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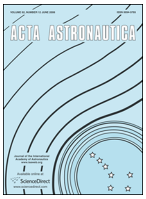

Salt balance: From space experiments to revolutionizing new clinical concepts on earth – A historical review

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For a long time, sodium balance appeared to be a “done deal” and was thought to be well understood. However, experiments in preparation of space missions showed that the concept of osmotic sodium storage and close correlations of sodium with water balance are only part of the regulatory mechanisms of body salt.

By now it has turned out that the human skin is an important storage place and regulator for sodium, that sodium storage involves macrophages which in turn salt-dependently co-regulate blood pressure, that body sodium also strongly influences bone and protein metabolism, and that immune functions are also strongly influenced by sodium. In addition, the aging process appears to lead to increased body sodium storage, which in turn might influence the aging process of the human body.

The current review article summarizes the developments that have led to these revolutionizing new findings and concepts as well as consequences deriving from these findings. Therefore, it is not intended in this article to give a complete literature overview over the whole field but to focus on such key literature and considerations that led to the respective developments.

1. Using microgravity as a tool to cross-examine principles of physiology

There are two major reasons to perform experiments with astronauts in microgravity. For operational reasons it first has to be made sure that astronauts in space remain healthy and able to perform on a high level. Secondly, microgravity provides an excellent tool to cross-examine principles of physiology. If a reaction that is thought to be well-understood occurs differently in microgravity than under 1 g conditions, then usually this is not only a phenomenon observed in space but an observation that tells us that we do not understand the underlying physiology of this reaction in general. Operational questions often lead to such basic scientific questions as operational questions only come up when reactions of astronaut physiology do not coincide with established textbook knowledge.

One example of this overlap between operational needs and the understanding of basic scientific principles is body fluid and salt balance.

Today, astronauts still consume salt and water before landings as described by Bungo et al. in 1985 [1] because microgravity initially leads to a fluid shift towards the head and a decreased body salt and fluid content, while earth gravity leads to a body fluid shift to the lower parts of the body. Thus the fluid return to the heart decreases postflight, while the risk of orthostatic intolerance increases. Due to this link to the orthostatic intolerance problem of astronauts, body salt balance is of high operational relevance. At the same time, the question how the human body handles salt balance in microgravity is also of

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basic scientific value, especially as looking at astronaut salt handling raised more questions than it answered.

2. Preparing an experiment for a space mission: strange results on sodium balance

Initially, the questions to be asked appeared simple. When our group started looking at fluid balance in microgravity, natriuretic peptides were just discovered and we had found that increases in atrial natriuretic peptide in humans also lead to increases in plasma cyclic Guanosine monophosphate (cGMP) levels and in urinary cGMP excretion [2]. So the simple task was to assess whether the headward fluid shift in microgravity would, as a consequence of increased atrial loading, increase atrial natriuretic peptide levels and in consequence increase plasma and urinary cGMP and induce a subsequent natriuresis. This was to be done in microgravity under basic conditions and after a defined isotonic salt load of about two liters within less than 30 min.

Already the first preflight laboratory tests with healthy subjects led to unexpected results. Salt load did not increase plasma atrial natriuretic peptide levels substantially and fluid excretion after a salt load was only slightly increased after the first three hours, while the majority of subsequent fluid and salt excretion occurred much later and showed no correlation with the atrial natriuretic peptide levels [3]. Subsequently, we tested a variety of situations where atrial load increases. In none of these situations was natriuresis directly linked to atrial natriuretic peptide levels and we had to come to the conclusion that atrial natriuretic peptide is not primarily involved in the physiology of natriuresis (e.g., [4,5]). These clear findings are still seldom found in textbooks or medical dictionaries today, probably since the name “atrial natriuretic peptide” is so convincingly suggestive and thus misleading.

3. Conducting experiments under weightlessness: the established concept of the regulation of body sodium balance Is incorrect

After these preparatory studies on ground it was not surprising to also find in studies under weightlessness that atrial natriuretic peptide neither rises during the beginning of weightlessness [6,7] nor after a 2 l salt load after initial adaptation to weightlessness [7]. In addition, we never found increased natriuresis nor increased diuresis during the first day inflight (e.g., [6,7]). These data confirmed our notion that the concept of sodium and fluid regulation is not completely understood. In addition, it was shown by other investigators that central venous pressure in space decreases, and does not, as postulated, increase – despite the headward fluid shift [8–12]. This is in line with a missing rise in atrial natriuretic peptide levels and with no natriuresis during initial weightlessness, but not with increased atrial volumes when the atria are visualized by ultrasound investigations early inflight. Maybe gravity or missing gravity, respectively, plays a role here as gravity on earth will compress the thorax regardless of an upright or supine body position, while missing gravity will not [10]. Results of a subsequent pilot study using the iron lung principle also point to this direction [13].

As fluid excretion did not increase in weightlessness, while there is a clear body mass loss in most astronauts that had been attributed to a fluid loss, we subsequently tested in a metabolic balance study under standardized energy, fluid and salt intake whether there might be a relative increase in fluid excretion in weightlessness. Surprisingly, we found a neutral balance of body water (ingestion and excretion were neutral as expected), while there was a high storage of sodium [14] that could not be explained by textbook knowledge, which states that water and sodium always go in parallel.

As these data were only collected from one astronaut (retrospectively, it appears that we were lucky to have seen this anecdotal observation), we subsequently tested whether this might be an unreproducible phenomenon or whether our experiments in space might have uncovered regulatory mechanisms that are not known and may be important.

4. Studies on healthy volunteers confirm the space data and trigger new concepts of physiology

In a next step, healthy young male subjects were fed under highly-defined conditions with a defined diet containing fixed amounts of fluid and sodium. We found out that indeed there is a dissociation between sodium and water storage on earth too. When subjects are consuming high amounts of sodium, then there is a clear and huge sodium storage without an additional storage of water [15]. Thus, the well-known osmotic mechanism of sodium and water balance is not effective alone during a high salt diet, but an additional sodium storage mechanism is then also activated.

Additional surprising findings, also pointing towards a novel mechanism of non-osmotic salt storage, were also obtained by the group of Kirsch et al. [16] during a space simulation study on ground where healthy subjects spent months under highly-defined conditions in a confined environment. The results of these studies showed that sodium balance is a cyclic process with periods of high net storage and with periods of high net sodium losses that are all independent on body water regulation [16].

5. Animal studies unravel the new mechanism of sodium storage

These findings triggered the question where the non-osmotically stored sodium is located in the body. The group of Titze therefore conducted animal studies to localize sodium storage after a high sodium diet in rats. Surprisingly, they found that the skin is a potent storage location for sodium [17] and stores the sodium in glycosaminoglycans by exchange with protons [17]. In addition, glycosaminoglycan expression is also upregulated [18]. This upregulation is also observed in humans when skin biopsies are obtained after a high sodium diet [19]. Close microscopic examination of rat skin also revealed microscopic changes after a high salt diet in rats. There is a macrophage migration into skin as well as increased