Reply to Dr. Weschler’s *Letter to the Editor*

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

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

2) 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.

In our studies in freely moving dogs, we induced alterations in 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, as 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 (2)). Furthermore, it is important to remark that all data on changes of TBSodium, TBPotassium, and 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 kg BM 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: (a) TBSodium increase accompanied by a TBPotassium decrease, (b) TBSodium increase accompanied by a TBPotassium increase, (c) TBSodium decrease accompanied by a TBPotassium increase, and (d) 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, irrespective 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 (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 ($R^2 = 0.93$), than of changes in TBSodium alone ($R^2 = 0.83$).

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, if extrarenal 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 prove for this storage, because K$^+$ balances were not assessed.” was well founded.

It would be most fortunate, if Dr. Heer and her co-workers could provide these crucial data, and thereby answer the question whether increasing Na$^+$ intake in her subjects was accompanied by (a) osmotically inactive Na$^+$ storage, (b) Na$^+$ / K$^+$ exchange, or (c) a combination hereof.
With regard to compartmental redistributions of Na\(^+\) and K\(^+\), our exemplary calculations are also based upon the respective balance data in conjunction with data on plasma Na\(^+\) and K\(^+\) concentrations. These calculations revealed that, at least in 4 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 2 protocols, and out of cells in 2 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 (i) the well known fact that primary changes in TBPotassium are almost regularly accompanied by compartmental redistribution of Na\(^+\) and K\(^+\), and (ii) some early reports that also found that primary changes of TBSodium can be accompanied by such redistributions (for references see (2)), it appears conceivable that redistributions could also have occurred in Heer’s subjects. However, a quantitative analysis as exemplified in our paper’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. 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 (2)).

Considering a variety of other well known differences between dogs and humans relevant for Na\(^+\), K\(^+\), and water homeostasis, for instance regarding (i) extrarenal loss via sweat (dogs only have sweat glands on their paws), (ii) maximum urine concentrating ability (about twice as high in dogs as in humans), (iii) metabolic turnover (basal turnover rate per kg BM is about...
twice as high in dogs as in humans), (iii) strikingly different feeding behaviour 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 kg BM 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 four 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.”

References

