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JSM Anatomy & Physiology

Opinion

Discontinuities Indicate Oral Chemoreceptor Research Opportunities

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Submitted: 26 November 2018

Accepted: 10 December 2018

Published: 13 December 2018

ISSN: 2573-1262

OPEN ACCESS

Keywords
• Taste; TRP; Postprandial hyperemia; Gastric emptying

Abstract

Interest is developing in the mechanisms by which food and drink influence digestion. This a research area that has been largely ignored, likely because it was believed that the enteric nerve system controlled digestion and because sensory psychologists were more interested in vision and hearing. During the last two decades the discovery of the cellular mechanisms for oral sensation, both taste and TRP, has encouraged research into the possibility that food and drink may impact postprandial hyperemia and gastric emptying. The experimental results clearly indicate that both these processes are modified by oral chemosensory stimulation. Currently there are many studies where the results would have been interpreted differently if the researchers were more familiar with digestive physiology and open to the concept that foods and drinks elicit changes in the digestive process. This lack of cohesion produces knowledge discontinuities. This article presents a number of discontinuities present in the literature, some have solved by the author while others are waiting to be addressed. Some of the difficulties and pitfalls of postprandial statistical analysis are outlined.

ABBREVIATIONS

dP/dt: Cardiac Contraction Force; SNS: Sympathetic Nervous System; PSNS: Parasympathetic Nervous System; CVS: Cardiovascular System

INTRODUCTION

When searching for areas to research, in any disciple, the occurrence of discontinuities suggests that investigations will yield interesting results. Discontinuities may be associated with

- Breakthroughs in physiology.
- Paradigms not supported by evidence.
- Developments in measurement technology.
- Unmeasurable, unmeasured or ignored variables.
- Inappropriate research models.
- Incorrect statistical analysis.

This article will give examples of discontinuities in the field of oral chemoreceptors, some discontinuities that the author has researched and reported on, as well as other discontinuities waiting to be explored.

BACKGROUND

The digestive process is dependent on an increased blood flow, hyperaemia, to the splanchnic circulation. In the initial of digestion, referred to as the gastric phase, blood flow increases in the celiac artery. The celiac artery supplies the stomach, liver, part of the pancreas, the proximal part of the duodenum and the spleen [1]. Following the ingestion of food and drink, postprandial hyperaemia supports the stomach wall in accommodating the mass, volume and temperature of the ingested articles. The gastric phase starts with ingestion and continues for about 15 minutes after ingestion has ceased [2]. At this time, or shortly after, gastric emptying begins, and the blood flow increases in the mesenteric artery providing nutrients for digestion, removal of digested nutrients and cellular wastes to the circulation, and peristalsis. The superior mesenteric artery supplies blood to part of the pancreas, the distal part of the duodenum, the whole small intestine and the proximal colon [1]. Importantly, postprandial hyperaemia reduces the circulatory volume which leads to autonomic adjustments to avoid circulatory distress. The most well-known response is an increase cardiac output due to increases of heart rate [3], and cardiac contraction force (dP/dt) [4]. When this response is adequate, as in the young healthy adults, blood pressure increases, but in the elderly and some pathologies the response may be inadequate resulting in postprandial hypotension [5].

Investigating responses elicited by a chemoreceptor agonist, a stimulus such as food or drink, on the cardiovascular system yields information on

- changes within the autonomic system;
- changes in the circulatory system;
- indicates how the digestive process is likely to be affected.

Blood pressure is maintained by both by heart activity and vascular tonus. Heart rate is under the influence of both the sympathetic nervous system (SNS) and the parasympathetic nervous system (PSNS) whereas dP/dt has only SNS innervation, as do the conductance (aorta and large arteries) and resistance (small arteries and capillaries) vessels [6]. Cardiac stroke volume is determined by breathing, capacitance vessel tonus and dP/dt, so it is also under SNS control. In steady state conditions, breathing and capacitance vessel are assumed constant, so changes in stroke volume reflect dP/dt. Cardiac output is the product of stroke volume and heart rate. Movements in blood pressure are limited by the baroreceptors, which regulate heart rate via feedback tissue located in the medulla [6]. Monitors are available that provide beat-to-beat, i.e. continuous, measures of some or all these parameters. Without measures of all these parameters, it is impossible to understand the physiological processes of leading to a change in blood pressure. To the best of the author's knowledge only the monitors Finometer [7], and Portapres supply all these parameters. The author used a Finometer in his research cited below.

DISCONTINUITY 1: TEA AND COFFEE BREAKS

Tea and coffee breaks in workspaces usually last 10 to 15 minutes, after this period workers return to their activities energised. Here we have a discontinuity because the absorption of caffeine is slower than the length of the break. Consequently, the cerebral effects experienced are unlikely to result from elevated plasma caffeine levels. To test whether the taste of caffeine elicited changes in autonomic activity, participants were tested with

- Hot regular coffee (containing 130 mg caffeine),
- Hot decaffeinated coffee (<10 mg caffeine),
- A caffeine capsule (130 mg) with room temperature water,
- A placebo capsule with room temperature water (control).

Changes in CVS parameters were compared with the control [8].

Both coffees increased heart rate in the first 5 minutes after ingestion. For the regular coffee, the heart rate increase for continued for 30 minutes, whereas increases in heart rate for the decaffeinated coffee were limited to the initial phase. The caffeine capsule elicited no changes in heart rate. These findings indicate that caffeine stimulates oral chemoreceptors eliciting autonomic changes. As heart rate was changed, but not the other parameters under SNS influence, it appears that the taste of caffeine elicits vagal withdrawal. This would account for the energising effects of drinking tea and coffee.

DISCONTINUITY 2: BITTER TASTANTS

Bitter tasting herbs have traditionally been taken to promote digestion and it has long been proposed that bitter tastants stimulate oral chemoreceptors to enhance oral and vagal gastrointestinal secretory activity [9]. This mechanism is widely accepted within phytotherapy [10], and has been included in the European Medical Agency herbal monographs [11,12]. In a highly respected Germany phytotherapy text it is stated that some bitter herbs reduce cardiac output, as support for the theory that bitter herbs elicit vagal activity [13]. This is a discontinuity because digestion requires enhanced blood circulation, i.e. increased not reduced cardiac output. The information is based on an experiment that compared pre and post-ingestion values. The three authors, all professors of pharmacology, made a fundamental error, they failed to compare the pre-post changes of the bitter herbs with the control (water) pre-post changes. In fact, the bitter herbs produced no significant changes of cardiac output [14].

Oddly enough, when further investigated, the two bitter herbs Artemisia absinthium (Wormwood) and Gentiana lutea (Gentian) actually did reduce cardiac output, but not by increasing vagal activity, rather by increasing SNS activity. To test whether the bitter taste of gentian and wormwood elicited changes in autonomic activity, participants were tested with 100ml room temperature water and

- Fluid extract of gentian,
- Encapsulated gentian,
- Fluid extract of wormwood
- Encapsulated wormwood,
- A placebo capsule (control).

Changes in CVS parameters were compared with the control [4].

The two encapsulated herbs produced no parameter changes compared to the control for 10-15-minute post-ingestion period. In contrast, for the 5-10-minute post-ingestion period, both bitter tasting extracts elicited peripheral resistance increases, stroke volume and cardiac output decreases but no changes in blood pressure. It is probable that the decrease of stroke volume and cardiac output resulted from increased baroreflex activity as these reflexes acted to maintain normal blood pressure when peripheral resistance increased. Increases in peripheral resistance can be expected to support postprandial hyperaemia and reduce postprandial cardiac stress.

DISCONTINUITY 3: WATER AND PLACEBO/CONTROL

Water is not a neutral agent for the digestive system as it possesses mass, volume and temperature. Accordingly, the ingestion of water requires gastric accommodation, which is supported by postprandial hyperaemia. The temperature of water affects the type of CVS response – note, some oral chemoreceptors are also temperature sensitive, so care needs to be taken to avoid confounding when testing oral chemoreceptors in water. Hot drinks increase heart rate while room temperature drinks increase dP/dt. The increases in dP/dt can be so robust that heart rate actually decreases, presumably via baroreflex activity [15]. With this knowledge it is evident why meaningful oral chemoreceptor research will require the use of a control

condition. The control for water is simply no exposure, i.e. nothing, just a group of participants experiencing the procedure without any stimulus. Some researchers may prefer to use this type of control data and utilise "Between participant" rather than "Within participant" design and analysis models. For use in small groups, the statistical advantage of "Within participant" designs may be nullified by no shows, etc., and "Between participant" designs may be more trouble free for researchers.

It may surprise some readers that "no-control studies" are still published in reputable journals [16]. In 2014 it was reported that on the basis of pre-post comparisons the ingestion of 500 ml

- Body temperature water had no effect on CVS parameters
- Room temperature reduced stroke volume
- Cold water (3°C) reduced stroke volume

There is a discontinuity here because the findings suggest postprandial hypoaemia rather than the predicted postprandial hyperaemia. The study was conducted with participants sitting for circa 2½ hours and stationarity (a stationary process is one whose statistical properties do not change over time [17]) cannot be assumed for such a long lasting session. It is known that prolonged sitting results in venous pooling in the calf muscles [18], this leads to increases of blood pressure and peripheral resistance. Heart rate, stroke volume and cardiac output may also be affected [19]. Thus, the lack of a control condition introduces a confounding and prevents a clear understanding of the results. Additionally, the parameters dP/dt and arterial compliance were not measured. The author has previously criticised this study [20]. Two further studies with essentially the same design have recently been published [21,22].

DISCONTINUITY 4: ALCOHOLIC BEVERAGES

Ethanol, beer, wine and spirits have been shown to delay the gastric empty of both water and meals, yet the mechanism is unclear [23-26]. After the ingestion of a cheese fondue, where gastric emptying continued for 4+ hours, the ingestion of 20ml snaps (40% ethanol), 90 minutes postprandially, slowed gastric emptying [26]. Discontinuity: the authors suggested that the snap was eliciting responses in gastric tissue however, it is more likely that ethanol is stimulating oral chemoreceptors as these are freely available while much of the gastric tissue is covered in partly digested fondue.

DISCONTINUITY 5: CINNAMON

A decade ago, the ingestion of 6 g of cinnamon (Cinnamomum cassia) powder with food was reported to reduce postprandial plasma glucose levels [27]. In follow-up studies, 3g but not 1g Cinnamomum cassia reduced the postprandial insulin response [28] while 6g Cinnamomum zeylanicum powder reduced postprandial plasma glucose levels [27]. In contrast, encapsulated Cinnamomum zeylanicum at doses of 3 [29], 6 [30] and 10 [31] g had no effect on gastric emptying, the insulin response or plasma glucose levels in the 2 hours post-ingestion. The discontinuity is that cinnamon powder has a postprandial effect but not encapsulated cinnamon. The most likely explanation is that cinnamon powder is stimulating oral chemoreceptors, eliciting a decrease in gastric emptying and causing glucose to enter the blood more slowly and therefore the insulin response is reduced. If correct, it would mean that oral TRP receptors are regulators of gastric emptying.

DISCONTINUITIES 6: SOME RESEARCHERS AND REVIEWERS ARE NOT STATISTICIANS

In the physical sciences undergraduates usually study statistics and later use statistics in their everyday work. In contrast, researchers in the medical sciences may only study the use of statistical analysis programs in postgraduate program. For statistical validity, data often needs to be organized before it can analysed. This particularly true for postprandial data.

There are 3 postprandial phases which can be considered CVS independent and are best analysed individually when cardiovascular responses are of interest. The initial phase includes swallowing responses and lasts several minutes are ingestion has ceased. During swallowing, parameter measures may change up to 50% over 10 seconds making this period difficult to analyse even with beat-to-beat measures. The gastric phase lasts 15-20 minutes after which the intestinal phase starts. The initial 5 minutes of the gastric phase are best ignored as the swallowing responses pollutes the CVS measures associated gastric accommodation. The last 5 minutes may be also being ignored as it is uncertain, unless measured, when an individual's gastric phase ends. Either the 5-10, 10-15 or 5-15-minute period is suitable for assessment. If testing a capsule, the 10-15-minute period is preferred as the disintegration time for both cellulose and gelatine capsules is just under 10 minutes. The intestinal phase may last for hours but more data is not necessarily statistically advantageous. With increasing time stationarity cannot be assumed and standard deviation generally increases. Furthermore, vascular pooling occurs even in the sitting position and this corrupts the data. Consequently, the 25-30-minute postprandial interval becomes the preferred period for data analysis of the intestinal phase.

An additional complication in analysing postprandial response is the failure of researchers to understand the difference between "repeated measures" and "serial measures" [32, 33]. When a recording is made over time, the data cannot be divided into different time sections, "serial measures", unless the sections are physiologically different. Thus, the 5-10 and the 10-15-minute postprandial cannot both be compared to pre-test values because the readings in the second period are dependent on the first period. On the other hand, the 5-10 and the 25-30-minute periods are physiologically different and be both validly compared to pre-test values or each other. "Repeated measures" refers to repeated experimental sessions and not multiple measures taken from a single session. When comparing pre-post parameter changes to a control, it is preferable to use t-tests rather than F-tests, as the t-test requirements are less restrictive. Also, having accepted that pre-test values are valid e.g. blood pressure values, they are no longer of interest, rather it is the change values that are of interest. F-tests are necessary for trends.

The discontinuity with "inappropriate statistics" is that a correct statistical analysis is more likely to yield significant results than an incorrect analysis with polluted readings. A review of the 125 studies reported that in 70% at least one

inappropriate statistical procedure was applied. Post hoc t-tests and Repeated Measure ANOVAs were incorrectly applied in 56% and 52% of cases respectively [34]. Reanalysis of the original data resulted in a 14% increase in significant effects compared to the original results, i.e. one in seven published studies reported false negatives.

It appears that once a journal publishes faulty statistical analysis it risks becoming the standard for that journal i.e. the peer review system breaks down. A recent publication in Nature's journal Scientific Reports [22], disregards many of the methods of correct statistical analysis outlined above.

Finally, in original areas of research, P values in the range 0.05 - 0.10 should be further investigated rather than automatically rejected. These values may reflect a lack of statistical power in the design (insufficient n) or insufficient stimulus intensity.

REFERENCES

1. Mensink PBF, Moons LMG, Kuipers EJ. Chronic gastrointestinal ischaemia: shifting paradigms. Gut. 2011; 60: 722-737.
2. Someya N, Endo MY, Fukuba Y, Hayashi N. Blood flow responses in celiac and superior mesenteric arteries in the initial phase of digestion. Am J Physiol-Regul Integr Comp Physiol. 2008; 6: R1790-R1796.
3. Sidery MB, Macdonald IA. The effect of meal size on the cardiovascular responses to food ingestion. Br J Nutr. 1994; 6: 835-848.
4. McMullen MK, Whitehouse JM, Whitton PA, Towell A. Bitter tastants alter gastric-phase postprandial haemodynamics. J Ethnopharmaco. 2014; 3: 719-727.
5. Lipsitz LA, Nyquist RP, Wei JY, Rowe JW. Postprandial Reduction in Blood Pressure in the Elderly. N Engl J Med. 1983; 2: 81-83.
6. Levick JR. An Introduction to Cardiovascular Physiology. 5th ed. London: Arnold. 2010: 1-414.
7. Guelen I, Westerhof BE, van der Sar GL, van Montfrans GA, Kiemeneij F, Wesseling KH, et al. Finometer, finger pressure measurements with the possibility to reconstruct brachial pressure. Blood Press Monit. 2003; 1: 27-30.
8. McMullen MK, Whitehouse JM, Shine G, Towell A. Habitual coffee and tea drinkers experienced increases in blood pressure after consuming low to moderate doses of caffeine; these increases were larger upright than in the supine posture. Food Funct. 2011; 2: 197-203.
9. Hale White W. Materia Medica, Pharmacy, Pharmacology and Therapeutics. 1st ed. London, UK: J. & A. Churchill. 1892: 614.
10. Mills S, Bone K. Principles and Practice of Phytotherapy. Modern Herbal Medicine. 2 ed. Edinburgh: Churchill Livingstone. 2013: 1056.
11. Koch J. Community herbal monograph on Artemisia absinthium L. herba. London: European Medicines Agency; 2009.
12. Knöss W, Stolte F. Community herbal monograph on Gentian lutea L., radix. London: European Medicines Agency. 2009.
13. Schulz V, Hänsel R, Tyler VE. Rational Phytotherapy. A Reference Guide for Physicians and Pharmacists. 5th ed. Berlin, Germany: Springer. 2004: 417.
14. McMullen MK. Evidence does not support the suggestion that gustatory exposure to bitter tastants reduces cardiac activity. J Ethnopharmaco. 2013; 149: 838-839.
15. McMullen MK. Oops! Who Forgot to Measure Cardiac Contraction Force (dP/dt)? Austin J Pharm Ther. 2014; 11: 1-4.
16. Girona M, Grasser EK, Dulloo AG, Montani JP. Cardiovascular and metabolic responses to tap water ingestion in young humans: does the water temperature matter? Acta Physiol. 2014; 211: 358-370.
17. Nason GP. Stationary and non-stationary time series. Statistics in Volcanology. 2006: 1-29.
18. Shvartz E, Reibold RC, White RT, Gaume JG. Hemodynamic responses in orthostasis following 5 hours of sitting. Aviat Space Environ Med. 1982; 53: 226-231.
19. Shvartz E, Gaume JG, White RT, Reibold RC. Hemodynamic responses during prolonged sitting. J Appl Physiol Respir Environ Exerc Physiol. 1983; 54: 1673-1680.
20. McMullen MK. It is unlikely that the drinking of cold and room temperature water decreases cardiac workload. Acta Physiol. 2015; 213: 3-4.
21. Grasser EK, Dulloo A, Montani JP. Cardiovascular responses to the ingestion of sugary drinks using a randomised cross-over study design: does glucose attenuate the blood pressure-elevating effect of fructose? Br J Nutr. 2014; 112: 183-192.
22. Monnard CR, Grasser EK. Water ingestion decreases cardiac workload time-dependent in healthy adults with no effect of gender. Sci Rep. 2017; 7: 7939-7948.
23. Kasicka-Jonderko A, Jonderko K, Bożek M, Kamińska M, Mgłosiek P. Potent inhibitory effect of alcoholic beverages upon gastrointestinal passage of food and gallbladder emptying. J Gastroenterol. 2013; 48: 1311-1323.
24. Franke A, Teyssen S, Harder H, Singer MV. Effect of ethanol and some alcoholic beverages on gastric emptying in humans. Scand J Gatsroenterol. 2004; 39: 638-644.
25. Franke A, Nakchbandi IA, Schneider A, Harder H, Singer MV. The effect of ethanol and alcoholic beverages on gastric emptying of solid meals in humans. Alcohol. 2005; 40: 187-193.
26. Heinrich H, Goetze O, Menne D, Iten PX, Fruehauf H, Vavricka SR, et al. Effect on gastric function and symptoms of drinking wine, black tea, or schnapps with a Swiss cheese fondue: randomised controlled crossover trial. BMJ. 2010; 341: c6731-735.
27. Hlebowicz J, Darwiche G, Björgell O, Almér L-O. Effect of cinnamon on postprandial blood glucose, gastric emptying, and satiety in healthy subjects. Am J Clin Nutr. 2007; 85 6: 1552-1556.
28. Hlebowicz J, Hlebowicz A, Lindstedt S, Björgell O, Höglund P, Holst JJ, et al. Effects of 1 and 3 g cinnamon on gastric emptying, satiety, and postprandial blood glucose, insulin, glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and ghrelin concentrations in healthy subjects. Am J Clin Nutr. 2009; 89: 815-821.
29. Markey O, McClean CM, Medlow P, Davison GW, Trinick TR, Duly E, et al. Effect of cinnamon on gastric emptying, arterial stiffness, postprandial lipemia, glycemia, and appetite responses to high-fat breakfast. Cardiovasc Diabetol. 2011; 10: 1-9.
30. Wickenberg J, Lindstedt S, Berntorp K, Nilsson J, Hlebowicz J. Ceylon cinnamon does not affect postprandial plasma glucose or insulin in subjects with impaired glucose tolerance. Br J Nutr. 2012; 107: 1845-1849.
31. Beejmohun V, Peytavy-Izard M, Mignon C, Muscente-Paque D, Deplanque X, Ripoll C, et al. Acute effect of Ceylon cinnamon extract on postprandial glycemia: alpha-amylase inhibition, starch tolerance test in rats, and randomized crossover clinical trial in healthy volunteers. BMC Complement Altern Med. 2014; 14: 351.
32. Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ. 1990; 300: 230-235.

33. Matthews JNS. Summary Measures Analysis of Longitudinal Data. In: Armitage P, Colton T, editors. Encyclopedia of Biostatistics 2nd ed. London: Wiley-Blackwell; 2005: 6100-6103.

34. Burke DA, Whittemore SR, Magnuson DSK. Consequences of Common Data Analysis Inaccuracies in CNS Trauma Injury Basic Research. J Neurotrauma. 2013; 30: 797-805.

Cite this article

McMullen MK, Pilato F, Calandrelli R, Distefano M, Profice P, et al. (2018) Discontinuities Indicate Oral Chemoreceptor Research Opportunities. JSM Anat Physiol 3(1): 1020.