NEURONAL AND SYNAPTIC ORGANIZATION OF ENTERIC NERVOUS SYSTEM- THE PREMISES OF THE MULTIDISCIPLINARY THERAPEUTIC APPROACH

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Abstract

The aim of present work is a double one. On the first hand we tried to collect together the newest data concerning the enteroneurons' morphology, their association in the parietal plexuses and their synaptic interconnections. All classes of enteroneurons were discussed in detail, but, despite their diversity, we have concluded that, essentially, they can be classified as motor, sensitive and interneurons, are disposed in layers and have the same functionality as the cerebral cortex neurons. According to their neurochemistry, we have imagined reflex circuits subserving motor and secretory functions, illustrated with original diagrams. Enteroglia and interstitial cells of Cajal are also assessed in interrelation with neurilema and myolema of gut muscles fibers. The second goal of our study was focussed on serotoninergic enteroneurons, their contribution to both motor and secretory gut functions and also on synuclein production in the enteroneurons, named by us extraparietointestinal. Their contribution to trigger the initial stages of Parkinson disease is proposed.

Key words: enteric nervous system, enteroneuron, enteroglia, interstitial cells Cajal, digestive reflexes, enteric secretion, serotonin, synuclein, Parkinson disease.

The importance of knowing the enteric nervous system constitutes a relevant starting point for the therapeutic approach aimed at the cephalic territory in the context of interdisciplinarity[1-15].

The functional organization of ENS is similar to that of the CNS and consists of **ganglia**, that correspond to central nuclear structures and **interganglionic fibers** corresponding to the white substance tracts. Like intranevraxial nuclei, ganglia consist of afferent and efferent **enteroneurons**, associated through **interneurons** in local microcircuits and of **enteroglia**. Overall, ENS has reticular organization, its microganglia being connected by interganglionar axons bundles in plexuses with variable morphology and topography, distributed in all layers of the gut walls. Each microganglion is composed of heterogeneous neuronal population and of nerve fibers compacted by enteroglial cells. [16,17]

The interganglionic nervous cords are bundles of nervous fibers composed from the **intrinsic axons** of Dogiel I enteric neurons and of **extrinsic axons** represented by vagal afferent and efferent axons, sympathetic postganglionic cholinergic axons and by visceral afferent axons with origin in the thoracolumbar spinal ganglia. Depending on their dimensions, the cords are classified as type I (thick, interganglionic), type II (medium size, intercordal) and type III (thin), forming the fine, terminal reticulum.

Myenteric plexus is located between the external longitudinal and internal circular layers of the *tunica muscularis* of the digestive wall and is continuous, both circumferentially and longitudinally, along the entire gastrointestinal tract. Its morphology and topography varies considerably by species and depends on the digestive region considered, but the general pattern of organization is always recognizable [18,19,20]. Classically, the myenteric plexus is composed of three subdivisions, primary, secondary and tertiary plexuses (Fig.1).

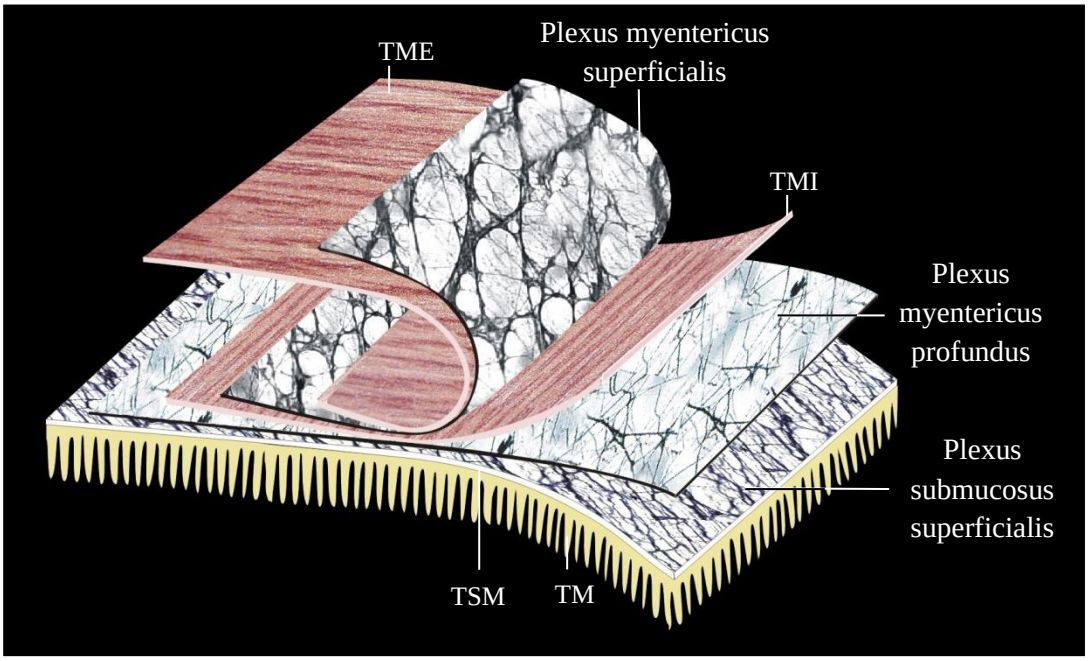


Fig 1. General organization of gut´s wall plexuses. TME – tunica muscularis externa (longitudinalis); TMI – tunica muscularis interna (circularis); TSM – tunica submucosa; TM – tunica mucosa.

Primary plexus consists of enteric microganglia and type I interganglionic cords.

Microganglia contain 5-200 neuronal bodies but, within interganglionic cords, there are also described solitary, erratic enteroneurons. The interganglionic cords uniting microganglia, are disposed parallel with the fibers of longitudinal muscle layer and richly anastomoses, forming the actual network of the primary myenteric plexus, whose geometry has species character. It is worthy to note that the shapes of microganglia and of primary network, as they appear on histological preparates, are relative because myenteric plexus structures are distorted continuously during gut motility [21-25].

Secondary plexus consists of thinner bundles of nerve fibers which arise from microganglia or from interganglionic cords of the primary plexus and is situated on the deep aspect of primary plexus and the outer surface of circular fibers layer, being parallel with last ones. The nerve fibers of the myenteric secondary plexus distribute to the circular intestinal muscle. **Tertiary plexus** is a dense anastomosed reticulum of fine, sinuous fibers, located in

the depth of the circular muscle layer[26-32].

Submucous plexus is continuous, both circumferentially and axially, along the entire thoracoabdominal digestive tract, but has significant regional and species variations. In humans, submucuous plexus consists of a deep component corresponding to the initial description of Meissner and another superficial component (Shabadash or Henle plexus), in relation to the inner surface of circular muscle layer. Some of its neurons contribute to the innervations of the most deep, circular fibers [33-36]

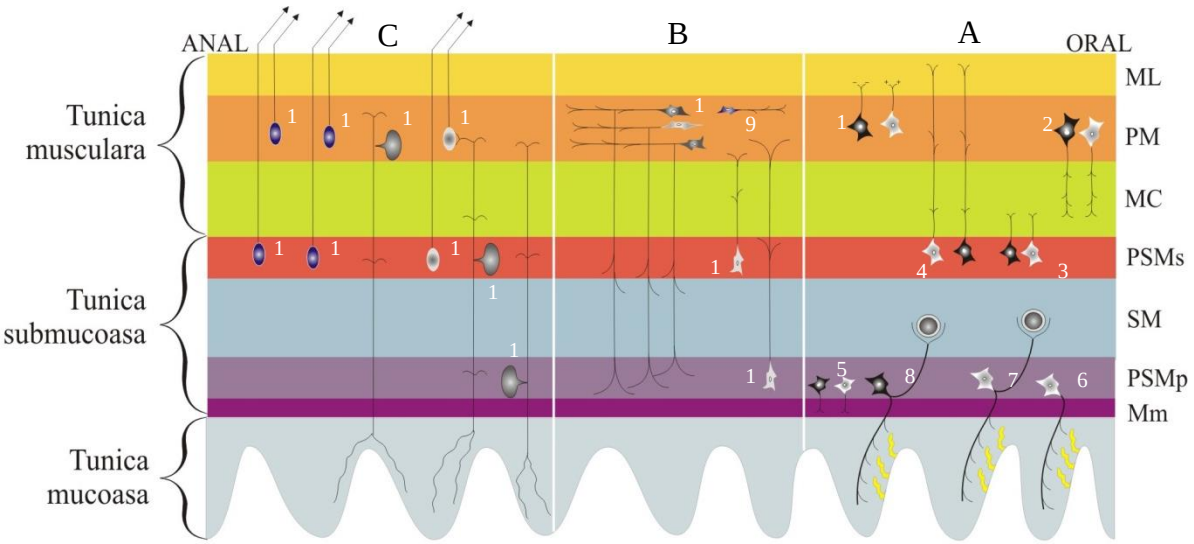


Fig. 2. Neuronal types of enteric nervous system.

A – **Motor neurons** (excitator – light grey; inhibitor – dark grey;). **PM** 1 motor enteroneuron of longitudinal muscle; 2 motor enteroneuron of circular muscle; **PSMs** 3 motor enteroneuron of circular muscle; 4 motor enteroneuron of longitudinal muscle; **PSMp** 5 motor enteroneuron of longitudinal muscle; 6 Secretory nonvasomotor enteroneuron ;7 Secretory, vasomotor,Ach-ergic enteroneuron; 8 Secretory, vasomotor nonAch-ergic enteroneuron; **B** – **Interneurons**: **PM** 9 Ascendent interoneurons; 10 Descendent interneurons; **PSM** 11 Interplexual interneurons. **C** – **Efferent neurons** (sensitive) 12 Enteroneurons IPAN chemically stimulated; 13 Enteroneurons IPAN mechanically stimulated; 14 Enteroneurons IFAN with peripheral connections; 15 Enteroneurons IFAN with central spinal connections;16 Enteroneurons IFAN with central medullary connections:

Mucous plexus is composed of oligoneuronal microganglia disseminated through *lamina propria* of intestinal mucosa, on the deep aspect of *muscularis mucosae* that separate it from the deep submucos plexus. The plexus network is organized in relation with characteristical structures of digestive mucous membrane and can be subdivided into **subglandulary**, **periglandulary**, **villous subepithelial** and **villous axial** components. The thin terminal fibers of the mucous plexus are intimately related with the intestinal epithelium cells, enteroendocrine cells and with that of the immune system but neuroreceptor or neuroeffector junctions are not yet [37,38,39]

Subserosal plexus, located in the *lamina propria serosae*, is composed of a network of thin nerve strands containing both own fibers and extrinsic fibers consisting of afferent and efferent axons traveling via vagus nerve and of sympathetic postganglionic axons carried by the splanchnic nerves. Rare microganglia with few neuronal bodies are especially found in the esophagus, stomach, along the mesenteries insertion on the intestine and on the front side of rectum [40,41,42].

Cranial extension of intramural plexuses. Remak, 1840 described the existence of intramural microganglia in the pharynx and tongue's root. The observation is reinforced by numerous recent studies supporting the existence of pharyngolingual ganglionated plexuses (Sbarbati, 2007; Furness, 2006). Their omologation with the incipient segment of ENS is justified ontogenetically and by numerous immunohistochemical and experimental studies that seem to confirm that these structures, placed strategically at the cranial end of the body's import system[1], *id est* digestive system, could be considered as a "chemical eye" of the "second brain". These criteria allow to consider as components of ENS, the biliary and pancreatic microganglia plexuses and also tracheal and bronchial plexuses, which are also derived from the anterior intestine.

Functional structure of enteric microganglia. The enteric microganglia consist of the **somata** of **enteroneurons,** of **enteric neuropil**, which contains the neurites, synaptic complexes and **enteroglia** that solidarizes them in compact structures without a collagen capsule. **Enteroneurons** are classified acording to their histological shape, immunohistochemical affinity, physiological properties, synaptic connexions, neurotransmitters and by type of innervated structures [43,44,45]

The shape of enteric neurons on histological sections refers to the geometry of somata, to the morphology of dendritic tree and of axonal emergences. Most studies perfomed over the past 20 years, especially on guinea pigs, confirmed the existence of three types (I, II, III) of neurons described by Dogiel (Dogiel, 1899) and allowed the identification of six new morphological types of which the first four, noted IV-VII in order of discovery, are considered an extension of the Dogiel classification, and the last two, are the **mini enteroneurons** (VIII) and the **giant enteroneurons** (IX) that are found only in some mammal species. It should be noted that this classification has purely morphological significance because the dimensions of enteric neurons are directly proportional with the size of considered specia, neuronal bodies being smaller and the geometry of neurites simpler, in smaller mammals. The neurons of the same morphological type (e.g. Dogiel I) could be either **excitatory motor enteroneurons**, either **inhibitory** and also **interneurons** of local enteric circuits (Dogiel, 1899). Therefore, the classical principle that neurons with the same shape have the same function, perfectly applicable to cortical pyramidal neurons, Purkinje neurons of the cerebellum cortex, retinal ganglionic neurons and the pseudounipolar neurons in spinal ganglia appears to be not valid in ENS [46,47].

Electrophysiologically, there are described two classes, **S** and **AH**, of enteroneurons. The action potential of **S**

enteroneurons is followed by fast hyperpolarization, whilst at the **AH** ones, the hyperpolarization is biphasic, with an initial **fast phase** untill to partial restoration of membrane potential and a terminal **slow phase** untill complete restoration of membrane potential. The progress of intracellular recording technics, allowed the detailed comparative study of action potential particularities of S and AH enteroneurons and also of biology of enteroneuronal membrane's ion channels [48,49]. Recent enteroneurobiological studies, correlating morphological and physiological criteria, have estabilished functional profiles which allowed classification of enteric neurons as **motor**, **intrinsic primary afferent** (IPAN) and **interneurons** (Fig.2).

Motor neurons are located mainly in the myenteric plexus but also in the superficial submucous plexuses of esophagus, stomach, gallbladder, small intestine and colon. Each muscular structure of the gut wall, i.e. the longitudinal muscle, circular and muscularis mucosae, is innerved by couples of activator and inhibitor motor enteroneurons. Morphologically, they are Dogiel I type and electrophysiologically, "S" type, but neurochemically, they are different. The motor activator neurons are preominantly cholinnergic and the inhibitor neurons are NO, VIP or purine-ergic and differ by region and through the variety of co-transmitters.

The motor neurons of circular muscle layer, located only myenteric in guinea pig, have myenteric or submucous location in humans and large mammals. They could be excitatory, immunoreactive to acetylcholine-transferase, and inhibitory, VIP immunoreactive. Related to the neuronal body, the axon directs either cranially, in oral direction, either caudally, in anal direction, and its terminal branches are distributed to a circular muscular band about 2-8 mm wide. The terminal ramifications of excitatory neuron axon distributes circumferentially, the to a 7 mm band of the circular muscle, approaching it at the union of 5mm oral with and 2mm anal, with respect of the cellular body, while the terminations of inhibitory neuron axon distributes to 1-6 mm wide band, approaching it orally only. Due to the substantial thickness of the circular muscle layer, the innervations of a muscular ring involves several hundred neurons and the motor units are disposed concentrically [50].

The motor neurons of longitudinal muscle are located in the depth of muscular layer on small mammals, their axonal termination forming the superficial myenteric plexus. In humans and big mammals, the axons terminals branch in the longitudinal muscle parallel with the muscular fibers. The territory of a single axon is shaped as a small rectangular island, 2mm long and 1mm wide, whose small size explains the great number of these neurons, counting almost 25% of the myenteric plexus .

Motor neurons of muscularis mucosae, located in deep submucous plexus, are also excitatory and inhibitory, fact demonstrated experimentally and immunohistochemically, but their neurobiology remains still unclear .

Vasomotor and secretor enteroneurons. The gut exocrine secretion, that involves the transfer of water and electrolytes from the blood to the intestinal lumen, is functionally coupled with vasodilatation and the submucous plexus

contains motor enteroneurons which supply both functions and enteroneurons that are only vasodilators. In terms of neuromediation, the secretor and/or the vasodilator neurons, may be noncholinergic or cholinergic. The noncholinergic neurons are VIP-ergic and stimulate the intestinal secretion. They are not influenced by the extrinsic denervation or by the destruction of myenteric plexus, suggesting the muco-submucous independence inside ENS (Gwynne R.M., Bornstein J.C., 2007). The cholinergic neurons can be only secretors and have neuropeptide Y (NPY) as cotransmitter, or both, secretor and vasodilator, having calretinine as cotransmitter. These neurons are activated by the enteric intrinsic afferents and are inhibited presynaptically by the extrinsic sympathetic postganglionic afferents with origin in the prevertebral ganglia.

Enteric interneurons are present everywhere, along ENS regions but unlike the sensory or motor enteroneurons that are isoforms, the shape of enteric interneurons considerably varies. The interneurons of myenteric plexus are assembled into axially stretched chains, one consisting of orally ascending interneurons, and three anally descending interneuronal chains. Neurochemically, the enteric interneurons are acetylcholine-ergic (ACh-ergic) and acording to their co-transmiters, they are distinguished as calretinin-ergic (ascending neurons), NO-ergic, serotoninergic and somatostatinergic (descending neurons). The first three types are involved in reflex parietal motility, the cholinergic and somatostatinergic interneurons are also involved in migratory myoelectric complexes. All descending interneurons send collaterals to submucous plexus that cholinergic and serotoninergic being involved in secretory and motor reflexes. The interneurons of submucous plexus, less numerous, are VlP-ergic or NO-ergic and their oligobranched axons tree ramify in the myenteric plexus.

Sensory afferents enteroneurons

The afferent innervation of thoracoabdominal digestive tract is double, extrinsec and intrinsec and is assured by afferent extrinsec and afferent intrinsec enteroneurons.

Afferent extrinsec enteroneurons

The axons of **afferent extrinsec enteroneurons** connect the receptors of the gut walls with the rest of the autonomic nervous system. They may be classified as extraparietointestinal and intra-parietointestinal.

The **extraparietointestinal** neurons are either **parasympathetic**, located in the vagal petrous and jugular ganglia or **sympathetic**, located in thoracolombosacral spinal ganglia. The **intraparietointestinal neurons**, also called **intestinofugal afferent neurons** (IFAN), have the somata located in both myenteric and submucous plexuses and represent the only neuroenteric afferent structure which interconect directly the enteric nervous system with the rest of nervous system, peripheral and central. According to their peripheral or central conection, there are described two classes of intestinofugal neurons.

The **IFAN with peripheral connections** whose central axons travel through periarterial sympathetic plexus and synapse with the postganglionic neurons of the sympathetic paravertebral ganglia. The peripheral axons of primary afferent neurons from myenteric plexus are stimulated by the parietal distention and that of the submucous plexus by the

intestinal chemistry. Both types form the afferent arm of enteroenteric, vasoconstrictory and hyposecretory reflexes. Recent studies have shown that some IFAN neurons receive afferents from the sensory intrinsic enteroneurons and thus become secondary afferent neurons in polineuronal enteric reflexes. In this situation the afferent branch of the enteroenteric reflexes becomes polysynaptic, illustrating once more the complexity of ENS.

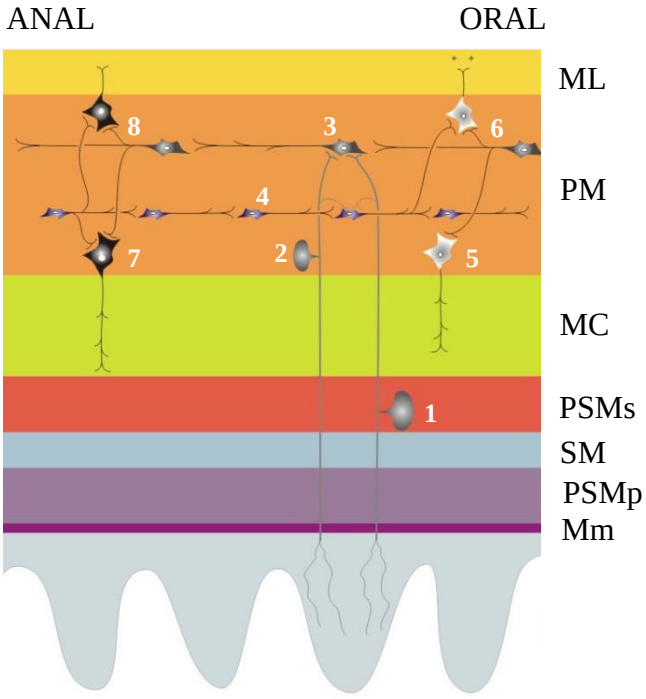


Fig. 3. Synaptic organization of peristaltic movement microcircuit 1. IPAN in submucous plexus. 2. IPAN in myenteric plexus. 3.Descendent interneurons. 4. Ascendent interneurons. 5. Motor neuron excitator of circular muscle. 6. Motor neuron excitator of longitudinal muscle. 7. Motor inhibitor neuron of circular muscle. 8. Motor inhibitor neuron of longitudinal muscle.

The **IFAN with central connections**, located at the oral and anal extremities of the digestive tube, have the neuronal bodies situated in the myenteric and submucous plexuses. IFAN's afferent axons from the stomach travel via gastric branches of the vagus nerve towards the nodose ganglion where synapse with postganglionic neuron whose axons project in the dorsal nuclear medulary complex. Similarly, the ones from the rectum take the way of inferior hypogastric nerves and synapse with secondary neuron of hypogastric ganglion. The axons of secondary neurons project in the S_2-S_4 intermediolateral zone of the sacral spinal cord (Fig. 3).

Afferent intrinsec enteroneurons

Intrinsic primary afferent neurons, are after-hyperpolarising (AH) sensory neurons (IPAN) with Dogiel II morphology, located in both, myenteric and submucous plexuses. They are more numerous in the most active motor and secretory areas of the digestive tube. Quantitative studies on guinea pig jejunum demonstrated that $1mm^2$ of intestine

surface contains, in the myenteric plexus, approximately 2500 enteroneurons, 650 being IPAN, and in the submoucous plexus around 1100 enteroneurons, from which 100 being IPAN (Fig. 4).

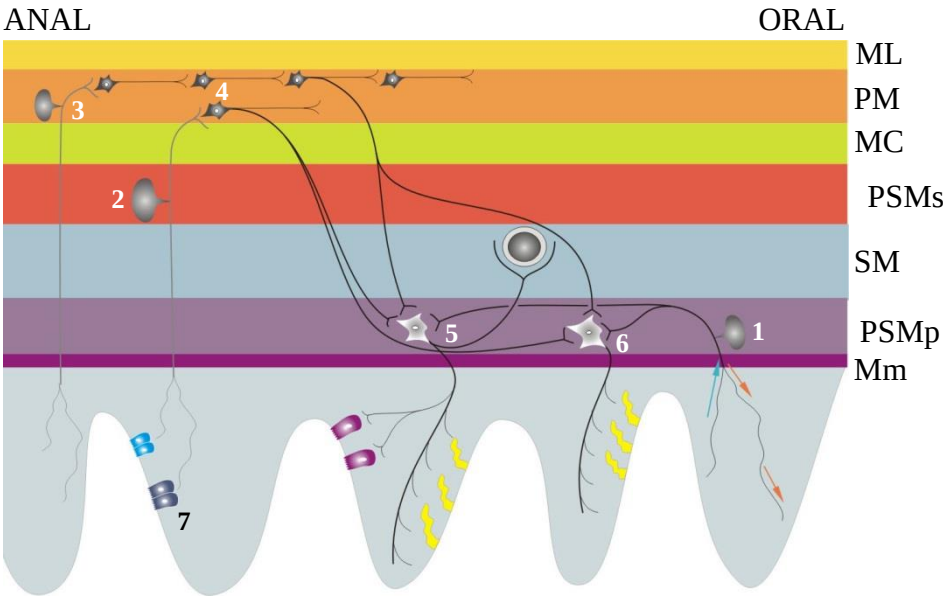


Fig. 4. Synaptic organization of enteric secretor and vasodilator microcircuits. 1. IPAN of mononeuronal reflex in plexus submucosus profundus; 2. IPAN in plexus submucosus superficialis; 3. IPAN in plexus myentericus; 4. Ascendent interneurons; 5. Secretomotor and vasodilatator neuron; 6. Secretomotor neuron. 7. Entero-endocrine cells. Red and blue arrows indicate the efferennt respectively afferent arms of the transsomatic secretory reflex.

Functionally, they classify in IPAN stimulated by the intestinal lumen chemistry, located only in the submucous plexus, and IPAN that react to the intestinal deformation and distention, located in both plexuses. There are also described **polymodal IPAN neurons** with **nociceptive role** that respond to both chemical and mechanical stimuli and are involved in triggering strong enteroenteric reflexes (diarrhea) in the presence of pathogens agents or of their toxins [51].

Interstitial cells of Cajal (ICC)

The interstitial cells of Cajal were discovered by Cajal in 1892 using Golgi argentic impregnation and methylene blue staining. The eponymous denomination "of Cajal" seems to belong to Dogiel. Although ICC they resembling the neurons, they are non neuronal cells because of somatic prolongation organization, lack of of axons and of neurotransmitter vesicles. Their small body has numerous elongated processes interposed between the terminal branches of motor enteroneurons and smooth muscle fibers. Depending on the intraparietal location, the interstitial cells of Cajal are classified as ***myenteric***, located in the longitudinal muscle layer, ***intramuscular***, located in the thickness of the circular layer and ***deep intramuscular*** located in the deep circular muscle layer. Since the ICC is the final target for motor excitatory or inhibitory enteroneurons, their membrane consists **neural** and **jonctional** functional areas (Struijs et all 2008). **Neural zones** are contacted directly with the axonal endings' varicosities of the

motor enteroneurons and present specific receptors for their neurotransmitters. The ***junction zones*** estabilish gap junctions, functioning as electrical coupling between the neighbors interstitial cells and and between them and smooth muscle cells. Simultaneous intracellular recording of electrical phenomena in interstitial Cajal cells and smooth muscle cells demonstrated the pacemaker potential of the interstitial cell. Each intestinal fragment generates slow waves of own frequency but, due to the electrical coupling among ICC, duodenum zones that have a higher frequency become dominant and generate a gradient of frequency in oroanal sense. The low waves generated by gastric ICC have a very low frequency which allows the reservoir function of the stomach [52].

Enteroglia.

The enteroglial cells (EGC), first described by Dogiel in 1899 constitute the largest component of ENS. The estimated number of enteroglial cells is four times higher than that of neurons (Rühl A, 2005). They are located perisomatic, around neuronal bodies in the ganglia and periaxonally, in the interganglionic nerve bundles of all parietal digestive plexuses, contributing to compaction of both ganglionic and nerve fibers structures. The glia-neuron relationship in the enteric nervous system is surprisingly unconventional because the EGC does not completely isolate neuronal bodies leaving, especially at the periphery of ganglia, extended nude membrane areas directly related to the extracellular liquid [53].

The same phenomenon is found in the interganglionic neuropil where the glial cells processes isolate axonal bundles but not each axon separately, allowing interaxolemic direct contacts. Moreover, this structural disposition has specia variation, in humans each axon having its own glial sheath. The quantitative proportion enteroglia-enteroneuron increases with species size (1:1 in mice; 5:1 in sheep) and, within the same species, is higher in myenteric plexus. The same phenomenon occurs at the level of interganlionic strands where the lamellar extensions of EGC associates bundles of about 600 axons, but the axons number significantly reduces in larger species. Structurally, EGC are similar with astrocytes in CNS, expressing the glial fibrillar acide protein (GFAP), but differs by neuroreguline dependence .

Enteroglia functions.

Mechanical support function, anticipated by the authors of early nineteenth century, by analogy with the central nevroglia is now elucidated by electron microscopy (Bassotti et all., 2007). EGC are anchored to the microganglia surface by GFAP beams and respond to mechanical stimulation by increasing c-fos gene expression which results in increased intracellular Ca2 +. Thus, EGC supports, stabilizes and permanently adapts ENS to metabolic changes of the intestinal wall. Even more, EGC controls K + channel activity by preventing the accumulation of extracellular K + which disrupts synaptic transmission and dynamics of enteroneurons ion channels [54].

Homeostatic function

Enteroglia is essential for ENS homeostasis. It is shown experimentally that enteroglia cell destruction results first by chemical alteration and finally degeneration of enteric neurons bodies. Dipeptide transport contribute to the

neuropeptide clearance in the ENS and synthesis of glial neurotrophic factor and of neurotrophin-3, are arguments in favor of trophic role of the EGC, but the dependence of enteric nervous system structure and function integrity on the enteroglial trophic factors synthesis which is still not demonstrated .

Role in neurotransmission

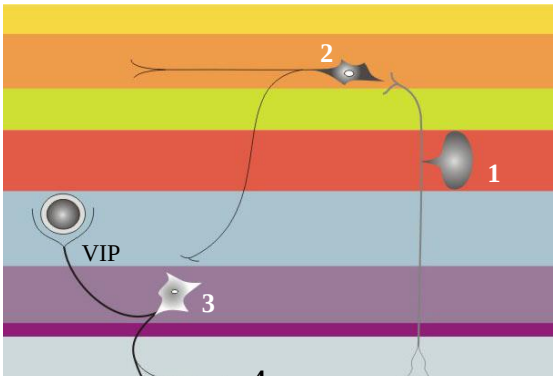
The role of enteroglia in neurotransmission is illustrated by the glutamate-immunoreactive of the human EGC that suggests the role played in glutamatergic neuro-transmission. Enteroglia is a source of glutamine for neuronal glutamate resynthesis and particularly for gamma-aminobutyric acid (GABA) which also contain the GAT2 transporter which rapidly removes GABA from extracellular environment. An argument for the nitrergic neurotransmission is the immunoreactivity for L-arginine, which is a precursor of nitric oxide .

Synaptic organization of ENS.

The enteroneurons are organized in local microcircuits that assure the independence of parietal motility, secretion and vasomotricity of thoracoabdominal digestive tube. Gastrointestinal motility includes complex propulsion, mixing and migration movements and essentially consists of successive contractions and relaxations, in oroanal sense, of the parietal digestive muscles.

Apparently simple, this activity involves a complex neuromotor apparatus, able to react promptly and adequately to a multitude of the, constantly changing, local functional needs. (Furness et all, 1994, Furness, 2006, Costa and Brookes, 2008). It consists of afferent and motor enteroneurons, interneurons and ICC organized in parietal microcircuits with complex synapses, for which we propose the following model (Fig. 5).

Peristaltic movement microcircuit, belonging predominantly to myenteric plexus and to its afferents, is organized like an classical reflex arch type. The peripheral axon of the afferent enteroneurons of submucous plexus branches profusely in the submucosa basal membrane of intestinal epithelium (which appears as a component of mucos plexus) and are stimulated by distention (Grundy D. 2008). The central axons of IPAN myenteric neurons enter the myenteric plexus and recruit circumferential an important number of interneurons, both ascendant and descendent. In turn, the ascendant interneurons activate the motor excitatory neurons located orally and determine a circular contraction area. The descendent interneurons activate the motor inhibitory neurons causing anally a distal relaxation zone. This way the excitation is moving along the intestinal wall in the food mass proximity.



Secretomotor and vasomotor microcircuits are activated equally by the mechanic excitation of the mucosa and by the intestinal chemistry in presence of endoluminal glucose as one of the most important factors for physiological stimulation (Fig. 7). The afferent path of these circuits is represented by IPAN neurons, mostly from the submucous plexus, but also from myenteric plexus which have smaller receptor fields (Xue J., Askwith C., Javed N.H., Cooke H.J. 2007). Peripheral axons of these neurons cross submucosa and richly branches in close relationship with the basal membrane of glandular epithelium and basal pole of enteroendocrine cells, forming the **mucous plexus**. They constitute the anatomical pathway for the mononeuronal transsomatic reflex which closes the circuit in the IPAN neuron body of the submucous plexus, and stimulates the secretion in the excited area .

The central axon branches in numerous collaterals and form two synaptic variants (Xue et all, 2007). The shortest of submucous plexus collaterals bypass the myenteric plexus closing a monosynaptic reflex arc with secreto-motor/vasodilator neurons. IPAN neurons' long collaterals from both submucous and myenteric plexuses synapse with interneurons of descendent chains and stimulates secretion distally from the excited area (anally). Excitation of intestinal mucosa by pathogens or their toxins lead to depolarisation of enteroendocrine cells and release of 5-hydroxytryptamine (5-HT) .

The 5-HT stimulates the submucous IPAN neurons and their central axons synapse with interplexus interneurons which activate the VlP-ergic neurons facilitating the preinflammatory vasodilatation. In the gut, the same type of stimuli triggers both motor and secretor events and the functional synchronism between these two activities is ensured by the enteric nervous system.

Polymeropoulous et all. (1997) have been demonstrated that enteroglial cells, stimulated by various digestive pathological events, especially by chronic constipation or diarheea, induce in the endoplasmic reticulum of submucous enteroneurons the production of alpha-synuclein, a 140-amino acid protein, identical with that contained in Lewy corpuscles. Further studies restricted the

synuclein secreting enteric neurons to the group of **afferent extraparietointestinal enteroneurons** with vagal connections. So appeared the ideea, soon demonstrated (Aldecoa et all. 2015) of retrograd transport of alphasynuclein via vagus axons, towards the mesencephalic dopaminergic nuclei, substantia nigra and ventral tegmental area. Based on this findings, Phillips R. J., et all., (2008) emited the hypothesis that the *primum movens* of the Parkinson disease pathophysiology is the production of alphasynuclein in the enteric system

As we have showed above, the enteric neurons through their neurilemal *nude areas*. are directly in contact with the environment, that confirms the Braak's postulate that "*they could represent a route of entry for an hitherto unknown environmental factor to initiate the pathological process*".

Conclusions

Our study allowed us to point out that enteric nervous system is a functional organization similar to that of cerebral cortex in terms of layer organization and motor sensitive and associative specialization of enteroneurons. The patterns of motor and secretory digestive reflexes imagined were illustrated with original diagrams. The mechanical, trophic, neurosecretory roles of enteroglia are described, insisting on functional regionalization of enteric neurilema into synaptic glial and *nude area.* The importance of the last one consist of its direct contact between extracellular liquid that allows the contact between luminal pathogens and enteroneurons. By this way, the special category of extraparietointestinal afferent enteroneurons could be stimulated in order to produce alphasynuclein, the protein of Lewy bodies, that transported via vagus nerve towards dopaminergic brainstem nuclei, substantia nigra and ventral tegmental area may be the earliest pathogenical event in Parkinson disease.

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