The following is the abstract of the article discussed in the subsequent letter.

Hermann, Gerlinda E., R. Alberto Travagli, and Richard C. Rogers. Esophageal-gastric relaxation reflex in rat: dual control of peripheral nitrergic and cholinergic transmission. Am J Physiol Regul Integr Comp Physiol 290: R1570–R1576, 2006; doi:10.1152/ajpregu.00717.2005.—It has long been known that the esophageal distension produced by swallowing elicits a powerful proximal gastric relaxation. Gastroinhibitory control by the esophagus involves neural pathways from esophageal distension-sensitive neurons in the nucleus tractus solitarius centralis (cNTS) with connections to virtually all levels of the dorsal motor nucleus of the vagus (DMV). We have shown recently that cNTS responses are excitatory and primarily involve tyrosine hydroxylase-immunoreactive cells, whereas the DMV response involves both an α1 excitatory and an α2 inhibitory response. In the present study, using an esophageal balloon distension to evoke gastric relaxation (esophageal-gastric reflex; EGR), we investigated the peripheral pharmacological basis responsible for this reflex. Systemic administration of atropine methyl nitrate reduced the amplitude of the gastric relaxation to 52.0 ± 4.4% of the original EGR, whereas Nω-nitro-arginine methyl ester (L-NAME) reduced it to 26.3 ± 7.2% of the original EGR. Concomitant administration of atropine methyl nitrate and L-NAME reduced the amplitude of the gastric relaxation to 4.0 ± 2.5% of control. This reduction in the amplitude of induced EGR is quite comparable (4.3 ± 2.6%) to that seen when the animal was pretreated with the nicotinic ganglionic blocker hexamethonium. In the presence of betahexanol, the amplitude of the esophageal distension-induced gastric relaxation was increased to 177.0 ± 10.0% of control; administration of L-NAME reduced this amplitude to 19.9 ± 9.5%. Our data provide a clear demonstration that the gastroinhibitory control by the esophagus is mediated via a dual vagal innervation consisting of inhibitory nitrergic and excitatory cholinergic transmission.

Comments on: “Esophageal-gastric relaxation reflex in rat: dual control of peripheral nitrergic and cholinergic transmission”

To the Editor: Hermann, et al. (3) in the DISCUSSION of their paper criticize the paper we recently published in the American Journal of Physiology–Regulatory, Integrative and Comparative Physiology (2). Their first criticism is that we claim to have employed the same reflex stimulating technique as Rogers, et al. (7). As we pointed out in an earlier exchange of letters to the editor (Am J Physiol Regul Integr Comp Physiol 290: R1151–R1152, 2006), the purpose of our study was to use the same reflex stimulating technique (esophageal distension) but the initial parameter used failed to alter the end point that we were measuring. Using a decrease in intragastric pressure (via a balloon recording) as a marker of gastric relaxation, esophageal distension of 0.2 ml failed to elicit a significant effect on intragastric pressure (see Fig. 1 of Ref. 2) in our experimental preparation. Hence, we had to use a greater volume to evoke a response. A decrease in intragastric pressure was noted in some animals when the volume of distension was 0.6 ml and this decreased further, when the volume was increased in 0.1-ml increments. To elicit stable responses, we used a volume that ranged from 0.6 to 0.8 ml for most of our pharmacological microinjection studies. Our data are comparable to those of Wei, et al. (8) who reported that esophageal distension with 0.5 ml reduced intragastric pressure in the rat. Additionally, in an earlier study of Rogers, et al. (6), a reduction in gastric motility was observed in the rat with a distension volume of 0.4 ml.

The second criticism is that we did not investigate an esophageal-gastric reflex but probably a gastro-gastric reflex. Their reason for assuming this is that the motility traces in Figure 2 of our paper (2) show a transient increase in antral tone and motility during balloon distension. Although there is a sharp gastric contraction at the start of the esophageal distension (see Fig. 2A, Ferreira, et al. (2)), the predominant response was a decrease in intragastric pressure that was comparably long lasting and was always evident before the cessation of the esophageal distension (see Figs. 1 and 2, Ferreira, et al. (2)). Furthermore, the sharp gastric contraction did not always occur (see trace C of Fig. 2, Ferreira, et al. (2)); and if it did, it was markedly decreased, and/or completely absent (see, e.g., Figs. 1A, 2C, and 10B, Ferreira, et al. (2)). It is possible that the transient contraction shown in Figure 2A of our paper (2) is an artifact due to the transient pressure gradient arising from an injection of the fluid used to distend the balloon.

Hermann and colleagues (3) state that in our study we were monitoring antral gastric tone. We disagree; rather we were monitoring global intragastric pressure by an intragastric balloon introduced via the fundus of the stomach and positioned around the corpus/antrum area. The balloon was inflated with 2 to 3 ml of warm saline to produce a baseline pressure of 6 to 15 mmHg. Since the balloon inflation distended approximately the whole stomach, we interpret the resultant baseline pressure as indicative of the global gastric pressure.

As a third criticism of our paper, Hermann, et al. (3) cite the work of Dong et al. (1) to question the appropriateness of our esophageal distension volume. However, Dong et al. (1) did not use the end point of gastric relaxation; instead, their end point was a change in distal esophageal rhythmic contraction.

Furthermore, Hermann, et al. (3) criticize us for using an intragastric balloon inserted via the fundus for measuring gastric tone. We used the same method described by Krowicki, et al. (5) and Krowicki and Hornby (4) to measure gastric tone. In each case, an intraluminal latex balloon was inserted into the stomach through an incision in the fundus for recording intragastric pressure. In our study (2), we did not obtain any evidence for the presence of a gastro-inhibitory nonadrenergic, nonchoolinergic (NANC) pathway described by Hermann, et al. (3). In the studies of Krowicki and colleagues (4, 5), decreases in intragastric pressure were obtained as evidence for the activation of this pathway. However, failure to perform ipsilateral vagotomy suggests that the effect may be of nucleus tractus solitarius and not of dorsal motor nucleus of the vagus (DMV) origin.

Finally, Hermann, et al. (3) criticize us for using chloral compounds (e.g., chloral hydrate or α-chloralose) as an adjunct to urethane anesthesia. They state that chloral compounds are known to induce adynamic ileus. (We did not use chloral hydrate in our study; only chloralose was used in combination with urethane.) They cite two studies as evidence for adynamic ileus with these compounds (their Refs. 43 and 48). Their Ref. 43 is a paper by Sababi and Nylander and our reading of that paper provides no evidence that chloralose induces any more adynamic ileus than the anesthetic used by Hermann, et al. (3), namely inactin. Their Ref. 48 is a paper of Silverman and Muir in which adynamic ileus was reported for chloral hydrate but not for α-chloralose. In addition, Krowicki, et al. (5) and
Krowicki and Hornby (4) used α-chloralose in their studies, which they concluded, provided evidence of a DMV gastric inhibitory vagal pathway, i.e., a NANC pathway.

In conclusion, we affirm the adequacy of our method for recording the end point we were measuring, namely esophageal distension-induced gastric relaxation. Furthermore, it is our assertion that neither the distension volume, nor the anesthetic used in our study interfered in any way with our observations or our conclusions.

REFERENCES

REPLY

To the editor: We are delighted to see that Gillis and colleagues recognize that our two laboratory groups are not using the same reflex stimulating or recording techniques used to study the esophageal-gastric relaxation reflex (see Table 1 and Fig. 1). This was exactly our point in our earlier exchange of Letters to the Editor (Am J Physiol Regul Integr Comp Physiol 290: R1151–R1152, 2006). Unfortunately, this controversy was started in a previous paper from Gillis’ laboratory (1) where the authors stated the express purpose of their studies. To quote their paper, they state: “The specific purpose of the present study was to employ the same [emphasis, mine] reflex-stimulating technique as Rogers et al. [Am J Physiol Regul Integr Comp Physiol 285: R479–R489, 2003]. . . .”

Table 1. Comparison of reflex-stimulating or recording techniques used to study the esophageal-gastric relaxation reflex

<table>
<thead>
<tr>
<th>Technique</th>
<th>Hermann, et al. (2, 3)</th>
<th>Ferreira, et al. (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal stimulation</td>
<td>160 μl fluid</td>
<td>600–800 μl fluid</td>
</tr>
<tr>
<td>Response recording</td>
<td>Gastric wall strain gauge secured to the fundus (i.e., receptive portion of the stomach)</td>
<td>Intragastric balloon inserted through the fundus (i.e., receptive portion of stomach is damaged)</td>
</tr>
</tbody>
</table>

Numbers in parentheses are references. *As per manufacturer, Edwards LifeSciences; see Fig. 1.

techniques. The strain gauge elements we use can detect luminal stretch forces as small as 75 mg and as large as 5 g. Parallel measurements in which we place strain gauges on the lumen while measuring gastric pressure changes in response to gradual fluid filling shows that this translates into the ability to detect pressure changes smaller than 1 mm and larger than 8 mmHg, as measured with a P75 low pressure transducer.

Fig. 1. A: UNSTIMULATED. Esophageal stimulation balloon used by Rogers et al. (2, 3) is positioned in esophagus ending ~1 cm from the lower esophageal sphincter. This esophagus-stomach preparation was removed from a 300 g Long Evans rat. The 1-cm black dot is provided for additional scale purposes. This is the size of the esophageal stimulation device used by the laboratory of Gillis (1). B: STIMULATED. Esophageal stimulation balloon used by Rogers et al. is now fully inflated as described in experimental protocols (2, 3). Note that the outer diameter of the esophagus has been increased from ~2 to 4 mm. The 1-cm black dot is provided for additional scale purposes. Again, this is the size of the esophageal stimulation device used by Gillis’ laboratory (1).
Although not described in their most recent study (1), previous studies performed in the Gillis lab cite the use of Statham P23 transducers to detect intraluminal pressure changes. These transducers have a very broad range (−30 to 300 mmHg) and proportionally lower sensitivity to small changes in pressure. Indeed, many years ago we attempted to use the same transducers without success. This was the main reason we made the change to strain gauge measurements or measurements with pressure transducers designed for low pressure.

While we have tried to offer potential explanations for our very divergent observations, we must leave it that our stimulation and response recording techniques are vastly different than those used by Gillis’ laboratory. As such, we were quite successful in observing that esophageal distension elicited gastric relaxation reflexes (2–5 mmHg) at noticeably lower levels of stimulation than those required in the studies by Gillis’s laboratory (1). This rather delicate esophageal-gastric reflex was susceptible to pharmacological investigation as we reported in our recent manuscripts (2, 3).

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The following is the abstract of the article discussed in the subsequent letter:

Seeliger, Erdmann, Mechthild Ladwig, and H. Wolfgang Reinhardt. Are large amounts of sodium stored in an osmotically inactive form during sodium retention? Balance studies in freely moving dogs. Am J Physiol Regul Integr Comp Physiol 290: R857–R858, 2006; First published December 22, 2005; doi: 10.1152/ajpregu.00676.2005.—Alterations in total body sodium (TBSodium) that covered the range from moderate deficit to large surplus were induced by 10 experimental protocols in 66 dogs to study whether large amounts of Na⁺ are stored in an osmotically inactive form during Na⁺ retention. Changes in TBSodium, total body potassium (TBPotassium), and total body water (TBWater) were determined by 4-day balance studies. A rather close correlation was found between individual changes in TBSodium and those in TBWater ($r^2 = 0.83$). Changes in TBSodium were often accompanied by changes in TBPotassium. Taking changes of both TBSodium and TBPotassium into account, the correlation with TBWater changes became very close ($r^2 = 0.93$). The sum of changes in TBSodium and TBPotassium was accompanied by osmotically adequate TBWater changes, and plasma osmolality remained unchanged. Calculations reveal that even moderate TBSodium changes often included substantial Na⁺/K⁺ exchanges between extracellular and cellular space. The results support the theory that osmocontrol effectively adjusts TBWater to the body’s present content of the major cations, Na⁺ and K⁺, and do not support the notion that, during Na⁺ retention, large portions of Na⁺ are stored in an osmotically inactive form. Furthermore, the finding that TBSodium changes are often accompanied by TBPotassium changes and also include Na⁺/K⁺ redistributions between fluid compartments suggests that cells may serve as readily available Na⁺ store. This Na⁺ storage, however, is osmotically active, since osmotic equilibration is achieved by opposite redistribution of K⁺.

UNDER WHAT CONDITIONS IS INGESTED SODIUM RENDERED OSMOTICALLY INACTIVE?

With respect to the conclusions of Seeliger et al. (3) regarding the fate of ingested sodium, I wish to make two points. First, Heer et al.’s (2) potassium excretion data are consistent with osmotic inactivation of sodium and not with Seeliger et al.’s sodium-potassium exchange hypothesis. Secondly, it is inappropriate to compare results of the two studies because of significant differences in experimental details.

If the fate of ingested sodium is to remain osmotically active, then a positive sodium balance can have one or a combination of two straightforward consequences: an increase in body water osmolality or an increase in total body water (TBWater) resulting from increased water ingestion. In experiments on beagle dogs, in which total body sodium (TBSodium) was increased or decreased, Seeliger et al. (3) observed primarily the latter, and never the former. TBWater was a linear function of TBSodium ($R^2 = 0.83$) and an even stronger function of the sum of TBSodium and total body potassium (TBPotassium; $R^2 = 0.93$). However, they also report instances where a TBSodium increase was accompanied by a TBPotassium decrease, as ascertained by urinary excretion data. The authors concluded that there is a third way for osmotically active sodium to increase, namely, to exchange with intracellular K⁺. If this sodium/potassium exchange mechanism is operative, then when TBSodium increases, sodium remains osmotically active while TBWater or osmolality remain constant and TBPotassium decreases. Evidence for this mechanism is a negative potassium balance, that is, potassium excretion is greater than potassium intake. Thus, to conclude that the sodium of a positive sodium balance has been rendered osmotically inactive requires not only that there be no increase in TBWater or osmolality but also a zero potassium balance. (More precisely, the positive sodium balance must exceed the total that can be accounted for by changes in potassium, TBWater, and osmolality.)

In recent sodium balance studies, Heer et al. (2) observed positive sodium balances, of up to 1700 meq, without a change in either TBWater or body water osmolality and concluded that sodium had been osmotically inactivated. Seeliger et al. (3) challenge this conclusion, saying that Heer et al. did not account for potassium balance. Although correct, this is misleading. Heer et al. do report potassium excretion. If sodium is exchanging with potassium, then potassium excretion should increase. Significantly, when sodium intake was doubled from 220 to 440 meq/day and then tripled to 660 meq/day potassium excretion remained constant at 90–96 meq/day [calculated from their Table 1]
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Seeliger et al.’s dogs vs. 40 ml fluid once a day in the morning between 8:30 and 9:00 AM. In our human study, the test subjects were provided with three main meals (8:00 AM, 1:00 PM, and 7:00 PM) and three snacks (11:00 AM, 4:00 PM, and 9:00 PM) in which the daily sodium amount was distributed. The entire amount of sodium was given by dietary intake and fluid supplied together with the meals. This is a significant difference in study design because the entire sodium regulation system has been challenged six times a day by high salt intake in our study compared to only once per day in Seeliger’s experiment.

As already mentioned by Weschler, fluid intake was kept constant at a level of 40 ml/kg body weight/day in our study, whereas the dogs received 100 ml/kg body weight/day. Considering our subjects’ daily fluid and sodium intakes, the calculated concentration of ingested sodium was about 214 meq/l, i.e., a clearly hypertonic saline solution. However, fluid intake of 3 l/day, of which two liters are taken as beverages, is already higher than average in Germany. The average day-by-day fluid intake in Germany is rather low, especially in elderly people. One might argue that the chosen level of sodium intake in our study is extremely high. Yes, this is true; but on the basis of salt intake levels in the Western world and the average fluid intakes, it is not uncommon that, calculated as the concentration of sodium, the daily fluid intake be hypertonic. Under the chosen study conditions, which, albeit to some extent extreme, indeed do reflect characteristics of nutritional habits; positive sodium balances occurred without any changes in potassium excretion or extracellular volume, which inevitably led to osmotically inactive sodium storage.

Another difference between these studies is the level of potassium intake. Although in our study, we did not balance potassium intake, our test subjects received an intake, independent of body weight, between 50 and 100 mmol/day (meaning 0.65 to 1.3 mmol potassium/kg body weight/day) provided by meals. In the studies by Seeliger (3), potassium intake was 3.5 mmol/kg body weight/day, which was about 3 to 5 times higher than in our study and the recommended intake for humans in Germany (1). This high potassium intake could also have influenced Na^+\text{}/K^+ exchange.

In their experiments, Seeliger et al. (3) went directly from a low salt intake (0.5 mmol/kg body weight/day) to a high salt intake (5.5 mmol/kg body weight/day). A study group with average normal sodium ingestion was apparently not examined. Now, one might speculate that the onset level of sodium intake rather than the total body sodium (TB Sodium) content is important in the regulation of sodium balance because the organism is adapted to a certain level of intake. More precisely, the effect when starting from a low-sodium diet and then switching to an average sodium intake might be different from that of starting from an average sodium intake and then switching to a high-sodium diet. So, it might well be that in the first case, the increase in TB Sodium is compensated by fluid retention, i.e., the undisputed physiological mechanism. This would most likely fit very well with the correlation that Seeliger et al. (3) found in their dogs. However, in the second case, i.e., when starting from an average intake level and then switching to a high-sodium diet, the mechanism might be different, namely, sodium is stored in an osmotically inactive form. Serum sodium levels would increase in both cases, and sodium has to be excreted by the kidney, but the maximum excretion capability of the kidney might have already been reached when being on an average intake level. Then, other

data (2)]. In a second study, potassium excretion (124–134 meq/day) did not vary among males on 24-day sodium intakes of 50, 200, 400, or 550 meq/day [calculated from their Table 2 (2)]. Thus, these results are not consistent with the Seeliger sodium/potassium exchange hypothesis. Instead, they support Heer et al.’s hypothesis of sodium osmotic inactivation and storage.

Additionally, according to the Seeliger hypothesis (3), 1700 meq of sodium must enter the intracellular space for TB Water not to increase. The intracellular volume can be increased at ~31 liters for the Heer et al. (2) 76.8-kg males (assuming TB Water of 0.6 x weight, and intracellular fluid volume of 2/3 of TB Water)(1). Intracellular sodium concentration would therefore be required to increase by 1704/30.7 = 55.5 meq/l, an improbably large number.

Experimental details differ significantly between the Seeliger et al. (3) and Heer et al. (2) experiments. Two points are the most significant. First, Seeliger et al. induced sodium retention in Beagle dogs by several techniques, including stimulating the renin-angiotensin-aldosterone system, and/or administering aldosterone and/or angiotensin. Heer’s human subjects simply increased their dietary sodium intake. Second, daily water intakes were fixed at significantly different levels, 100 ml kg^-1-day^-1 for Seeliger et al.’s dogs vs. 40 ml kg^-1-day^-1 for Heer et al.’s humans. Thus, a 75-kg Heer et al. subject ingested 3 l/day. The same subject on a Seeliger et al. schedule would have ingested 7.5 l/day, and it should be noted, in one feeding period (see Seeliger et al.’s Ref. 3).

The conclusions of both Seeliger et al. (3) and Heer et al. (2) are consistent with their respective studies. Osmotic inactivation of sodium remains a viable hypothesis. The challenge is to characterize the conditions under which ingested sodium is or is not rendered osmotically inactive.

REFERENCES


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REPLY

To the Editor: First of all, I would like to note that I support every single point Dr. Weschler made in her discussion of the two papers (2, 3).

However, I would also like to underline further the differences in study designs between our examinations in humans and Seeliger et al.’s (3) examinations in dogs. As outlined by Weschler, the dogs in Seeliger’s experiments were given food and fluid once a day in the morning between 8:30 and 9:00
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mechanisms have to compensate for the increased serum sodium level. Because there was no intermediate sodium level in the studies by Seeliger et al. (3), this would mean that increasing sodium intake from low to high intake demands activation of both mechanisms: compensation by fluid retention and storage of osmotically inactive sodium. Obviously, total body fluid content and TBSodium must correlate in Seeliger et al.’s (3) studies because total body fluid is retained up to a certain level.

Certainly, additional studies (animal and human) are mandatory to further improve our knowledge of sodium and water metabolism, including the capability to store sodium in an osmotically inactive way.

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REPLY

To the Editor: We appreciate Dr. Weschler’s interest in our paper (2) and gladly take the opportunity to answer the two comments Dr. Weschler gave in her Letter to the Editor.

Answers

First, the question of whether Heer et al.’s (1) results are compatible 1) with osmotically inactive sodium storage, 2) with sodium-potassium exchange, or 3) with a combination of both, can only be answered unequivocally by data on potassium. We do hope that it might be possible for Dr. Heer and her coworkers to provide these crucial data.

Second, we are completely aware that it is inappropriate to directly compare the results of our study with those of Heer et al. (1) for several reasons. The most important reason, as we had already pointed out in our paper (2), is that there are striking species differences between dogs and humans with regard to kinetics of Na⁺ homeostasis and the response to changes in Na⁺ intake.

Explanations

In our studies in freely moving dogs, we induced alterations in total body sodium (TBSodium) that covered the range from moderate deficit to large surplus. These alterations in TBSodium were induced by a variety of methods (10 protocols), not just by changing Na⁺ intake, because it is well known that the effects of changes in Na⁺ intake on TBSodium are usually very small in normal dogs and rats, as opposed to human beings (for references, see Ref. 2). Furthermore, it is important to remark that all data on changes of TBSodium, total body potassium (TBPotassium), and total body water (TBWater) reported in our paper are not only based on excretion data, but on balance data for all three variables, i.e., Na⁺, K⁺, and water. It is most noteworthy in this context that the daily intake of Na⁺, K⁺, and water of our dogs was fixed on a per kilogram body mass basis and controlled for its completeness.

The results obtained are a bit more comprehensive than described in Dr. Weschler’s letter: we did not only report instances where TBSodium increase was accompanied by a TBPotassium decrease. In fact, we found that primary changes in TBSodium were accompanied by changes in TBPotassium in the majority of protocols. Four scenarios were observed: 1) TBSodium increase accompanied by a TBPotassium decrease, 2) TBSodium increase accompanied by a TBPotassium increase, 3) TBSodium decrease accompanied by a TBPotassium increase, and 4) TBSodium decrease accompanied by a TBPotassium decrease. Most remarkably, the sum of changes in TBSodium and TBPotassium was always accompanied by osmotically adequate changes in TBWater, regardless of the degree and direction of changes of TBSodium and TBPotassium. Accordingly, plasma osmolality remained unchanged in all instances.

Thus, our present results corroborate various previous observations (for references, see Ref. 2) indicating that primary changes in TBSodium are very often accompanied by changes in TBPotassium and that osmocontrol effectively adjusts TBWater to the body’s present content of the major cations, Na⁺ and K⁺. This is the reason behind the finding that individual changes in TBWater were a markedly stronger function of simultaneous changes in both TBSodium and TBPotassium (R² = 0.93) than of changes in TBSodium alone (R² = 0.83).

Therefore, we completely agree with Dr. Weschler’s comment that to conclude the Na⁺ of a positive Na⁺ balance has been rendered osmotically inactive requires not only that there be no increase in TBWater or osmolality but also a zero potassium balance. To be more precise, the change in TBSodium plus the change in TBPotassium must exceed the total that can be accounted for by changes in TBWater and osmolality.

The published data of Heer et al.’s study (1) include balance data, i.e., data on intake, extrarenal loss, and urinary excretion for Na⁺ and water. With regard to K⁺, only urinary excretion data were included (given as μeq/min), i.e., the crucial information whether or not K⁺ intake was measured or controlled for was not included. It is also not mentioned whether extra-renal K⁺ loss or its changes with varying Na⁺ intake were assessed. Thus, the comment made in our paper (2) regarding Heer’s study, “The data of Heer’s study in humans that hitherto appeared to demonstrate that osmotically inactive Na⁺ storage is a rapid process, can no longer be regarded as positive proof (sic) for this storage, because K⁺ balances were not assessed.” was well founded.

It would be most fortunate if Dr. Heer and her coworkers could provide these crucial data and thereby answer the question whether increasing Na⁺ intake in her subjects was accompanied by 1) osmotically inactive Na⁺ storage, 2) Na⁺/K⁺ exchange, or 3) a combination hereof.

With regard to compartmental redistributions of Na⁺ and K⁺, our exemplary calculations are also based on the respec-
tive balance data in conjunction with data on plasma Na\(^+\) and K\(^+\) concentrations. These calculations revealed that, at least in four of our protocols (2 with increase in TBSodium and 2 with decrease in TBSodium) primary changes in TBSodium included redistribution of substantial amounts of Na\(^+\) and K\(^+\) between extracellular and cellular space. In each case, an (almost) quantitative, osmotically neutral Na\(^+\)/K\(^+\) exchange between the fluid compartments must have occurred. Because this redistribution was observed even with moderate TBSodium changes and occurred rather rapidly and because Na\(^+\) moved into cells in two protocols and out of cells in two others, we conclude that cells may serve as a readily available Na\(^+\) store. This Na\(^+\) storage would be osmotically active, as osmotical equilibration is achieved by opposite changes in cellular K\(^+\) content.

Considering these results in conjunction with 1) the well-known fact that primary changes in TBPotassium are almost regularly accompanied by compartmental redistribution of Na\(^+\) and K\(^+\) and 2) some early reports that also found that primary changes of TBSodium can be accompanied by such redistributions (for references, see Ref. 2), it appears conceivable that redistributions could also have occurred in Heer’s subjects. However, a quantitative analysis as exemplified in our article’s appendix would require a complete set of data, including data on K\(^+\) balance.

In her second comment, Dr. Weschler implies that we had directly compared our data with those of Heer et al.’s study (1). This is not the case; in fact, we clearly pointed out that major differences of our study and those of Titze et al. (3) and Heer et al. (1) include, but are not limited to, study duration and species differences. As already mentioned in our paper, kinetics of Na\(^+\) homeostasis and the response to changes in Na\(^+\) intake vary considerably among species (for references, see Ref. 2).

Considering a variety of other well-known differences between dogs and humans relevant for Na\(^+\), K\(^+\), and water homeostasis, for instance regarding 1) extrarenal loss via sweat (dogs only have sweat glands on their paws); 2) maximum urine concentrating ability (about twice as high in dogs as in humans); 3) metabolic turnover (basal turnover rate per kilogram body mass is about twice as high in dogs as in humans); 4) strikingly different feeding behavior of carnivores (as dogs are) and human beings with regard to time courses and amounts of food intake, as well as salt and water intake, we would refrain from comparing intake data between these species on a per kilogram body mass basis.

The results of our balance studies (2) clearly indicate that changes in TBSodium are often accompanied by TBPotassium and frequently include osmotically active Na\(^+\)/K\(^+\) redistributions among fluid compartments, whereas we did not observe osmotically inactive Na\(^+\) storage within our 4-day study period in dogs. Thus, with regard to the validity of the notion that, during Na\(^+\) retention, large portions of Na\(^+\) are usually stored in an osmotically inactive form, we would like to repeat the conclusion expressed in our paper (2): “Further studies are needed that address the time course of TBSodium changes, involve different species, and must include measurements of TBPotassium or its changes.”

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