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Short Commentry

Acknowledging Sex Differences in *In vivo* Experiments: Dilemma

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The role of the Autonomic Nervous System (ANS) and its organ-specific functions are largely elucidated. Heart Rate Variability (HRV) analysis is a popular tool for the assessment of autonomic cardiac control. Heart rate and its changes are a sensitive indicator of ANS function, therefore cardiovascular autonomic regulation is considered to be the most reliable indicator of ANS activity and status. HRV refers to beat to beat variation in the heart rate that quantifies the interplay between sympathetic and parasympathetic activity of the ANS. Although patterns of HRV hold considerable promise for clarifying issues in clinical applications, the inappropriate quantification and interpretation of these patterns may obscure critical issues or relationships and may impede rather than foster the development of clinical applications [1].

The aim of this paper is not to do down the excellent and valid results of experimental *in vivo* studies in rats, but to refer to the possibility of improvement of the design of the experiments themselves at the recpect not only sex differences but also chronobiological principles.

At creation or planning the design of *in vivo* experiments, researchers can often meet with several problems. Established and proven methodologies are often used and they are precisely focused on the type of experiment, whereas other factors that may affect and consequently misinterpret the results themselves are not taken into account.

In the predominat majority of experimental studies, only male rats are used, whereas there is also a second sex, in which differences may already exist in the very essence of the monitored functional system and in which can be a different respond to interventions. At the same time, the study of sex differences is a driving force for development and, in many cases, the basis of health and medicine. However, there are opinions that the study of sex differences is ineffective and does not deserve extensive research [2].

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The ANS is an important control system that affects the function of many organs and its activity is affected by various factors as age, gender, lifystyle and by internal processes like circadian rhythm and hormonal fluctuations to slowly rise and fall over the course of 24 hours.

Sex differences are also seen in ANS activity. The rat study of Koresh et al. [3] refers to the fact that during resting conditions, male rats exhibit a significantly higher HR and lower HRV than female rats. This state is not only during the active (dark), but also during the inactive (light) phase of the rat regime day [3].

Further studies from *in vivo* rat experiments confirmed the results of Koresh et al. [3] that there are significant sex differences in HRV and depend on the LD cycle even in conditions of general anesthesia [4]. LD differences with nonsignificantly lower HRV were found in females in the light part compared to the dark part in contrast to males, when the HRV was significantly higher in the light part of the rat regimen day. In terms of sex differences, female HRV was significantly lower compared to males in the light period, while in the dark part of the regimen day it was, on the contrary, significantly higher in females compared to males.

Similarly, sex differences were found in the effect of HRV on HR, where it was found that in females, changes in HR were primarily due to changes in HRV, whereas in males, changes in HRV had no effect on HR in both light parts of rat regimen day. In both light periods, in females, changes in HRV were the result of sympathetic (VLF) and baroreflex (LF) activities and in males, parasympathetic (HF) activity dominated. As the results of these studies show, that not only sex but also the time of conducting experiments also plays an important role [5].

There are several reasons why the female sex is not accepted, but the main reason why females are omitted from the experiments is the same: males and females are biologically different. From other reasons, some scientists consider males to be representative for the human species and differences from male norms are considered atypical or abnormal. Others try to "protect" females from the adverse effects of various interventions [6]. Others generalize findings from males and females regardless of differences, and generally speaking, most scientists use male rats because they do not want to account for hormonal cycles in female rats, which may reduce the homogenity of the studied population and affect the impact of experimental interventions [7].

When acceptance of the inclusion of females into the experiment, two problems arise:

- The sample size is halved - the economic aspect
- The differences increase and thus the ability to detect differences between the experimental and control groups decreases.

One of the reasons why the variance increases is the simple fact that males and females are different and these differences increase the range of variability. But if males and females are mixed, scientists can

find a beneficial effect of the tested drug, which, for example, lowers blood pressure as well in males as in females [2]. On the other hand, at obtaining results from *in vivo* rat experiments, errors in general interpretation may arise from reason of differences related to sex. These sex discrepancies occur not only in behavioral studies [8-10]. There are also differences in drug metabolism and the action of liver enzymes depending on sex [11], in internal environment [12], in the activity of the autonomic nervous system and cardiovascular system [3,4] and most probability also in other functions.

In common practice, experiments are performed during working hours, even after synchronization of rats to the LD cycle (12h:12h). Although this synchronization is described often in the methodologies, the time, when the experiments were performed, is not mentioned. Therefore, we assume that the experiments are performed during the day (ie during the light) and thus on the "sleeping" rats, in their inactive period of the regime day. But the question is, what are the reactions of animals in their active period if there are fluctuations in the functions of single systems in both sexes? Is the status alternatively reactivity of the system different, or is there a uniform reaction in both sexes? But, if sex differences in the results of various experimental studies are documented, so it is necessary to respect this fact. Future studies should decode these questions and try to include females in the experiment, if it is possible.

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