Medical Hypotheses 130 (2019) 109282

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

The iso-osmo-resistivity theory of digestion

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A B S T R A C T

This novel, iso-osmo-resistive theory offers electro-resistivity of food components as a new dimension for digestion. Firstly, fats, carbohydrates and proteins differ markedly in their resistivity, which offers a way to monitor them, especially when digestive enzymes cause consistent and distinctive changes. Secondly the state of iso-resistivity is in theory most likely to pass through the membranes of absorbing cells and be compatible with plasma in portal blood vessels. Hence, the theory proposes that the aim of the digestive process in the upper gut is to present digesta to absorption sites in a state at, or close to, iso-osmo-resistivity.

It requires a method of monitoring resistivity which could be achieved by neuronal endings based in the upper gut mucosa. They could be simple nerve endings or, probably less likely, part of the structure of duodenal Brunner's Glands. They would monitor the overall effect of the various digestive processes initiated by the G-protein-coupled receptors (GPCRs). The combination of sensitive electroreceptor and osmoreceptor output would provide a system that would accurately monitor the overall progress of digestion to conserve enzyme production.

Background

The mechanisms of control of gastric emptying and digestion are poorly understood. Grossly hypertonic solutions of "fake food" such as saline provoke vomiting yet we do not reject normal hypertonic food such as cheese or glucose solutions. The stomach is more than a simple hopper since there is a physiological brake, known as the duodenal brake, on gastric emptying when normal liquid foods are drunk, and there is clear evidence that lipids and high osmolarity increase the effect, but the detailed mechanism is not known. There is also evidence that fluids in the gastric antrum constantly pass through the pylorus into the duodenum and back again, meaning that sensors in the duodenum sample the contents of the stomach, presumably as part of a control of the rate at which the stomach empties. This means the system is sensitive to the physical presence of food and this theory makes the case for that to be based partly on the differences in electro-resistivity of its contents, fat, carbohydrate and protein (FCP).

One reason is the simplicity of resistivity monitoring since it could be done by relatively unsophisticated nerve endings. Another reason is the large differences between FCP, which would facilitate detecting individual molecules. Thus lipo-proteins would have both conductive and resistive portions on the molecule, possibly in distinctive patterns for nerve endings or GPCRs to identify. Then, resistivity (or its reciprocal conductivity) could explain the hypertonic saline, "fake food" effect mentioned above which cannot be due to irritant effects on the stomach as in the case of other emetics such as ipecac. Hypertonic saline would have a combination of exceptionally high osmolarity and conductivity far outside the normal ranges, so it would instantly be identified as un-physiological. It would contrast with chyme consisting of half-digested cheese where there would also be large, lipid-containing molecules of lower conductivity, bringing the average into a more physiological range. Concentrated glucose solutions are well absorbed. They could have high osmolarity but near normal resistivity, which would distinguish them from hypertonic saline.

The idea that resistivity could be a dimension of food used by the digestive system was triggered by research into developing a non-invasive method of monitoring gastric filling and emptying plus a remarkable report over 20 years ago that Brunner's glands in the human duodenum closely resemble electroreceptors in the duck-billed platypus [1]. It raised the possibility that Brunner's glands have a role in monitoring electro-resistivity or that there might be other nerve endings serving that function. Clearly it would have to run in parallel with the GCPR system that has more recently been identified as capable of identifying various substrates and causing the release of the targeted hormones and enzymes necessary for digestion [2]. However, a range of specific GPCR effects does not necessarily amount to overall control of digestion, which is needed to hold digesta within range of the enzymes being released from the pancreatic duct and to give sufficient time for the enzyme processes to complete within the jejunum. It seems possible that such a mechanism could be an extension of the duodenal brake distally. It implies that the aim of digestion is to render digesta suitable to be passed further on down the small intestine to the ileum, an aim that is not yet defined in molecular terms. The IOR theory suggests that it could be iso-osmo-resistivity because that would be compatible with passing through the cell membranes of the intestinal villi and consistent with tissues and plasma in portal blood vessels.

Aims

The three main aims of this article are:

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https://doi.org/10.1016/j.mehy.2019.109282
Received 8 February 2019; Received in revised form 20 May 2019; Accepted 13 June 2019
0306-9877/

Table 1
Specific electrical resistivities and conductivities of reference fluids and meals used in epigastric impedance research.

Fluid	Resistivity Ohm.cm^{-1}	Conductivity mSiemen.cm^{-1}
A*. Chicken soup neutral conductive meal in epigastric impedance	± 200*	± 5.5
B. Non-conductive meal in epigastric impedance	> ± 500	< ± 2.0
C. Conductive meal in epigastric impedance	± 117.6	± 8.5
Normal Saline (0.9% w/v, pH 6.11, osmolarity 296 mOsmol/L)	75.7	13.22
Saline with 10% Glycerin [7]	80–110	12.5–9.1
Physiological Fibrinogen [7]	309	3.2
Tapwater [8]	1–5 × 10^3	1–0.2
10% Glucose solution in tapwater [8]	2.9 × 10^3	0.34 ± 0.02
De-ionised water [8]	18.3 × 10^6	0.054 × 10–9

The meals ABC were explored during development of Epigastric Impedance [5,6].
*Meal A resistivity matches the iso-resistive point and it was found by varying the salt content of chicken soup until it produced no deflection as a test meal. It has a higher resistivity than normal saline/glycerin solution because it includes all the tissues between electrodes on the anterior and posterior surfaces, notably relatively resistant skin.
The non-conductive meal B contained the simple polysaccharide maltodextrin, double cream and Nesquick flavouring. Resistivity was adjusted upward by adding double cream.
Conductive meals C were the same as B but laced with saline.
The 6 other fluids are included in ascending order of resistivity to show the wide range. Note that de-ionised water resistivity is 242,000 times greater that normal saline.

1. To show whether the differences in electro-resistivity of food contents are large enough to act as a basis for their differentiation by the digestive system.
2. To show whether similarities in the structures of known mammalian electroreceptors and human Brunner's glands are close enough to infer that the latter could act as electroreceptors.
3. To suggest practical ways of testing the theory.

Methods

Aim 1. Data on the resistivity of food components is scarce, presumably due to low interest, but large differences became evident during the development of the non-invasive, epigastric impedance (EI) method of measuring gastric emptying [3–6]. They are shown as meals A, B and C in Table 1 where A is broadly iso-conductive, B is hyper-conductive and C is hypo-conductive. Meal B hyper-conductivity was achieved by adding fat in the form of double cream. The opposite was achieved for meal C by adding sodium chloride [5,6].

The EI method passes a small electric current through the epigastric region to monitor its resistivity when the subject drinks a fluid "meal". EI has been used clinically to measure gastric emptying and gastric muscular activity in pathological conditions such as diabetes [9,10] and to monitor pharmacological effects [3,11–13]. An example of an EI trace is shown in Fig. 1. It shows a stable baseline period, a steep increase when the subject drank a resistive drink and a decline that mirrors gastric emptying. Typically the increases are in the region of 1–3 ohms when 500 ml of resistive fluids are drunk, so they generate a relatively large signal in biological terms. Similar negative decreases occurred after conductive fluids. Note that there is a brief plateau in the descending curve in Fig. 1.

Aim 2. Monitoring resistivity requires electroreceptors. Applied to the overall resistivity of the duodenal and upper jejunal contents, it seems possible that it could be achieved by morphological structures ranging from simple nerve endings to evolved structures. Assessments of the resistivity of individual molecules could also be a function of the GPCRs and even a way of identifying them since individual lipoproteins

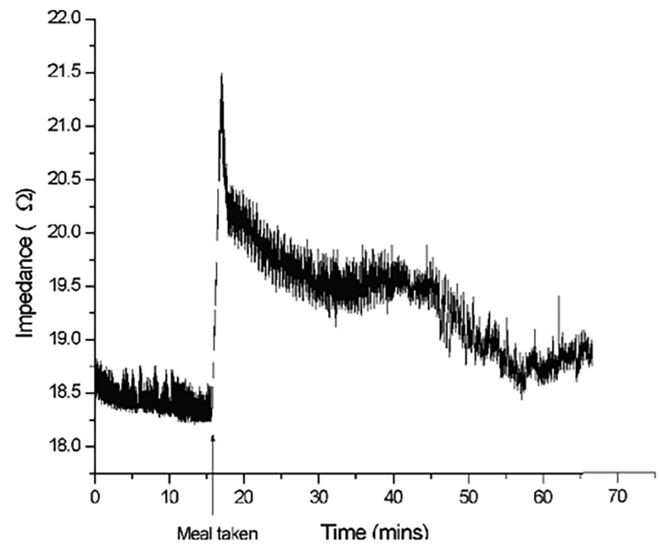

Fig. 1. A trace from an epigastric impedance monitor when a 3mAmp alternating current was passed through the epigastrium of a volunteer who drank 500 ml of 10% glucose solution after a 15 minute baseline period. During and just after drinking the solution there was an increase in overall resistivity of almost 4 ohms which showed gastric filling. The subsequent decline recorded gastric emptying. Note the plateau during which emptying was suspended. The trace is wide because respirations cause the descending diaphragm to distort the stomach which the device detects as a waveform with a frequency of approximately 15 cycles per minute. The trace also includes a slower frequency of approximately 3 cpm that is due to gastric contractions. They are more visible in the decline that follows the plateau suggesting that it was a period of more active gastric motility.

would be expected to exhibit unique patterns of resistivity and conductivity. Suitable structures have never been identified in man, although they do not seem to have been specifically excluded. The evolved structure possibility arises because Andres et al. [1] have reported the marked similarity between known electro-receptors in monotreme species and mucus glands in the human duodenal mucosa known as Brunner's glands. They wrote: "Monotreme electroreceptors have similar structures to classic, human duodenal mucus glands and were even designated "sensory mucous glands." They also suggested that the existence of electroreceptors in one mammalian species means that they are not an evolutionary impossibility in other mammals. Gregory et al. [14] gave a detailed exposé of the structure of the platypus electroreceptor. At the end of a densely myelinated axon they describe " *… a small gap in the myelin through which penetrates a slender filament of the axon that is free of any investing Schwann cell. The axonal protrusion is in contact with cells of the wall of the mucus sensory gland's duct. This tongue of axon represents the terminal of the sensory nerve fibre and is likely to be involved in the transduction process.*"

Andres et al provided the diagrammatic structure of platypus glands reproduced in Fig. 2. The left hand panel shows a main mucus channel leads to the exterior in a similar fashion to the channel within the histological slide of a Brunner's Gland in Fig. 3 which extends through the basal layer of epithelium into the gut lumen.

Discussion

Gaps in our knowledge of the digestive system

We have a detailed knowledge of many individual mechanisms of our digestive system, from non-specific responses to the presence of food in the upper gut to specific hormonal and enzyme releases from G-protein receptors. Clearly, uncontrolled non-specificity would be wasteful by causing more enzyme release than necessary, while a system

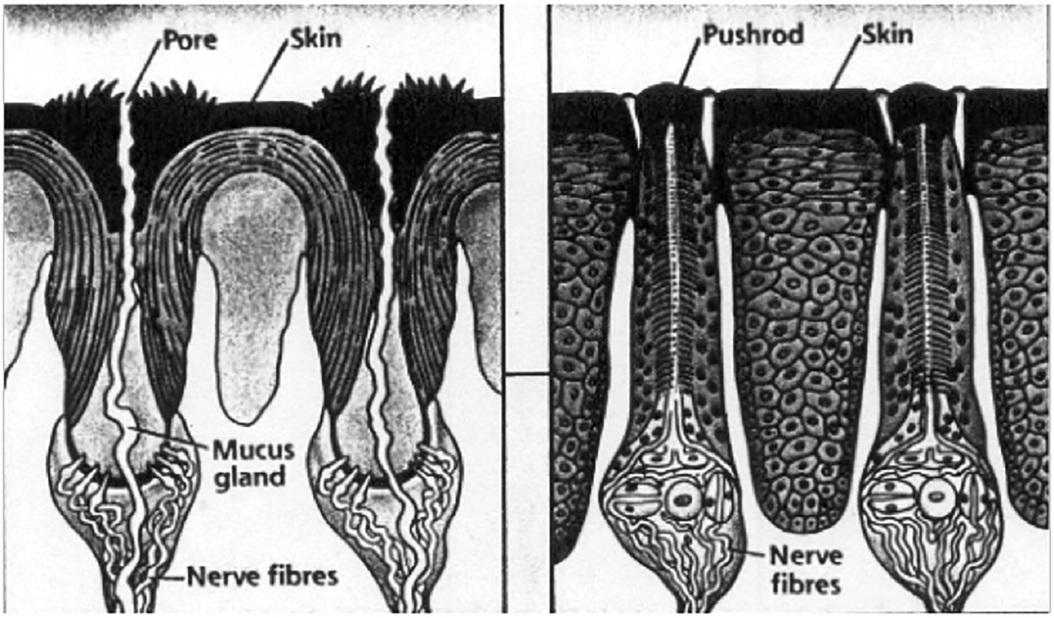

Fig. 2. Platypus bill's two kinds of pore. The electrosensitive pore (left panel) is the opening of a mucus gland duct while the touch-sensitive pore on the far right contains a pushrod device that triggers nerves when compressed by a mechanical wave in the water or when it comes into contact with an object (Australian Geographic. Reproduced with permission).

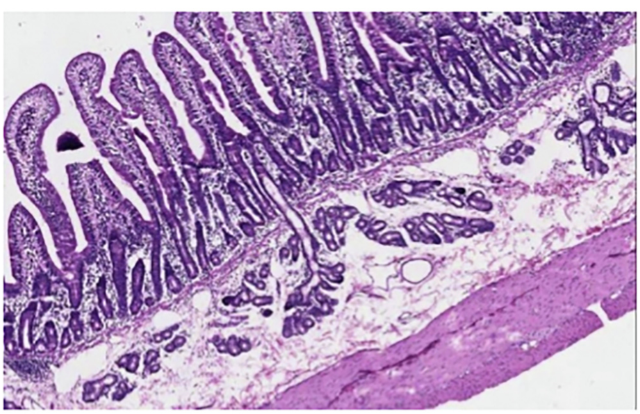

Fig. 3. A histological slide of a mucus-producing Brunner's Gland, the central clear structure resembling an asparagus spear in shape. It penetrates the submucosal layer beneath a layer of intraluminal villi in the duodenum. (Image courtesy of Studydroid.com.)

restricted to highly specific GPCR mechanisms would have to be extremely extensive to cope with all the different ingredients of food. In fact G-proteins appear to act with a range of similar molecules. For example Wausen et al. [2] in their review of G-protein-coupled receptors mention that some will bind with a range of amino acids or taste receptors to orchestrate digestive hormone release. With regard to glucagon-like peptide, GLP, they write "*Diverse studies have linked sweet taste receptors and α-gustducin to intestinal secretion of the amplifying hormone glucagon-like peptide 1 (GLP-1), which affects gut motility, increases satiety, and enhances insulin secretion from pancreatic β-cells in response to glucose.*" However there remains a need to co-ordinate the overall response and for a feedback mechanism that identifies the point at which digesta is fit to pass on to the absorption sites.

In addition, it appears that the duodenal brake mechanism is a non-specific response to lipid in particular and to the mere presence of digesta in general via osmolarity. It is interesting that EI traces such as Fig. 1 usually included a brief plateau in gastric emptying, even when the fluid drunk by the subject was a simple crystalline solution of glucose or pure water. This implies that the duodenum and stomach act as one unit for all meals, including de-ionised water and simple crystalline solutions such as 10% glucose where a GPCR response might not be expected. It would be logical to predict that the brake mechanism can be extended to the upper jejunum where it would function as holding on to digesta until it is ready to be passed on down to the ileum for absorption. In that case the gap in our knowledge would concern the state that digesta must reach to become absorbable. Logically one criterion is to achieve iso-osmolarity because it simplifies the passage of digesta contents through the membranes on the surfaces of cells in ileal villi. A parallel, hitherto unsuspected criterion, could be iso-resistivity.

A well targeted system would distinguish FCP in order to release the most appropriate enzymes since that would avoid considerable waste of molecules that are metabolically expensive to produce. An example would be when the period of maceration of solid lumps of protein-rich meat in the stomach exceeds the time required for amylases to digest relatively easily accessed, more soluble carbohydrates. The protein would continue to appear in the duodenum after the carbohydrate had gone, but when there was no reason to continue supplying amylases. While GPCRs offer specificity, it is not known whether they cover the entire range of food components and their very specificity implies the need for an overall control for the reasons explained above.

Roles of electro and osmo-receptors

Electroreceptor morphology

Electroreceptor function could be achieved by a nerve ending sending an action potential into the local environment and monitoring current flow. This is consistent with the structure recorded by Gregory et al where such a nerve ending emerges from a more complicated structure [14]. There is a precedent in the work of Andres et al. [1] who not noted that they were not suspected for decades despite the fact that their structure was well known. They cited Proske et al who stated that for many years structures on the platypus snout were not considered to be electroreceptors due to a general lack of awareness of the functions of electroreceptors and their extraordinary sensitivity in particular [15]. They wrote "*The ability of animals to be able to detect weak electric* *fields in their environment was recognized only relatively recently, perhaps because we, ourselves, are unaware of any but the strongest fields. Thus, the ampullae of Lorenzini in elasmobranch fish were first thought to be mechanoreceptors, then thermoreceptors and chemo-receptors. It was not until the late 1950s that convincing behavioural evidence was provided for an electro-receptive role. Platypus and echidna need them to detect the minute currents emitted by the muscles of small river crustaceans and worms."* (upon which they feed). This history led Andres et al to suggest that a similar delay in recognition is possible for the human duodenum.

The morphological similarity between platypus and shark receptors to human mucus glands that Andres et al described includes both being filled with mucus that could conduct the necessary current between the mucosa surface of the cells and the sensory nerve ending. Some have a complex neuronal structure around the mucus channel but in the platypus it terminates in a simple nerve ending. Gregory et al point to the fine nerve endings that are in contact with the mucus channel in the platypus electroreceptor [14]. Their section on structure describes … "*a small gap in the myelin through which penetrates a slender filament of the axon that is free of any investing Schwann cell. The axonal protrusion is in contact with cells of the wall of the mucus sensory gland's duct. This tongue of axon represents the terminal of the sensory nerve fibre and is likely to be involved in the transduction process."* Similar nerve endings seem possible in the human mucosa where they could function without the more complex structure such as the platypus axolemma that may be required by creatures living and actively hunting for minute currents in variable aqueous or marine environments. In that case there would be no distinct structure by which to identify them, a possible reason for not suspecting their existence before. There is a parallel in that there is no distinct histological structure for osmoreceptors in the duodenum. The function is achieved by water-sensing channels in nerve membranes that appear normal morphologically, although they contain specific proteins called aquaporins that have the remarkable ability to control the water content of cells [16]. Ten types have been found in humans and they are common to bacteria, plants and animals. Overall, if resistivity and osmolarity can be hosted by the same nerve endings it would increase the specificity of the system since both would be identifying the same molecules.

Electroreceptor sensitivity

To be efficient the iso-osmo-resistivity system process requires an exceptional degree of sensitivity, virtually down to the molecular level, so that it can identify individual food components. The platypus electroreceptors are sensitive enough to detect extremely small currents emitted by the muscles of prey as small as worms and freshwater shrimps. Moreover, they do so in river water that itself varies continually in resistivity. The sensitivity of electroreceptors in fish and elasmobranch sharks is the highest known of any receptors in the animal kingdom [17–20]. For example, sharks can detect 0.01 μV/cm which has been illustrated by the Reefquest Shark protection organization's website as "*the equivalent to the electric field of a flashlight battery connected to electrodes some 10,000 <u>miles</u> [16,000 km] apart in the ocean* [19]. In freshwater fish species electroreceptors are reported to detect 0.1–10 μV/cm approximately one tenth the sensitivity of sharks [20]. Even at this level, based on the basic V = IR concept of voltage being result of current times resistance, and assuming that the receptor uses an action potential of constant current, such receptors in humans would detect a change of 0.1 <u>micro</u>-Ohm. An indication of the possible sensitivity can be seen by comparing this value with the range from an iso-resistive (Meal A) to hyper-resistive (Meal B) shown in Table 1, ie 300 Ohms, a factor of 3 million greater. Gregory et al found a threshold for generating an action potential at 20 micro-V in the platypus receptor, which remains highly sensitive despite a reduction of 200 fold.

Electroreceptor function

The key event is sensing the voltage difference across the nerve ending membrane, achieved by the nerve generating its own impulse along its membrane in the classic nerve function mode and detecting resistance to it. As explained above, each type of FCP molecule would produce its own distinct resistance, which would change with the specific effects of enzymes, providing the basis for a feedback mechanism by which further enzyme release could be modified. Osmoreceptors would have an important role by recording the rate of the change. Bile and acid would produce similar but less specific changes. G-proteins would also have a role, probably to identify specific molecules although they appear to stimulate hormone and enzyme production rather than enable the system to avoid breaking down valuable molecules such as vitamins.

Osmoreceptor roles

The concentration of digesta is monitored by osmoreceptors in the duodeum and it is long established that their output influences the tone of upper gut muscle, the production of gastric secretions and pancreatic digestive peptides [21–27]. They could not distinguish between C, P and L at equal concentrations, but their information <u>combined</u> with electroreceptor data would <u>quantify</u> changes in the amounts present of three elements CPL, providing a mechanism for correctly modifying the amount released of the appropriate enzyme.

At the start of digestion relatively resistive lipids would be identified in the proposed system by their <u>supra</u>-iso-resistive state. That would trigger the release of specific lipolytic enzymes that would break them up, tending to increase osmolarity. At the same time bile would cause micelle formation, an aggregation that would tend to have the opposite effect while simultaneously decreasing resistivity because the detergent effect of bile adds ionised particles to lipid micelle surfaces. In contrast proteins would start in an <u>infra</u>-iso-resistive state and become less resistive and more osmotic as they are broken up by the action of enzymes and acid. Carbohydrate such as starch would be near resistivity-neutral at the start and enzymes would not greatly change it, but they would increase osmolarity by fragmentation of larger molecules.

It is also possible that the combination of resistivity and osmolarity provides a zone of physiological states for digesta that would identify an aberrant food or liquid with parameters outside it such as hypertonic saline.

Pattern of gastric emptying

The new iso-osmo-resistivity theory suggests that digestion involves analysis of digesta before enzymes and bile are released. It is reasonable to suppose that this takes time, so it would be necessary to delay gastric emptying until the correct response is known. This would seem to be the physiological reason for the plateaux often seen in EI recordings, including Fig. 1, that represent a temporary halt to gastric emptying after ingestion of a dilute glucose solution. It occurs after a significant fall from the peak, suggesting that some of the meal has been allowed to enter the duodenum for the sampling process to begin.

EI displays these plateaux clearly in individual traces because it assesses liquid meals continuously and liquids empty more uniformly than solid meals. Group data may obscure them by curve-fitting processes due to different plateau timings. They may represent times of retro-pulsive flow. The eminent gastroenterologist Robert Heading once showed me video made by an epigastric ultrasound after a volunteer had swallowed a clear liquid laced with biscuit crumbs. The particles shone brightly in a dark background and they formed a procession passing out through the pyloric canal and then, surprisingly, back again into the antrum, proving that gastric emptying is bi-directional. In this way the duodenal digestive system can A) Sample the gastric contents in order to release the correct enzymes before the digesta leaves the stomach B) Detect the effect of acid on the duodenal contents, which would aid identification of FCP as explained above.

The importance of a plateau may not have been fully realised before because the gold standard method of measuring gastric emptying, scintigraphy, requires finite sampling periods to make the necessary radioactive counts and sampling periods tend to obscure these quite brief events. In addition, scintigraphy mainly uses solid meals because they are more physiological, but such meals obscure these plateaux completely.

On the other hand the existence of gastric delay, if not plateaux in emptying, is well known under the term "duodenal brake". It has long been linked to osmolarity following the discovery that hyperosmotic solutions and food in the duodenum or upper intestine retard gastric emptying [24–27]. In their report of experiments to determine the mechanism Thompson and Wingate [22] wrote that "*The mucosa of the duodenum is known to be sensitive to the pH, osmolality and lipid composition of its intraluminal content.*" but they have no comment on the mechanism of the known sensitivity to lipid. They define the plateau period by stating "*Intraduodenal nutrient outside an acceptable range for any of these constituents slows the passage of food from the stomach until the efflux is rendered more acceptable by further gastric secretion.*" The iso-osmo-resistivity theory offers an additional criterion, iso-resistivity, by which the state of being "more acceptable" could be achieved, especially for lipids since they are the component of food that has relatively high resistivity.

Increased efficiency of digestion

An advantage of the proposed system is the conservation of enzymes. While an empty stomach after a meal is currently thought to be the main trigger for halting their release, it lacks specificity. Iso-osmo-resistivity would identify the time it becomes unnecessary to continue their production, as with the lumps of meat illustration above.

A different kind of efficiency could be derived if the electroreceptors have exceptional sensitivity because it would permit the accurate detection of small amounts of food, presumably a distinct evolutionary advantage for survival of individuals. G-proteins could also have this role.

This new theory also suggests a new end point for digestion; namely when digesta is rendered close to the iso-electro-resistive point since it is likely that would prepare it for passing through the membranes of the gut wall and sub-mucosal blood vessels.

Finally, it is worth noting that the proposed system does not require food to be broken down into small molecules, which could be another aspect of increased efficiency over current models. It could allow larger molecules such as vitamins and vital lipoproteins to pass through intact.

Testing the hypothesis

An innovative hypothesis should suggest ways to test its assumptions and predictions and in this case the list includes the following:

1. The simplest test in the laboratory is to measure the resistivity and osmolarity of meals that are known to be rapidly absorbed and compare the data with those from meals that are not rapidly absorbed.
2. In the laboratory assess the resistivity and osmotic changes caused by digestive enzymes acting on their usual substrates, such as lipases on lipids. Do they cause a shift towards iso-resistivity as the theory predicts?
3. Compare the permeability of live gut and blood vessel membranes to liquids of varying resistivity. Iso-resistive fluids should pass more easily through them than hyper- or hypo-resistive liquids.
4. A closer comparison of known electroreceptor structure and that of Brunner's Glands. A key item is the nerve supply, although it would not have to be as complex as that of the monotremes that must monitor changes in small electric currents emitted by their prey.
5. In volunteers compare gastric emptying of meals close to and distant from the iso-resistive point since the theory predicts the former would empty faster than the latter. Other methods than EI could be used for gastric emptying such as scintigraphy or paracetamol absorption rates, as was done by Murphy et al with morphine induced gastric delay [11].
6. Also in volunteers, provide meals of varying osmo-resistivity and sample gastric and ileal contents to monitor changes in osmo-resistivity. The ileal contents would converge on iso-osmo-resistivity if the theory is correct. This could be extended to measuring the specific effect of enzymes introduced into the duodenum via intra-gastro-duodenal tubes.
7. A possible extension of the theory is based on the fact that electroreceptors would depend upon nerves functioning normally, so in patients who have pathological gastro-paresis there may be evidence of non-function, ie: they do not produce the same changes in foods that are observed in healthy volunteers in test 5 above. The most clear example would be in patients who have the autonomic neuropathy that is sometimes observed in late stage diabetes.
8. Finally, if man has electroreceptors it would be more likely that other animals also have them, so the above experiments could be worth doing in other species.

Declaration of Competing Interest

The author is the sole sponsor of this article and is not aware of any conflicts of interest in publishing it.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109282.

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