each article and the author retains the copyright to the article. Please contact me if you would like to consider writing an article.

Michael M. Patterson, Ph.D.
Science Editor
David Kopf Instruments
954-288-5518
954-452-6812 (FAX)
drmikep1@me.com