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Nutrition, Digestion and Psychopathological Disturbances – A Review

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The article gives an overview about recent neurobiological insights into the interplay between the gastrointestinal tract and neurophysiological information processing. These have revealed a complex, bidirectional communication system that not only ensures the proper maintenance of gastrointestinal homeostasis and digestion, but also likely has diverse effects on affect, motivation and higher cognitive functions, including intuitive decision-making. In addition, mental disorders have been linked to a variety of medical conditions, including functional and inflammatory gastrointestinal disorders, obesity, and eating disorders.

Key-words: Digestion & psyche; Gastrointestinal and psyche; Brain & gut; Psychopathology and digestion

Introduction: Can the Stomach Think?

“Love goes through the stomach”, “having butterflies in the stomach”, but also “anger in the stomach”, “that upsets my stomach”, “a full stomach doesn't like studying” - the interaction between gastrointestinal functions and certain emotional states is deeply rooted in our language. Is there actually a connection between the head and the digestive organs or are the phrases mentioned just the result of creative popular usage?

There is a saying that you should make some decisions based on your gut. Can the stomach really think? The interaction of neurophysiological processes in the brain and internal organs has been the basis of numerous scientific theories for many years. As early as 1884, William James and Carl Lange formulated a concept according to which stimuli that trigger emotions such as anger, fear or joy initially cause changes in visceral functions via the autonomic nervous system, but then the afferent feedback of these changes to the brain is responsible for the emergence of specific emotional feelings [21]. A fundamental scientific breakthrough occurred with the discovery of the so-called enteric nervous system by John Newport Langley around the year 1900 [17]. The enteric or intrinsic nervous system is one of the main components of the autonomic nervous system and consists of a network-like system of neurons that controls the function of the gastrointestinal tract.

The autonomic nervous system is known to consist of the sympathetic and the parasympathetic nervous system. The sympathetic nervous system accelerates the heartbeat, breathing and increases blood pressure in stressful situations. The

influence of the sympathetic nervous system on the processes of the gastrointestinal tract and its role in modulating gastrointestinal function has been divided into subgroups of postganglionic vasoconstrictor neurons, secretory inhibitory neurons and antimotility neurons [32]. The sympathetic nervous system acts inhibitory in a fight-or-flight situation, as good digestion is secondary in life-threatening situations, and slows down gastrointestinal transit function and secretion. This inhibitory effect is achieved largely through cholinergic transmission as well as a stimulating effect on the smooth muscles in the sphincter regions. The sympathetic nervous system accelerates the heartbeat, breathing and increases blood pressure in stressful situations. The influence of the sympathetic nervous system on the processes of the gastrointestinal tract and its role in modulating gastrointestinal function has been divided into subgroups of postganglionic vasoconstrictor neurons, secretory inhibitory neurons and antimotility neurons [32]. The sympathetic nervous system acts inhibitory in a fight-or-flight situation, because good digestion is secondary in life-threatening situations, and slows down gastrointestinal transit function and secretion. This inhibitory effect is achieved largely through cholinergic transmission as well as a stimulating effect on the smooth muscles in the sphincter regions.

The parasympathetic nervous system, on the other hand, slows the heart rate and stimulates the digestive tract during recovery phases [41,45]. The vegetative centers of the parasympathetic nervous system are located in the sacral spinal cord

(pars sacralis, sacral cord) and in the brain stem, with the tenth cranial nerve, the “vagus nerve”, plays a central role: The vagus nerve represents the fastest and most direct communication connection between the brain and intestines. The internal organs in the chest and abdominal cavity are reached by the nerve fibers of the vagus nerve - primarily for the transmission of reflexes (visceral afferents) [36]. The nerve connection between the intestine and the brain consists of 80 percent afferent nerve fibers (bottom-up) and 20 percent efferent nerve fibers (top-down) [10]. Function-specific vagal motor neurons supply the stomach, small intestine and the proximal part of the colon [42].

Excitatory vagal signals travel to ganglia within the enteric nervous system to mediate vagovagal motor reflexes and the cephalic phase of gastric acid secretion. The cephalic phase describes the stimulation of the vagus nerve by smell and taste stimuli and thus a stimulation of the parietal cells by the vagal transmitter acetylcholine [22]. The vagovagal reflex controls the peristalsis of the gastrointestinal muscles, particularly in response signals reach enteroendocrine cells and histamine-releasing enterochromaffin cells, as well as enterochromaffin cells that regulate the release of serotonin [40].

Enteroendocrine cells have a hormonal endocrine function. They can produce hormones through various stimuli, such as gastrin, which is released in the stomach. Gastrin travels through the circulatory system in the body and acts on enterochromaffin cells, for example, to promote the production of the signaling molecule histamine. Histamine causes the release of acid to help break down food in the stomach [1]. Enterochromaffin cells are neuroendocrine cells that are located in the epithelial tissue of the digestive tract [5].

The Second Brain

The enteric nervous system mentioned at the beginning can act both depending on the sympathetic and parasympathetic nervous systems as well as distinctly from them. Due to its size, complexity and similarity in terms of neurotransmitters and signaling molecules, it is often referred to as the “second brain” [19,33]. In terms of evolutionary biology, homologous variants of the enteric nervous system exist throughout the animal development – it is found also in insects and snails [18,38]. Caspers (1966) proposed that the ganglia that form the primitive brains of worms and ultimately the brains of higher mammals arose from these more primitive enteric neural circuits. According to the authors, the enteric nervous system could have arisen from precursor cells that migrated from the neural crest along the vagus and finally settled in the intestine.

The neurophysiological processes of the brain and the gastrointestinal tract are connected by an extensive network of neurons, chemical messengers and hormones. There is ongoing communication between these two entities about whether we are hungry or under stress and whether we have ingested a harmful microbe [12]. Communication takes place via several parallel routes: Here, the two branches of the autonomic nervous system, the hypothalamus-pituitary-adrenal axis and the sympatho-adrenal axis, are involved in the regulation of the intestinal-associated lymphoid tissue.

Furthermore, the complex communication takes place via descending monoaminergic pathways, which serve to strengthen spinal cord reflexes and the excitability of the dorsal horn. The monoamines include, for example, norepinephrine, serotonin and dopamine [39], whose imbalance is known to be

responsible for many psychological disorders. The dorsal horn describes the gray matter in the back of the spinal cord, through which information from the sensory cells in the skin, organs and bones travel to the brain.

Complex Neural Circuits

The neuronal systems in the CNS have now been well researched, but are extremely complex. Two important subcortical structures in this system are the amygdala and the hypothalamus, which receive their information from a network of cortical regions such as the medial prefrontal cortex including subregions of the medial prefrontal cortex and the anterior cingulate cortex [31,34]. The medial network of the prefrontal cortex receives information from the network of lateral prefrontal and orbitofrontal cortex, which, among other things, also provides integrated multisensory information about the representation of complex homeostatic body states. This also includes information about body conditions related to intestinal homeostasis, visceral pain and food intake. Outputs from subregions of the medial network, amygdala, and hypothalamus are integrated into distinct motor patterns within the mesencephalic periaqueductal gray.

The periaqueductal gray - also called central cave gray - consists of an accumulation of nerve cell bodies. The periaqueductal gray is located in the tegmentum, where it also surrounds the cerebrospinal fluid of the midbrain. This core complex is of great importance for opioid pain suppression. To do this, it directs efferents to the serotonergic raphe nuclei [26]. Interestingly, according to Bartels and Zeki (2004), the periaqueductal gray plays a crucial role in maternal behavior: it contains a high density of vasopressin and oxytocin receptors and has direct connections to the orbitofrontal cortex. Another caudal component of the central autonomic networks is represented by the pontic nuclei (core areas of the pons) and medullary nuclei, including the serotonergic raphe nuclei, the locus coeruleus complex (including the Barrington nucleus, which controls micturition behavior), and the dorsal vagal complex. This system of cortico-limbic-pontine networks is referred to as the emotional motor system and consists of integrated motor-autonomic, neuroendocrine, and pain-modulating components [16,28]. Mason (2011) proposes that the medial component of the emotional motor system (including the raphe nuclei) is involved - via the tonic modulation of various spinal cord reflexes - in the regulation of gastrointestinal functions. Furthermore, pain sensitivity is regulated by serotonergic, noradrenergic and opioidergic descending spinal cord tracts as well as by neuronal modification of the dorsal horn.

Communication with Bacteria

The system is made even more complicated by the fact that we also apparently communicate with bacteria. The intestines are particularly full of *Escherichia coli*, which helps us with digestion. Bacteria are essentially primitive creatures; in the course of evolution they have not even managed to form a decent cell nucleus. Nevertheless, they communicate with each other. Hostile bacteria that have invaded the body can form a film that our immune system basically bounces off of. They can survive in these fortresses for years, waiting for a period of immune deficiency. They form networks with other bacteria and exchange information. It is therefore not surprising that the microbiome, i.e. microorganisms that are not part of our own cells but colonize the body (especially the skin and intestines), also have an influence on how we feel.

Since our microbiome plays a central role in the brain-gut interaction, the term gut-brain axis has recently been modified: The current term is therefore "gut-brain-microbiome axis" [9,11]. The intestinal microbiome - i.e. the intestinal flora - includes all microorganisms that have settled in the intestine. According to Wall et al. (2014), the bacteria living in the intestine are able to produce neurotransmitters that are also found in the central nervous system. For example, there is evidence that a strain of *Lactobacillus brevis* can produce GABA in the intestine [3]. GABA (gamma-amino-butyric acid) is one of the transmitters that have an inhibitory effect and, for example, makes us calm, balanced, content and tired.

Pain and Digestion

But what does this have to do with mood and digestion? Foo and Mason (2009) found in an animal experiment that the consumption of tasty food appears to have an analgesic effect. Moderate painful stimuli caused by heat were tolerated better when eating chocolate compared to less tasty foods, which was reflected in reduced eating breaks. The authors assume that the analgesic effect of food intake ensures that food consumption is continued despite aversive, painful stimuli. These findings demonstrate the involvement of endogenous brainstem pain inhibitory mechanisms during food intake. The brainstem-induced continuation of consuming tasty foods could at least partially explain why we often find it so difficult to abstain even in the face of counteracting factors, such as the desire to lose weight or simply "to be full". The gut-brain axis thus functions in the sense of an optimally coordinated, hierarchical sequence of reflexes: from the reflex circuits within the enteric nervous system to the insula and the anterior cingulate cortex.

The intestinal reactions to nociceptive - i.e. pain-sensitive stimuli - typically include spinal and supraspinal reflexes and are usually accompanied by strong emotional reactions. Due to neural circuits outside the intestinal wall, interoceptive as well as exteroceptive information is integrated to maintain the balance of intestinal function [11]. Pontomedullary nuclei (including the midline raphe nuclei and the locus coeruleus complex) exert a tonic inhibitory influence on the enhancement of reflexes of the gut-brain-microbiome axis. In contrast, top-down influences processed in prefrontal regions regulate sympathetic and vagal outputs and are potentially capable of enhancing reflexes. Top-down influences on the gut are also involved in responses to environmental stimuli (e.g., threats) and in memory retrieval, including body memory [43]. Body memory is an exciting topic here; apparently conditioned reactions can be stored not only in the brain, but directly in the body organs. Foods that once made you feel sick also trigger a reaction on a very primal, peripheral level.

The conscious perception of interoceptive images - for example, created by signals from the gastrointestinal area or by recalling interoceptive memories - are directly related to the perception of feelings such as pain, disgust or well-being [6,43]. The nucleus tractus solitarius - responsible for taste perception - receives information from function-specific vagal afferents that send information from internal organs to the brain and forwards signals to the vagal motor neurons in the nucleus dorsalis nervi vagi (NDNV). The nucleus dorsalis nervi vagi is one of four cranial nerve nuclei of the vagus nerve in the brainstem. A1, A2, and A5 are medullary catecholaminergic nuclei in the Rostral Ventrolateral Medulla (RVLM) and Ventromedial Medulla (VMM). Catecholaminergic neurons produce the neurotransmitters dopamine, adrenaline and norepinephrine, i.e. the

monoamines already mentioned, which can be responsible for many psychological disorders, among other things.

Primary afferents from the intestinal environment send information to dorsal horn neurons of lamina I of the spinal dorsal horn or to cells of the vagal Nucleus Tractus Solitarius (NTS), supplying the brain with a wide range of gut-related information. The periaqueductal gray receives information from the parabrachial nucleus and also from regions of the forebrain, including the hypothalamus, amygdala, and anterior cingulate cortex, as well as the Prefrontal Cortex (PFC). The PFC also relays information to the Insula (INS) and the anterior cingulate cortex. The knowledgeable reader should perhaps just remember that everything in the body is actually connected to everything else, that what happens in the intestines has a lot of effects on the brain and, in particular, that even the bacteria living in the intestines influence us mentally and emotionally.

Bad stomach pain can often be seen at first glance in the face of a patient. Finally, the top-down activation of the subgroups of function-specific sympathetic and parasympathetic neurons mediates the reported emotion-related changes in motor and secretory activities in the gastrointestinal tract, which may be analogous to the different emotion-related facial expressions - mediated by the somatic branch of the emotional motor system - can be considered [2]. These emotion-related changes in peripheral target cells influence interoceptive feedback to the brain (e.g., through changes in smooth muscle activity) and may contribute to the long persistence of many emotional states over time. If the corresponding signals from the autonomic nervous system to the intestine last longer, this may lead to changes in peripheral target cells - such as the downregulation of adrenergic receptors on immune cells [13] - or to changes in primary afferent neurons [25] that alter the amplification of signaling from the gut to the brain. Such permanent changes in signaling between the brain and intestines can be associated with tonic dysfunction of the autonomic nervous system, which is associated with altered emotional states and, finally coming to psychological disorders, promotes the development of anxiety disorders and depression [37].

Anxiety and Depression and the Health of the Intestinal Flora

The specific physical mechanisms of anxiety disorders and depression are still the subject of a wide range of research. To date, neurotransmitters located in the brain such as serotonin, dopamine and norepinephrine have been classically used to explain the pathophysiology of anxiety and depression (Olivier & Olivier, 2020). However, as already indicated above, intestinal microbiota have also become more important in this regard and have revealed an interaction with the neurotransmitter system (Rieder et al., 2017): intestinal microbiota and their metabolites are at least partially involved in the afferent input of the vagus nerve and in the regulation of the hypothalamus. Pituitary-adrenal axis and have been shown to be associated with tryptophan metabolism and neurotransmitter production [3,38,44]. Tryptophan, an amino acid and precursor of serotonin, is involved in the regulation of important physiological functions of the human body. Therefore, imbalances in tryptophan metabolism are associated with various diseases such as depression, Alzheimer's disease and other psychiatric and neurodegenerative disorders (Williamson et al., 1997). Regarding the importance of the vagus nerve and its correspondence with the gastrointestinal tract, McVey Neufeld et al. (2019) conducted a study worth reading on the effectiveness of SSRI antidepressants in control

mice and vagotomized animals (vagotomy = severing the main branches of the vagus nerve). In control mice, it was observed that orally administered SSRIs resulted in increased vagal activity, which was reflected in changes in the activity of the mesenteric nerve in the peritoneum. In addition, the antidepressant effect of the SSRI treatment was absent in the vagotomized mice after the vagus nerve was severed. These findings make it clear that SSRIs may be ineffective without the involvement of the vagus nerve.

Can Antibiotics Make you Depressed?

As is known, serotonin is a neurotransmitter with great physiological importance in the human body. It is involved in the regulation of many important processes such as behavior, mood, sexuality, gastrointestinal secretion and peristalsis (Berger et al., 2009). Antidepressants that affect serotonin levels are extremely frequently used in the treatment of psychological disorders such as depression, post-traumatic stress disorder, anxiety and bipolar disorder (Masand, 1999). Interestingly, although serotonin can be found throughout the body, 90-95% of it is located in the gastrointestinal tract (Gershon & Tack, 2007). Logically, antidepressants not only have a mood-stabilizing effect in the CNS, but they also develop their effect in the stomach. At this point, the study by Hoban et al. (2016) is worth mentioning: An increased occurrence of depressive behavior was found in male rats due to antibiotic-related depletion of the intestinal microbiome. In parallel to the clear behavioral changes, less serotonin was also found in the hippocampus and hypothalamus (Hoban et al., 2016).

Another essential neurotransmitter is dopamine; it plays a central role in numerous processes such as emotions, memory, attention, motivation, reward, food intake and the ability to move (Klein et al., 2019). Dysregulation of the dopaminergic system is associated with anxiety and depression (Carpenter et al., 2012). Regarding gut-brain crosstalk, the results of Hoban et al. (2016) emphasized that the vagus nerve plays a fundamental mediating role: The study showed that antibiotic administration reduced the intestinal microbiota of male Sprague-Dawley rats, which resulted in lower dopamine levels in the amygdala and striatum and was associated with depressive and depressive disorders was associated with anxious behaviors.

In addition to serotonin and dopamine, norepinephrine has long been known for its relevance in the genesis of anxiety and depression (Kalk et al., 2011; Seki et al., 2018). Interestingly, norepinephrine also appears to be important in the feeling of hunger/satiety (Asarian & Bächler, 2014). Palma et al. (2015) demonstrated that depletion of gastrointestinal microbiota by administration of antibiotics increased depressive-like behavior in rats and that this effect was associated with increased levels of norepinephrine in the striatum.

Administration of the bacteria *Lactobacillus helveticus*, heat-killed *Enterococcus faecalis* and *Bifidobacterium* reduced anxiety-like behavior in various stress-related animal models (Kambe et al., 2020; Moya-Pérez et al., 2017). Here, noradrenaline was released via the activation of the central adrenoceptors β_3 , with the test mice expressing more adrenoceptors β_3 in the prefrontal cortex when administered *Enterococcus faecalis* than the control mice.

According to an animal study by Liang et al. (2015), achieved the administration of *Lactobacillus helveticus* had an antidepressant effect in male rats that were under chronic stress. This resulted

in an increase in norepinephrine levels in the striatum, but not in the prefrontal cortex.

Nutrition as Psychotherapy

In view of the findings presented, it is only logical that special nutritional therapies are being used more and more frequently for mental disorders (Lakhan & Vieira, 2008). If you take a look at the diet of depressed patients, you may quickly notice that depressive behaviors are usually associated with restricted food intake, which - due to a lack of essential vitamins and minerals - increases the depressive symptoms in the sense of a vicious circle. A deficiency of neurotransmitters such as serotonin, dopamine, norepinephrine and GABA is often associated with the genesis of depression (Brown et al., 1982; van Praag, 1982). Therefore, it may be advisable to include the amino acids tryptophan, tyrosine, phenylalanine and methionine in the diet as these have been shown to be effective in treating many mood disorders, including depression (Bourre, 2005; Firk & Markus, 2007). Furthermore, when taken on an empty stomach, tryptophan is quickly converted into serotonin and therefore has a sleep-promoting and mood-stabilizing effect (Salomon et al., 1994). Tyrosine and its precursor phenylalanine are converted into dopamine and norepinephrine and have a mood-enhancing and drive-increasing effect (Haenisch & Bönisch, 2011).

The intake of methionine promotes the production of the neurotransmitters serotonin, dopamine and norepinephrine in the brain (Sharma et al., 2017). The amino acids just mentioned are found in fish, meat, grains, dairy products as well as legumes and nuts. Omega-3 oil has also turned out to be a real miracle cure in the treatment of affective disorders: in the treatment of depressed patients, a reduction in symptoms was shown when given 2.5 grams of omega-3 oil daily over a period of eight weeks (Rizzo et al., 2012). In addition to omega-3 fatty acids, deficiencies in vitamin B - especially folate (B9) - and magnesium have also been linked to depression (Eby & Eby, 2006; Young, 2007).

Study results showed that patients who were treated with a daily dose of 0.8 mg folic acid or 0.4 mg vitamin B12 experienced a significant reduction in depression symptoms (Young, 2007). In addition, an antidepressant effect of magnesium has been demonstrated in several case studies: patients were given 125-300 mg of magnesium with every meal and before going to bed, which led to a reduction in depressive symptoms after just seven days (Eby & Eby, 2006).

A phenomenon that most people will probably be familiar with is mood stabilization through food intake. Consuming a meal rich in carbohydrates triggers the release of insulin in the body. On the one hand, insulin helps blood sugar reach the cells where it can be used to generate energy and, on the other hand, it promotes the entry of tryptophan through the blood-brain barrier. The mood-enhancing effect of tryptophan is based - as mentioned above in the text - on the fact that it is converted into serotonin. Increased serotonin levels contribute to improving mood (Beyer & Walter, 1991; Williamson et al., 1997).

A low-carbohydrate diet is therefore more likely to lead to the development of dysthymic or even depressive symptoms, as the synthesis of serotonin and tryptophan is catalyzed by foods rich in carbohydrates. It is considered that foods with low glycemic index, such as: B. some fruits and vegetables, whole grains, pasta, etc., have a moderate but longer-lasting effect on mood and energy levels than foods with a high glycemic index,

such as sweets, which usually have a quick, but can quickly provide temporary relief, leading to continued snacking. The glycemic index is a measure for determining the effect of a carbohydrate-containing food on blood sugar levels (Das et al., 2007). Not only carbohydrates, but also proteins have an influence on our well-being. Proteins are made up of amino acids and are important building blocks of life. Protein intake and therefore the production of individual amino acids can influence brain function and mental health. Many of the neurotransmitters in the brain are made from amino acids. As already mentioned, the neurotransmitter dopamine is made from the amino acid tyrosine and the neurotransmitter serotonin is made from tryptophan. If there is a deficiency in the corresponding amino acids, the named neurotransmitters are not synthesized to a sufficient extent, which can greatly influence the mood of those affected (Du et al., 2016; Madison & Kiecolt-Glaser, 2019).

Conclusion

In summary, it can be concluded that the popular saying quoted at the beginning, with its charming sayings, is actually correct: Science proves the close connection between the stomach and the head and you should pay close attention to what you put in your mouth.

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