REVIEW ARTICLES/PRACE POGLĄDOWE

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SMALL INTESTINE MOTILITY DEVELOPMENT IN NEWBORN MAMMALS*

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Abstract

Since the beginning of the 20th century, researchers have been working to improve the understanding of gastrointestinal motility. The first major discovery was the observation of a migrating myoelectric complex that turned out to be a universal occurrence among vertebrates. Further inquires resulted in a detailed description of its development during different stages of ontogeny. Some time before that, a cornerstone had been laid for a breakthrough that would come years later. That cornerstone came in the form of interstitial cells of Cajal whose true role could not be discerned until the discovery of a CD117 receptor – their main marker. With the ability to precisely mark interstitial cells of Cajal, a wave of subsequent new experiments and observations connected them to the occurrence of slow waves and allowed an understanding of the mechanism responsible for their generation. Some of these findings suggested that Cajal cells might have a role in the development of several motility disorders thus opening an avenue of research that requires the usage of both traditional and advanced diagnostic methods.

Key words: ICC, mammals, MMC, motility, slow waves, telemetry

Streszczenie

Od początku 20 wieku naukowcy pracują nad poznaniem motoryki przewodu pokarmowego. Kluczowym momentem było odkrycie wędrującego kompleksu mioelektrycznego (MMC), który okazał się zjawiskiem powszechnie występującym u kręgowców. Wyniki późniejszych badań stworzyły szczegółowy opis rozwoju tego kompleksu na różnych etapach ontogenezy. Kolejnym przełomem było odkrycie śródmiąższowych komórek Cajala oraz ich receptorów. Możliwość precyzyjnego oznaczania komórek Cajala zachęciła do kolejnych doświadczeń, które wykazały zależność istnienia komórek Cajala i występowania fal wolnych. Pozwoliło to zrozumieć mechanizm odpowiedzialny za ich powstawanie. Wyniki niektórych badań wskazują na ważną rolę komórek Cajala w rozwoju zaburzeń motoryki przewodu pokarmowego. Fakt ten skłania do kolejnych eksperymentów, w których niezbędne jest wykorzystanie tradycyjnych oraz nowoczesnych metod diagnostycznych.

Słowa kluczowe: ICC, ssaki, MMC, motoryka, fale wolne, telemetria

*This work was supported by Polish National Science Centre 2012/05/B/NZ9/00901.

INTRODUCTION

Motor activity of mammalian small intestine

In addition to the structural properties of its wall, the level of motility development is a key feature for assessing the maturity of the gastrointestinal tract. This is a direct expression of its capability to coordinate the myoelectrical functions of smooth muscles. In fact, both vomiting and diarrhea, two of the most common life threatening occurrences for infants, are accompanied by slow wave frequency distortions in the stomach and intestines. Human infants born at 32nd week of gestation have shown to be the most susceptible to such abnormal slow wave events and thus become one of the reasons for the need of a highly accurate prognostic model of gastrointestinal tract maturity that would incorporate structural, chemical and myoelectrical aspects of its workings.

History of gastrointestinal motility research

Documented experiments on the subject reach back to the end of 19th century when Bayliss and Starling formulated the so called "law of the gut" stating that the application of stimuli to a certain site of the intestinal wall invokes a response on behalf of smooth muscles incorporated into its structure. This response is composed of relaxation and contraction respectfully below and above the portion of the wall affected by the stimulating factor. In 1899, the same scientists provided additional data that suggested the existence of a neuronal compound in the regulation of smooth muscle activity in the small intestine wall. They did so by partially restoring its motility, lost as an aftermath of a laparoscopic procedure, through the means of vagotomy [1].

There was an underappreciated breakthrough in the early 1930s when Douglas and Mann observed a caudally-propagating organized sequence of intestinal smooth muscle contractions [2]. In 1969 Joseph Szurszewski dubbed this phenomenon "Migrating Myoelectric Complex" (MMC) and described it as an event of caudally moving high amplitude impulses [3]. This prompted the launch of further investigations, which revealed that MMC is common among adult vertebrates [4, 5, 6]. Interest shifted towards newborns and infants in the 1980s with data regarding motor function of the small intestine in piglets and both term and pre term human infants [7, 8, 9].

Small intestine motor functions during different stages of ontogeny

Proper description of small intestine motility development requires a time frame in which certain fixed occurrences take place. Then sub–chapters describe the sequence of events in the chain that leads to the emergence of fully-fledged intestinal motility.

Pre- and postnatal period

Most of the data concerning the prenatal period comes from observations performed on human preterm newborns born as early as 28th week of gestation. At this earliest point, myoelectrical activity of small intestine is expressed as solitary and random events of action potentials, which proceed to congregate into 1-2 minute, long fetal sequences observable in 32nd week of gestation. Further maturation includes an increase in both frequency of action potentials and time length of sequences in which they occur and result in the emergence of a true but not mature MMC as early as 37th week of gestation [8, 9].

Supplementary data comes from electrogastrographic (EGG) recordings of slow waves in stomach smooth muscles performed on a pre term newborn born at 26th week of gestation. EGGs were evaluated periodically over the time of six months and revealed a progressive increase in both amplitude and percentage of waves with a frequency between two and four cycles per minute (cpm). One aspect of slow wave frequency maturation is that it is not a linear process and possesses certain dynamics characterized by a drop in increase rate of waves fitting into 2-4 cpm range from 9% during the first two months of observation to 3% in the next four months [10].

Other experiments were performed on term-born piglets and dog and sheep fetuses. They provided results similar to human subjects in regard to the sequence of events, but with a different time frame of occurrence. In every case, solitary action potentials, that in time organize themselves into short bursts of activity, proceed the emergence of MMC. Progressively complicated sequences of the previously mentioned action potentials are present in the duodenum of piglets up to 8th day after birth at which point an MMC pattern emerges [11]. Dog intestines are relatively less developed at birth as their MMC pattern does not emerge until 15th day of postnatal life and reaches maturity within the next 25 days. On the other hand, sheep develop a MMC pattern as early as ten days prior to birth, which is completely mature between 10th and 15th days after birth [12].

Weaning

Weaning is a dietary transition from liquid to solid meals and occurs at a species specific moment of ontogeny [13]. Occurring between 16th and 26th days of postnatal life in piglets, it invokes considerable alterations in the MMC pattern which includes changes in the time ratio between I and II phases in favor of the latter as well as an increase in potentials' frequencies [14, 15, 16].

The observable changes in MMC during weaning are speculated to be additive in nature and to result from interactions between a normal development curve and environmental factors such as quality and quantity of ingested food. A positive correlation between age and time length of MMC supports this claim [17]. Similarly, the data acquired from piglets suggests that the observed increase in the time length of II MMC phase is a result of a progressively greater intake of milk volume [18]. It cannot be excluded that this food-dependent effect remains true for solid meals as they interrupt regular MMC and increase the duration of the post-prandial motor pattern [19, 20, 21].

Maturity

At this stage the specimen's gastrointestinal tract demonstrates the full range of its myoelectrical activity and, by extension, motor functions. Fasting activity

is represented by the presence of fully formed MMC with both segment- and specie-specific duration. In regard to humans, the time length of the duodenal MMC pattern is estimated to be around 120 minutes while in the jejunum between 100 and 110 minutes. The shortest MMC patterns are present in the ileum and last only about 94 minutes [22].

From the moment of its emergence, MMC pattern consists of three phases, but the proper time ratio between them forms the hallmark of its maturity. Phase I represents between 10% and 20% of MMC time duration and is referred to as the no spike activity phase (NSA) because of nonexistent smooth muscle contractions resulting in a lack of motility. Phase II represents between 70% and 85% of MMC time duration and is referred to as the irregular spike activity phase for self-explanatory reasons. During this period, the intestinal smooth muscle performs segmentation contractions responsible for mixing chyme with digestive juices and distal propulsion of the resulting mass [22]. This phase progresses somewhat organically into phase III, known as the regular spike activity phase (RSA). The frequency of action potentials steadily increases up to the point when it reaches the nominal value specific for phase III in the respective segment of the gastrointestinal tract. In regard to the small intestine, the frequency value is generally the highest in the proximal part of the jejunum (11-12 per minute) and declines distally toward the ileum (8-9 per minute). This phase represents only between 5% and 10% of MMC time duration and is expressed as strong, phasic contractions responsible for crushing and distal propulsion of chime (3, 23).

Food ingestion interrupts MMC and invokes a postprandial myoelectrical pattern similar to that observable during the IRS phase. For the postprandial pattern to emerge, time intervals are required between meals as data from research on pigs suggest that constant *ad libitum* ingestion does not interrupt MMC [6].

Interstitial Cells of Cajal

In accordance with current knowledge, Interstitial Cells of Cajal (ICC) form a major component of mechanism controlling gastrointestinal tract motility and smooth muscle activity in any organ that depends on the presence of cyclic self-propagating oscillations of membrane potential (heart being the most exceptional of them). They were discovered in 1911 by Ramon y Cajal, who described them as neuron-like cells present at the terminus of efferent neurons in peripherally innervated organs. ICC has long eluded attempts of classification, mostly due to their plasticity and presence of different morphological forms from one tissue to another. This ceased to be a problem with the discovery that ICC in the gastrointestinal tract extensively expresses the CD117 receptor, which is more commonly known as c-Kit kinase. CD117 is a proto-oncogene, a site of Stem Cell Growth Factor binding and as such has a key role in the survival, proliferation and differentiation of cells. Its role can be clearly seen in the case of mutant W/W^v mice, which possess only one active KIT allele and as a result suffer a drastic decrease in ICC near the myentric plexus. This is accompanied by uncoordinated motility, which results from a lack of slow waves generated by ICC [24].

ICC perform multiple supportive services for surrounding tissues which are most notably related to the modulation of smooth muscle contractibility. Some of their roles include stretch-sensing, CO production and interaction mediation between the enteric neuronal system and smooth muscles. Stretch–sensing is mediated by the presence of Na^+ membrane channels that respond to mechanical stimuli and result in alterations of base membrane potential, which may be connected to changes in slow wave frequencies [25]. ICC are local sources of CO thanks to the constitutive expression of hemoxygenase-2 which allow for heme breakdown. CO is known to be a potent hyperpolarizing agent and so provides ICC with the means to influence the membrane polarization level of surrounding tissues [26]. The muscle–neuronal coupling function is achieved through the presence of receptors in the ICC membrane for various neurotransmitters such as acetylcholine, neurokinins, VIP, somatostatin and serotonin [27]. Slow wave frequencies can then modify in response to neuronal stimuli.

Different layers of the gastrointestinal tract wall sport different and morphologically distinct networks of ICC. Some of these networks also seem to be segment specific, as they do not maintain a continuous presence through the entire length of the gastrointestinal tract. Networks seem to slightly differ in function, and some level of knowledge about their disposition is required to better understand their role in the holistic concept of gastrointestinal motility.

Disposition of ICC network

Three networks composed of distinctive ICC subpopulations are present throughout the gastrointestinal tract. Two of them, longitudal muscle ICC and circular muscle ICC (ICC LM and ICC CM respectively), are often combined into another group – intra muscular ICC – as they both are formed by morphologically similar ICC with one long axis. ICC CM differ from ICC LM because they have a greater number of processes, which, combined with smaller numbers of ICC LM, makes their network relatively denser especially in the small intestine.

The third network present throughout the gastrointestinal tract is formed by ICC accompanying the myentric plexus (ICC MY). Their morphological features are mostly dependent on structure of the particular plexus, though all of them seem to have many long processes orientating along different axes. This subpopulation seems to be a major provider of the peacemaker function as a decline in their numbers abolishes the slow waves [26].

Three other ICC subpopulations form networks present only in the selected segments of the gastrointestinal tract: submucosal ICC (ICC SM), ICC accompanying the sub mucosal plexus (ICC SMP) and ICC accompanying the deep muscular plexus (ICC DMP). Both ICC SM and ICC SMP have many axes and are located in the border space between the submucosa and circular muscle layer in the stomach and colon respectively. ICC DMP presence corresponds to the location of nerves associated with ganglions between longitudal and circular muscle layers [28].

Creation of slow waves

Slow waves are periodical oscillations of membrane potential in smooth muscle - a resultant event of ICC basic electrical rhythm (BER) propagation. Both amplitude and frequency of slow waves are values specific to specie of the specimen and segment of gastrointestinal tract. The general rule in the frequency of slow waves is that its value declines caudally [27]. The mechanism of their generation remains to be discovered, though cytosole Ca^{2+} oscillations are suspected to play a crucial role in it. These oscillations are believed to result from mitochondrial uptake followed up by Ca^{2+} release from ER. Mitochondrial Ca^{2+} uptake depends on a trans membrane electrochemical gradient, which oscillations in an unknown way correspond to the frequency of slow waves. Moreover, such a scenario anticipates a potential depletion of Ca^{2+} in ER and a need for its replenishment – an event mediated by a TRP4 nonselective store-operated ion channel present in ICC membrane. An uptake of Ca^{2} by TRP4 fits elegantly into the proposed mechanism and provides a tangible explanation for the periodical Ca^{2+} drop in intercellular space observed in the vicinity of ICC [29].

In the opinion of authors, a wealth of information can be derived from a study on subjects afflicted by diseases connected to this very topic. In this case, gastrointestinal motility disorders may provide further insight as most of them have a confirmed ICC note to them.

ICC and gastrointestinal motility disorders

The disruption of ICC network in the gastrointestinal tract during afflictions associated with motility disorders has been established to cause, at least partially, symptoms such as diarrhea, vomiting, gastro-oesphageal reflux and many more. The cause–event relation between the disease and anomalies observed in ICC networks is rarely clear, as it is impossible to tell whether the disruption is the primary source of the problems or is it just the adaptation to pathological conditions.

Chronic intestinal pseudo obstruction

Chronic intestinal pseudo obstruction (CIPO) is a condition accompanied by such symptoms as distention of a segment of the intestine, motility inhibition or bacterial overgrowth, similar to those of regular obstruction but without any presence of mechanical blockage. CIPO can develop as a result of mesenchymopathy in which case, the observed decline in numbers of ICC MY and ICC SMP contribute to a loss in density of their entire network in the affected area. This is best seen in the duodenum where these ICC subpopulations are nonexistent or in the colon where they are substituted by elements of ICC CM [24].

CIPO can also develop as a result of ENS neuropathy. An interesting case is when neuropathy is induced by an active John Cunnigham Virus (JCV) infection – a virus present in up to 80% of the CIPO-affected human population. JCV is a neurotropic representative of *polyomaviridae* which, in its active state, is capable of inducing progressive multifocal leukoencephalography (PML) – a rapidly advancing demyelinating disease similar to multiple sclerosis. A less known fact is the ability of JCV to infect neuroglia associated with ENS neurons of myentric plexus which result in its degeneration. An active lytic infection near the myentric plexus may trigger a drop in ICC numbers and thus disrupt the ICC network – an event occurring in up to 80% of JCV positive CIPO subjects [30].

There are three scenarios by which this event occurs. The first one assumes that the degeneration of the myentric plexus leaves the adjacent ICC deprived of neurotrophic stimuli and thus results in loss of their phenotype. This is supported by the fact that the nNOS concentration in the affected region is reduced, which in turn leads to a drop in NO concentration. A positive correlation has been established between ICC numbers and the presence of nitroergic enteric neurons, which suggests the trophic role of NO [31]. A similar situation can be noticed in regard to several other neurotransmitters and neuropeptides such as CGRP, NPY or VIP but their influence on ICC survivability remain unclear [27]. Another possibility is that JCV actively infects ICC and thus assumes direct responsibility for the observed decline in their numbers – a scenario that can not be acknowledged nor discarded on the basis of current knowledge. The third scenario suggests the indirect influence of the inflammation process on ICC by means of myriad interleukins involved in the process. Most data regarding this subject comes from research on Crohn's disease and will be discussed in the following sub chapter. It is worth noting that the complete description of the situation may in fact incorporate several elements from the presented explanations.

Crohn's disease

Disruption of smooth muscle contractibility is a known side effect of the inflammation process. In case of Crohn's disease, Th-1 phenotype lymphocytes are believed to be the main suspects, as their interleukins influence the activity of Ca^{2+} membrane channels. This may disrupt the Ca^{2+} - dependent mechanism responsible for the generation of slow waves in ICC (32). Th-2 and Th-17 phenotype lymphocytes involved in Crohn's disease are the source of IL-4 and IL-17 interleukins present at the inflammation sites. They are believed to be factors responsible for smooth muscle hyperconractibility events that can be observed in the course of illness [33].

None of this data directly indicates the involvement of ICC networks in abnormal motility as most of the symptoms can be explained by inflammation-altered actions of smooth muscle alone. What does point at the ICC abnormalities is the prevalence of motility disorders during regression of the disease, most notably the decreased amount of action potentials in the second phase of MMC.

Oesophageal achalasia

Oesophageal achalasia is a progressive disease accompanied by the inability to relax the smooth muscle of the lower eosophageal sphincter and subsequent blockage of the eosophagus emptying into the stomach. Loss of ICC network density in the later stage of the

illness is an established fact that seems to be a secondary development to the decrease in the number of nitroergic neurons – a well documented occurrence that results in the abolishment of the NO–mediated inhibitory effect [31]. In the early stages of the disease, the lack of NO-mediated inhibition and altered functions of ICC network are two factors linked to non-peristaltic phasic contractions that occur in neighboring segments of the eosophagus nearly simultaneously. The theoretical connection of ICC to that early symptom is based upon observations that papaverine analogs, which are known phosphodiesterase inhibitors, seem to diminish the frequency of contractions without influencing their amplitude [25]. Several isoforms of phosphodiesterases utilize cAMP as a secondary messenger. This known agent is able to enhance Ca^{2+} uptake from intercellular space thus increasing its concentration in cytosol, which in turn directly influences the frequency of slow waves [34]. This is a sound theory but requires further validation as it does not take into account several specific features of the ICC network present in the eosophagus – most notablely the anatomically lower density of ICC MY network and heavy presence of fibroblast–like cells positive for the pellet-derived growth factor receptor (PDGFr). These PDGFr positive cells form an elaborated network that remains in direct contact with ICC and seem to support the propagation of slow waves although the exact mechanism of this remains unclear [25].

Pyloric stenosis

A prominent feature of this disease is the hypertrophy of smooth muscle in the pylorus that hinders the ability of the stomach to propel its content into the duodenum. The obstruction is both mechanical and functional as the affected region displays an inability to relax. This is similar event as seen in the eosophageal achalasia where the inability to push food through the lower eosophageal sphincter was caused by high tonus of its smooth muscle. More similarities can be seen in the pathogenesis of both diseases, the most obvious is the gradual loss of the NO-mediated inhibitory effect caused by decreased numbers of nitroergic neurons accompanied by ICC network degeneration up to its complete disappearance in the affected region [35, 36]. As in achalasia, vomiting is present but the mechanism of its induction is somewhat unclear. It can be speculated that the discontinuity of the ICC network hinders the propagation of slow waves in the pylorus and interferes with BER frequency of the peacemaker region in a manner similar to that observed in the heart during atrial fibrillation where the action of sinoatrial node is disrupted by the presence of chaotic myoelectrical activity.

Research and diagnostic techniques in motility study

Several techniques designed to acquire and process data into values describing different aspects of gastrointestinal motor functions are in use today. These methods can be roughly divided in two artificial groups. The first group contains techniques that depend on the acquisition of myoelectrical signals with the use of electrodes. The second group relies on mechanical measurements of actual physical parameters such as pressure or the time it takes for the food content to be cleared out of the segment of the gastrointestinal tract. The following sub-chapters will focus on some of those methods that authors believe to be the most interesting in regard to actual research as well as most widely used in diagnostics.

Cutaneous Electrogastrography

Cutaneous electrogastrography (EGG) is a non invasive and a relatively simple method based on a signal acquisition by a series of electrodes placed on the skin. The subsequent analysis provides values regarding gastric motility-namely the main frequency together with its variation and amplitude. Frequency is described by the mean dominant frequency parameter calculated as the mean value of frequencies recorded on all channels. This is further supplemented by the instability coefficient parameter describing the variation of mean dominant frequency. Another possibility for acquiring the frequency value along with its variation is the application of Fast Fourier Transformation and Running Spectral Analysis (respectively) to the raw data. Acquisition of the amplitude value is less precise and allows only for the monitoring of its relative changes between pre- and postprandial periods through the evaluation of the EGG power ratio. Limited data suggest the possibility to monitor the propagation of slow waves with the use of multichannel recording [37].

Several factors provide a challenge in regard to the precision of the method. Most notable are the artifacts originating from electrical activity of other organs such as skeleton muscle, heart or other parts of the gastrointestinal tract. Skeleton muscles are responsible for the movement artifacts, which form a significant problem when the evaluated subject is unwilling to remain still. This brings up the matter of the considerable length of time required for the EGG evaluation, which is usually divided between pre- and postprandial recordings lasting 30 and 60 minutes respectively. Longer recordings are also known to be conducted but suffer from the increased risk of interference. This is one of the factors that hinder the reproducibility of results, which diminish along with the rise of recording time. Some pathological events, such as dyspepsia, are also known to produce highly varied readings between examinations and thus provide an additional challenge to the staff.

High – resolution manometry

High-resolution manometry (HRM) is an advanced technique based on real–time pressure measurements performed in the entire length of the eosophagus during a swallow-induced peristaltic event. The raw data, consisting of pressure values, time and relative distances from landmarks such as UES or LES, is organized into user friendly esophageal pressure topography (EPT) that allows for easy acquisition of the information regarding pressure at a specific point of time and place within the eosophagus [38].

Most importantly, the EPT forms data in a manner accessible for algorithms that provide several parameters which describe an esophageal motor performance such

as contraction front velocity (CFV), distal latency (DL), integrated relaxation pressure (IRP) or distal contractile integral (DCI). The CFV value is the quotient of division where the dividend represents the length of the segment displaying 30 mmHg pressure and the divisor represents the time needed for a pressure wave to terminate at the contractile deceleration point (CDP). It describes the propagation of pressure wave and is complimented by DL, which represents the time from the opening of UES to the termination of peristalsis at CDP. IRP describes the ability of the eosophagogastric junction (EGJ) to convey food into the stomach by assessing its highest tonus during the 10 s relaxation window following the UES opening. This is achieved by averaging the lowest values of the highest pressures detected in the 6 cm segment of EGJ. Measurements for the calculations are taken continuously or discontinuously from 4 s segments of EPT; the discontinuous option is designed to alleviate the anomalies originating from extra-eosophageal sources. DCI describes the eosophagus's ability to maintain optimal pressure during peristalsis. It is calculated as mean value of pressure higher than 20 mmHg measured in the whole length and time of the peristaltic event [39].

Many of the motor dysfunctions affect one or more aspects of motility described with the EPT-recording derived parameters and so they can be recognized by a cross-reference based key. This idea forms the groundwork for the current efforts to streamline the HRM–based diagnostic process known as Chicago classification criteria. Unfortunately, despite the presence of distinctive traces in EPT, up to 30% of motor dysfunctions lack diagnosis guidelines somewhat hampering the usefulness of HRM [40]. More importantly, parameter values described in the classification are acquired during single 5 ml wet swallows, which render it inappropriate for provocative testing with data acquisition based on viscous, solid or multiple swallows [39]. While easier than standard manometry, the procedure is somewhat invasive as the catheter forming the chassis for pressure detectors often irritates the eosophagus which not only results in temporary discomfort but also in temporary anomalies in measured values that pose a risk of decreased accuracy.

Ultrasonography

Cutaneous ultrasonography (USG) is a relatively simple and non-invasive imaging technique that may be used to acquire rudimentary information about motility of the gastrointestinal tract. USG evaluations were carried out to provide data on the volume of antro-pyloric section, diameter and area of antrum of the stomach, as well as monitoring pylorus emptying both in fed and fasted state. It is also possible to acquire the value of main gastric frequency by applying a FFT algorithm to a series of length values measured over time between two points located respectively on the superior and inferior walls of the stomach [41].

This method is seriously limited however as it not always possible to acquire a clear image of an entire section of the gastrointestinal tract. One reason behind this is the presence of gas pockets that dissent the surrounding structures pushing them out of the range of ultrasound penetration. This is connected to the issue of frequency used during the examination, which is positively correlated with the resolution of the acquired image and negatively correlated with the depth of ultrasound penetration. This is a special concern with cutaneous USG in the case of motility study, as it means that image acquisition of deeper structures is possible only by scarifying its quality and may render certain wall components indistinguishable from one another (longitudal and circular muscle layers for instance) [42].

A way to diminish these challenges is the use of endoluminal USG, which utilizes high frequency transducers located on the catheter. This technique is often simultaneously employed during HRM examinations of the esophagus to provide additional data in form of real–time three-dimensional HD view of smooth muscle mechanical activity during peristaltic events. The drawback of such a scenario is that the presence of two catheters may provide a challenge in case of uncooperative subjects as well as increase the number of anomalous readings resulting from irritation of the wall.

Telemetry recordings of gastrointestinal myolectrical activity

This technique is similar to EGG as it also utilizes electrodes for capturing the electrical signal from the gut. In this case, electrodes located within pockets between the abdominal muscles are connected with the telemetry implant placed outside the peritoneum. The insertion of both electrodes and telemetry implants is surgical in nature and as such prompts the need to provide a week long recovery period for the animal. Implants are coupled with an external receiving device by means of radio waves thus eliminating the problem of wires protruding from the body of the subject, which could potentially hinder its freedom of movement. This in turn makes recording over long periods of time feasible, limited only by data storage space and the battery charge of the implant.

This technique allows for the acquisition of the same data as cutaneous EGG but with greater accuracy of the values as the vicinity of the electrical signal source (smooth muscles of gastrointestinal tract) alleviates the problem of tissue impendence. This also partially negates the problem of anomalous readings originating from non-gastro intestinal centers of electrical activity. A relative lack of outside interference marks this method as especially useful for the registration of frequency, amplitude and propagation of slow waves, which usually are too faint to observe with other techniques. The monitoring of the circadian pattern changes in MCC by the registration of amplitudes, frequencies and propagation velocities of its spike potentials is a viable option that provides a major advantage over other techniques [21, 43].

There are relatively few downsides of this method. One problem is the presence of injury potentials observable up to one week after surgical implantation. However, it is easily alleviated by the introduction of the recovery period that allows the animal to return to its optimal condition. Another is the susceptibility to outside radio interference, which requires the use of Faraday Cage to

negate any changes in the electro magnetic field induced by outside sources. One practical limitation is that this method requires a staff, which is properly skilled and authorized to perform both anesthesia and the proper surgical procedure.

The high accuracy of readings that can be performed over long time periods combined with the lack of serious downsides should make telemetry recordings of gastrointestinal myoelectrical activity a method of choice for scientists engaged in motility studies.

SUMMARY

Many parts of the mechanism that function result in gastrointestinal motility remain not fully explained. It is unclear how exactly ICC generates the slow waves, as the non–selective ion channels that are supposed to operate in response to Ca^{2+} oscillations had not been identified. Limited data exist on the matter of interaction between networks of ICC and PDGFr positive fibroblast-like cells beyond the established fact of their physical connection. The exact way in which NO interacts with ICC also remains a mystery. Another interesting and possibly beneficial matter is the way in which ICC numbers diminish, whether it happens due to increased apoptosis or because ICC lose their phenotype and revert to a less developed state and if so how it exactly happens.

In addition to these problems, there are basic level matters that, despite a century of scientific effort, remain unresolved. The biggest of them is the lack of a complete and unified model of gastrointestinal development that could provide data about parameters, such as optimal enzyme activity, estimated histometrical parameters, nominal pressure values specific to the segment of the gastrointestinal tract, nominal frequency and amplitude of both slow waves and action potentials, in regard to the age and mass of the specimen. The creation of such a system would be highly beneficial both for medicine and research but requires the acquisition of further data. This is especially true for the period of time between birth and weaning, and the performance of experiments on model species (such as pig) of appropriate age should be considered the highest priority.

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Author's contributions/Wkład Autorów
According to the order of the Authorship/Według kolejności

Conflicts of interest/Konflikt interesu
The Authors declare no conflict of interest.
Autorzy pracy nie zgłaszają konfliktu interesów.

Nadesłano/Received: 03.11.2015 r.
Zaakceptowano/Accepted: 08.12.2015 r.

Published online/Dostępne online

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