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Intelligence for Food, Food for Intelligence

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Original Article

SUMMARY

Eating is a behavior addressed to get the necessary energy for the organism to survive and to contend with the demands of its environment.

Since our organism evolved within an environment lacking food, the genes that adapted us to the environment were those that promote the storage and optimization of nutrients, as well as those that evoke the skill of generating strategies of hunting and other behaviors addressed to such goal. These physiologic and biochemical mechanisms include a wide variety of genes, from genes that code for enzymes storing glycogen to enzymes that synthesize or degrade neurotransmitters. Several brain systems regulate food intake: The homeostatic system involves the lateral hypothalamus as the promoter of food intake through orexinergic and MCHergic neurons, the arcuate nucleus that synthesizes and releases neuropeptide Y and the peptide related to the agouti gene and as the promoter of satiety through the POMC and the CART. Different hypothalamic hormones and proteins take part in the performance of the hedonic system made up by the ventral tegmental area and the nucleus *accumbens*, creating a dialogue between the homeostatic and hedonic systems. Other brain systems that take part are the amygdala and the insular lobe that promotes the selection of food based on experience. The prefrontal cortex takes part in the preference for food and the decision making such as what, when and where to eat. It bears mention that neurochemical systems that regulate food intake also take part in cognitive functions and that any failure in these systems may affect the way in which the individual chooses his/her food and, in turn, the cognitive status of the subject. Therefore, psychoeducation for regulating eating habits must be a priority in the field of medicine.

Key Words: Reward system, hypothalamus, prefrontal cortex, amygdala, insula, orbitofrontal cortex.

RESUMEN

Comer es una conducta dirigida a conseguir la energía para llevar a cabo las funciones que mantienen al organismo y le permiten contender contra las demandas del medio.

Debido a que nuestro organismo evolucionó dentro de un ambiente con escasez de alimentos, los genes que nos adaptaron al medio fueron los que promueven el almacenamiento y optimización de los nutrientes, así como aquellos que promueven la habilidad de generar estrategias de cacería y otras conductas orientadas a ese objetivo. Estos mecanismos fisiológicos y bioquímicos incluyen una amplia variedad de genes, desde aquellos que codifican para enzimas que almacenan el glucógeno hasta enzimas que sintetizan o degradan a los neurotransmisores. Diversos sistemas cerebrales regulan la ingestión del alimento: El homeostásico involucra al hipotálamo lateral como promotor de la ingestión de alimento por medio de neuronas orexinérgicas y MCHérgicas, al núcleo arcuato que sintetiza y libera neuropéptido Y y al péptido relacionado al gen agouti y como promotor de la saciedad a través de la POMC y del CART. Diferentes hormonas y proteínas hipotalámicas participan en la función del sistema hedónico compuesto por el área ventral tegmental y el núcleo *accumbens*, produciéndose un diálogo entre los sistemas homeostásico y hedónico. Otros sistemas cerebrales que participan son la amígdala y el lóbulo de la ínsula que promueven la selección de los alimentos con base en la experiencia. La corteza prefrontal participa en la preferencia por los alimentos y la toma de decisiones tales como qué, cuándo y dónde comer. Es importante reconocer que los sistemas neuroquímicos que regulan la ingestión del alimento también participan en funciones cognitivas y que la falla en estos sistemas afecta la forma en que el individuo elige su alimentación y, a su vez, el estado cognitivo del sujeto. Por lo tanto, la psicoeducación para regular los hábitos alimenticios debe ser una prioridad en el campo de la medicina.

Palabras clave: Sistema de reforzamiento, hipotálamo, corteza prefrontal, amígdala, ínsula, corteza órbitofrontal.

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INTRODUCTION

The act of eating is obtaining the energy that the predator gets from its prey. Eating is a behavior addressed to get the necessary and sufficient energy that allows the organism to live, so that it may contend with the demands of its environment. Then, eating is essential to survive and, better yet, to live with advantage under the pressure of the selection.

It is estimated that the hominid that gave birth to the modern man appeared approximately 150 thousand years ago. Pressures of selection in Africa, as suggested by the discovery of Herto skull in Ethiopia, determined that the hu-

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man being was an organism with sufficient characteristics to adapt to all existing environments within our planet.[1] Therefore, our current genotypic and phenotypic mechanism is at least 150 thousand years old. Mutations and recombinations in the genome result in subjects with genetic variations that —exposed to the natural selection— take part in a gene flow and a gene drift, which finally are in charge of preserving and changing the proportions of variations.

In this range of variations, debilitating mutations or polymorphisms that strengthen the individual, there are changes that go unnoticed by cultural conceptions. One of these events is high food intake. Systematic studies have shown that, far from benefiting the individual, it eventually causes an irreversible damage that limits quality of life and longevity.[2] Thus, the perception that the overweight child who eats in abundance is healthy, in turn is an example of a health misconception caused by culture. Likewise, several families think that if the child sleeps and snores then he or she is resting. Snoring is a symptom that often comes with obesity that clearly indicates a breathing problem of the sleeping subject, with the resulting suffering of the organism at a cardiovascular, lung and brain level.[3] Its behavioral consequence is that the subject is drowsy during the day and he/she is not able to perform the tasks that society demands. Snoring not only affects obese persons, but occurs often in them. Medicine has proved that being overweight facilitates the development of several illnesses that not only reduce quality of life but become a cost burden for family and society.[4]

We know that our organism evolved in a moment in which the pressures of selection included lack of food. So it seems that the human body had a balance between those genes that regulate executive functions and generate strategies to get food and those genes that facilitate the food storage in the body. In the first group of genes we include those that participate in memory processes, in skills to create tools and in social skills, for instance, genes that code the enzymes synthesizing or degrading neurotransmitters such as glutamate, acetylcholine, GABA, with their respective receivers, to name but a few[5] (Table 1). Among the second group there are genes that have specialized in facilitating the storage of nutrients, for example, storing glycogen or lipids (Table 1). Thus, it is understandable that organisms that use a great amount of calories to get food —and what they obtain is scanty— benefit from having genes that help in the storage. But the genes that seem to be more directly involved in the generation of adaptive strategies seem to be under a constant and high demand. So, apparently, those fa-

Table 1. Example of Genes that Participate in Cognitive Processes and in Food intake and Glucose and lipids Storage

Gene	Protein	Function	Process in which it Participates
GAD1 (2q31)	Glutamic acid decarboxylase 1 (GAD67)	Synthesis of glutamate	Memory, attention, control of movement
CHAT (10q11.2)	Choline acetyltransferase (CHAT)	Synthesis of acetylcholine	Attention, memory, REM sleep, muscle tone
DBH (9q34)	Dopamine beta hydroxylase (DBH)	Synthesis of Noradrenaline	Wakefulness, alertness, attention
DDC (7p12.2)	Aromatic l-amino acid decarboxylase (AADC)	Synthesis of Dopamine	Hedonism, cognition, control of movement
CAMK2A (5q32)	Alpha-calcium-calmodulin kinase II (CaMK2A)	Facilitates the release of neurotransmitters Activates promoting factors of transcription	Promotion of long-term memory
PRKACA (19p13.1)	Protein kinase catalytic subunit alpha (PKA)	Activation of channels and promoting factors of transcription	Activation of neuronal systems and promotion of long-term memory
CREB1 (2q34)	Response element-binding to AMPc (CREB)	Promoting factor of transcription	Facilitates memory and learning processes
HCRT (17q21)	Orexins/hypocretins	Activation of several nuclei promoters of wakefulness and of the prefrontal cortex Activation of dopaminergic neurons of the VTA	Alertness Attention Promotion of the hedonic sensation caused by food
LEP (7q31.3)	Leptin	Inhibition of promoting nuclei of food intake Inhibition of dopaminergic cells of the VTA Facilitation of the hippocampus activity	Subjective sensation of satiety. Reduction of the hedonism sensation caused by food Facilitates memory processes
GYS1 (19q13.3)	Glycogen synthase	Synthesis of glycogen	Storage of glucose
GPAM (10q25.2)	Glycerol-3-phosphate O-acyltransferase	Synthesis of triglycerides	Storage of lipids
AGPAT2 (9q34.3)	1-acylglycerol-3-phosphate O-acyltransferase 2	Synthesis of triglycerides	Storage of lipids

Note. These are only examples of the existence of genes that participate in cognitive processes, in the executive functions, in decision making, in appetite and satiety control and in the storage of glucose and lipids.

cilitating the development of improved strategies have been selected, among others, the obtaining of food.

In this context, these "*farsighted*" genes caused the human being to domesticate animals and plants and to create physical spaces for storage. Thus, we evolved from comprehensive hunting and harvesting for immediate consumption to domesticating animals and plants, some bred in captivity and some in fields of crops, for scheduled consumption. Farsighted genes appeared and were quickly settled in humans; hence food has proliferated thanks to the refinement of strategies of procurement and storage in physical spaces, without the genes participating in the storage had modified their efficiency. As a result of this new balance it may be inferred that humans are vulnerable to obesity.

Within the systems involved in food selection there are senses that detect tastes, smells, textures and even sounds that —throughout experience— have been identified as associated with the energy benefit of food. Furthermore, the hedonic system provides the subject with a subjective feeling of pleasure when consuming food that is helpful for the body. The homeostatic imbalance that leads us to wish eating something and food causing us a sensual experience, is attenuated by the pleasure we receive from the strengthening system. Pleasure is not a stimulus; it is a construct that the brain establishes to guarantee the reoccurrence of behaviors. Pleasure is a consequence of sensual stimuli. It has capacity to affect taste, smell, sight or touch, or all of them simultaneously or in sequence. For example, in food intake humans enjoy something from its presentation to its smell, taste and texture. Sometimes even the sound of food can be enjoyable: bread, lettuce, apples or crispy tostadas may whet our appetite. All of these are stimuli that, at the end, will somehow stimulate the strengthening system and the brain will generate a subjective feeling of pleasure.

BRAIN SYSTEMS THAT REGULATE FOOD INTAKE

Homeostatic System. We basically refer to the hypothalamus. This brain structure that only weighs four grams in humans controls the homeostatic status of the subject. Among other physiological processes it regulates hunger and satiety. The nuclei primarily involved in promoting hunger and satiety are: a part of the arcuate nucleus, the neurons that synthesize and release the neuropeptide Y, and the peptide related to the agouti gene. Likewise, the lateral hypothalamus containing the orexinergic and MCH-ergic cells is involved. The first of these cells synthesize and release orexins A and B; the second the melanin-concentrating hormone (MCH). Both neuronal stocks evoke food intake. On the other hand is the neuronal group of the arcuate nucleus that synthesizes the cocaine- and amphetamine-regulated transcript (CART), promotes satiety

Homeostatic system

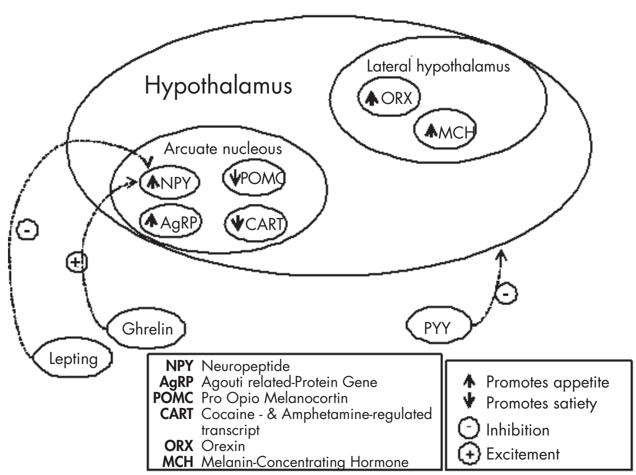

Figure 1. Schematic Illustration of the Homeostatic System. It has simplified for learning purposes. Interactions between nuclei and molecules are illustrated as well as the results from such interactions regarding appetite and satiety.

and the pro-opiomelanocortin (POMC) protein, which also decreases food intake. Ghrelin is released in the stomach, which whets appetite, affecting the cells that synthesize and release neuropeptide Y. Also, the adipose tissue releases leptin that inhibits neuropeptide Y-producing cells. Peptide YY, released by the colon, inhibits in turn food intake, affecting the hypothalamus (Figure 1).

Hedonic System. It is basically the strengthening system. It is made up by the ventral tegmental area (VTA) and the *nucleus accumbens* (NAc). VTA stimulation evokes the release of dopamine in the NAc. This causes the subject to experience pleasure.[6] Hypothalamic systems that facilitate appetite, like orexins, activate the VTA. Therefore, when we are hungry and eating, the orexinergic neurons stimulate the reward system and the hedonic component is activated. On the other hand, when leptin is secreted because it is stimulated by the lipids we consume in that moment, leptin, as mentioned above, reduces the activity of the arcuate nucleus neurons that release the neuropeptide Y and also reduces the VTA activity. As we can see, there is a very active dialogue between the homeostasis and the hedonism systems (Figure 2).

Brain Systems of Care

The Amygdala and the Insular Lobe. It is known that these two brain structures take part in several functions, among them is food intake. Such systems are in charge of food careful selection based mainly on experience.

The amygdala is a nuclei conglomerate located in the parenchyma of the temporal lobe. The insular lobe is a part of the cerebral cortex located between the frontal and temporal lobe—in schematic terms.

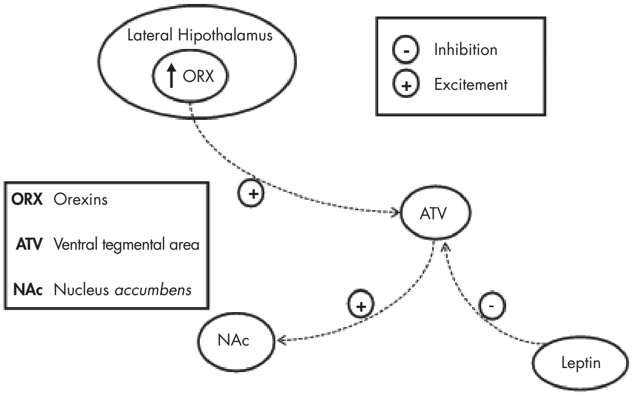

Figure 2. Diagram of the Hedonic System. Interactions of the promoter systems of appetite and satiety with the hedonic system are hereby illustrated.

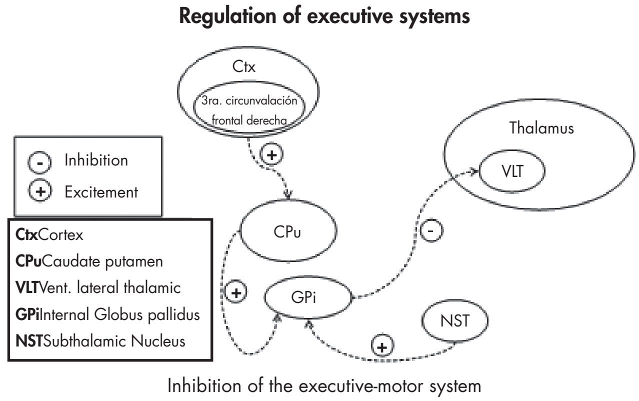

Figure 3. Schematic Illustration of the Control of the Executive Systems. The neuroanatomical components that regulate the behavior inhibitor control.

The insular lobe and the amygdala are anatomically connected with projections from the nucleus of the solitary tract or *nucleus tractus solitarii* (NTS). This is a nucleus that regulates the perception of tastes, since the cranial nerves VII, IX and X that perceive tongue tastes are projected towards such nucleus. The NTS also projects the lateral hypothalamus. Tastes, through the NTS, promote the activation of the orexinergic cells facilitating appetite, and by affecting the insular lobe and the amygdala they create the subjective feeling of food certainty. The opposite may occur if food is spoilt or contaminated, and may do more harm.[7]

The Prefrontal Cortex. It has different functions in food selection. For example, the orbitofrontal cortex participates in the selection of certain meal against another. The neurons of this region are activated proportionally, more when the subject prefers a tasty meal rather than another one.[8]

The Thalamus. In such action participate the thalamus nuclei—the intralaminar, the centromedian and the parafascicular. Such nuclei are activated to inhibit the response before the stimulus caused by the less strengthening, in other words the less appetizing, considering the expectation of a higher strengthening, the most appetizing one.[9]

The Executive Systems: *The Decision Making*. On the other hand the prefrontal cortex also fulfills the function of deciding to consume certain type of food as well as the place where it is consumed. In these mechanisms our decision making is implicit in the obtaining and consumption of food, given the threat of a predator and, also, the type of food. For example, consuming saturated *vs*. unsaturated fat. Today, we know that saturated fat gives rise to a shortage in the cognitive processes such as learning and memory;[10] while the unsaturated (omega-3 and- 6) fat not only improve the cognition but protect against the cognitive deterioration.[11] In experimental animals and humans the obesity diminishes the ability to perform learning tasks that include decision making, memory and inhibition control, among others cognitive processes.[12,13] This may be the result of changes in metabolism and glutamatergic neurotransmission that take place in the hippocampus as a result of a high fat diet.[14] In this context, it has been noted that the caloric restriction in obese rats induces an increase of the NR2A and NR2B subunits of the glutamatergic NMDA receptors, and thus an improvement in cognitive processes (Figure 3).[15]

Regulation of the Executive Systems. In these systems participate the cerebral cortex, particularly the third right frontal circumvolution (that interacts with the subthalamic nucleus) and the internal globus pallidus.[16] Both, being part of the nuclei of the base— cause the thalamus is inhibited, particularly its ventrolateral nucleus, which is part of the executive motor system, which in turn inhibits the motor behavior. Likewise, the habenula takes part in the activation of a series of GABAergic neurons located in the medial tegmental area (MTA), located caudally in respect of the VTA, which they inhibit.[17] Thus, the subject is able to inhibit his behavior and attenuate his motivation to take certain food (Figure 4).

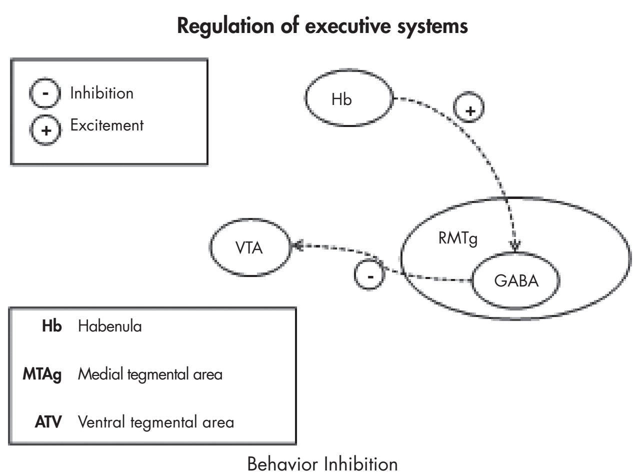

Figure 4. Diagram of the subcortical components that take place in the behavioral inhibition.

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Hormones and Neurotransmitters that Regulate Food Intake Also Regulate Cognition

The orexins increase the excitability of the prefrontal cortex, suggesting that they facilitate its function.[18] The orexins also activate the cholinergic cells of the front basal brain that activate the prefrontal cortex and the hippocampus. This leads to the activation of the attention and memory processes. As a matter of fact, in rats the antagonists of the receptor OX1R, which is the orexins-A receptor, interfere in learning spatial tasks when they are administered in the hippocampus.[19,20] Also, it has been documented that the intravenous or nasal administration of orexin A to Rhesus monkeys deprived of sleep for 36 hours, reduces the effects of such deprivation and improves the cognitive performance in a short-term memory task.[21] On the other hand, direct administration of leptin to the hippocampus facilitates the learning of spatial tasks and the development of bioelectrical signals associated with learning, such as long-term potentiation or long-term depression (LTP or LTD, respectively).[22] Furthermore, mice with deficiency of the leptin receptor (db/db) have difficulties to learn spatial tasks and poorly develop the LTP and the LTD.[23]

The Theory of Mind and the Diet Selection

The theory of mind refers to the capacity we have to represent and attribute emotional states and thoughts for ourselves and for others.[24] This skill allows social interaction and it is of crucial importance to the establishment of emotional, friendly and sexual relations.[25] Due to this skill we can have a vicar learning; that is, learn from our peers or educators and primary caregivers.[26] A great deal of progress has been made in the understanding of the brain systems that support this vicar learning with the description of mirror neurons.[27] Humans have to learn several skills in order to successfully deal with the demands of common life: walking, talking, learning, memorizing, paying attention, even fulfilling sleep schedules. All these processes have certain neurobiological determinism blended by uses and customs of our culture. As part of these skills it bears mention the establishment of the concept of food and the possibility to eat it.[28] That is, to differentiate between what is or is not eaten and whether, given the circumstances, it can be eaten or not. This decision making requires the integration of functions of all the brain structures mentioned in this text and maybe more. Therefore, the establishment of an individual's basic diet occurs in an early stage of development through learning, as happens with language. Diet, as language, has its cultural nuances and its local expression. Eating corn tortillas or wheat bread is an option that has a slant. Many Europeans in Mexico prefer accompanying their meals with bread instead of tortillas; while many Mexicans prefer tortillas. In the theory of mind we suppose that the person who eats tortillas enjoy them, feels good and considers them as an important part of his or her diet. Thus, establishing the diet that we later consider to be of our preference requires a series of cognitive processes established with learning, which mostly remain stable throughout our life. We believe that diet, as language, may be enriched. As we have a basic vocabulary distinguishing between one region of Mexico and another, diet equally distinguishes itself between Mexican regions and, obviously, distinguishes ourselves from other countries. Diet is difficult to be changed, as it is difficult change our language. We can add another language to our skills and force us to speak it if we live in the country where such language is spoken, but we always have our native language. We can adapt ourselves to the uses and customs of other countries; nevertheless, we do not forget what we learned during critical stages of development. Likewise, we will hardly substitute our diet for another. This is a Diet Theory.[28] The brain learns to be fed with a certain type of diet and if the subject becomes ill, for example, with a metabolic syndrome, then changing his or her diet would be a titanic task, like asking this person to speak English when he or she always has spoken Spanish only. Diet Theory suggests that the diet we use for feeding ourselves is the product of a series of cognitive processes that —after certain age— have helped to the establishment such diet at a certain extent that the subject may ask for the same dishes even daily (rice, beans, salsas and corn tortillas in Mexico).

The Brain Chef

"-Then, chef, what do you recommend to have an excellent brain? Chef: -Fish, fish and fish". We know that it sounds exaggerated, because it is true. However, we would like to emphasize that including fish in the diet is quite important to maintain our brain healthy. What other meals facilitate brain health and the cognitive processes? Fruits like kiwi, strawberry and cranberries; seeds like nuts and peanuts. Other products: mushrooms, asparagus, avocado, spinach, eggs, lettuce, olives. Finally, there is a wide range of food that allows us to provide our brain with the appropriate nutrients for its optimal functioning—its cognitive processes under optimum conditions (the Table 2 includes a food guide specifying what substances they provide us with).

CONCLUSION

As can be noted, there are several brain systems in charge of regulating food intake. It is important to mention that the systems that regulate more directly food intake also evoke cognitive processes. Consequently, it is reasonable to consider a Diet Theory. If this proposal is valid, it means that we should promote an advantageous diet from the earliest years of life. Otherwise, according to this theory, once the memory strokes are established and once the learning of a diet usage is consolidated, the possibilities to substitute it are reduced.

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Table 2. Examples of Food that Facilitate Cognitive Processes

Food	Nutritional Content	Benefited Function
Salmon and other fish; fruits such as kiwi; seeds such as nuts and pumpkin seeds.	Fatty acids, like omega-3	Improvement and prevention of deterioration of cognitive functions related to old age, mood disorders, Alzheimer's disease, craneoencephalic traumatisms, attention deficit-hyperactivity disorder. Their consumption during pregnancy, breast-feeding and childhood benefit brain development of the product, improving the cognitive and visual function, and it is associated to a lower prevalence with postpartum depression.
Curcuma longa or turmeric (the plant that yields the yellow ingredient to curry)	Curcuma	Reduces the cognitive deterioration of the Alzheimer's disease and of craneoencephalic traumatisms.
Onion, apple, broccoli, cherry, grape, red cabbage, beer and red wine	Flavonoids	Improvement of the cognitive processes, especially if combined with exercise. Delays deterioration induced by old age.
Pork and beef, liver, kidneys, fish, eggs, grains, whole wheat bread, milk, cheese, cauliflower, haricot beans, banana, spinach, watercress, cucumber, carrot	B complex (vitamin B1-B12)	General beneficial effects on the central nervous system. Improves the memory.
Egg yolk, chicken, turkey liver, all entrails, lettuce, cabbage, soy, chickpeas, lentils, rice, peanuts	Choline: generates acetylcholine	Beneficial effects on attention and memory, improves rapid eye movement (REM) sleep.
Meat, fish, eggs, dairy products, asparagus, chickpeas, lentils, peanuts, soy	Phenylalanine: generates dopamine (DA), noradrenaline (NE) and adrenaline (A)	As NE: facilitates wakefulness and alertness, attention and memory. Reduces pain. As DA: facilitates the sensation of pleasure and regulates motor control. AS A: improves fight-or-flight response.
Eggs, milk, whole grains, chocolate, oats, dates, peanuts, banana, squash, sunflower seeds	Tryptophan: generates serotonin (5-HT) and melatonin (Mel)	As 5-HT: Reduces the risk of depression, increases sensations of pleasure, and reduces stress and pain. As Mel: benefits the circadian cycles.
Parsley and raw spinaches; dairy products, (raw and smoked) meats, dry fruits: nuts, almonds	Glutamine (generates glutamate and GABA)	As glutamate: Improves memory, attention, and motor control, regulates fear and the sensation of pleasure. As GABA: reduces anxiety and promotes sleep.

Note. These are only some examples of food that improve cognitive processes.

On the other hand, the failure of any of these systems, for example, of the hedonic system or the regulation of the executive systems may cause a subject to eat food compulsively29 hence be conducive to have overweight and obesity.

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