Sex and gender-related issues in biomedical science

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Introduction

“Gender” is a term commonly encountered in the media these days, but it seems that many people are not familiar with the exact difference between sex and gender. “Sex” refers to the biological classification of humans based on their reproductive systems and functions derived from chromosomal type or hormones, while “gender” denotes cultural attitudes and behaviors associated with stereotypical attitudes regarding a person’s sex that shape our conceptions of masculinity and femininity [1,2]. I was also unfamiliar with this terminological distinction and was introduced to the importance of sex and gender-related issues in science at a meeting of the Korean Federation of Women’s Science & Technology Associations in 2014. The Korean Federation of Women’s Science & Technology Associations introduced the concept of gendered innovations to Korea and has been making efforts to spread awareness of these issues in all fields of science, including engineering, architecture, and biomedical science. As part of this effort, the Center for Gendered Innovations in Science and Technology Research was launched in February 2016.

In the biomedical field, the main sex and gender-related issues are the lack of gender-based analyses in clinical research and not using both sexes in animal experiments. Because doctors who treat patients know empirically that various diseases, such as irritable bowel syndrome, show a different clinical course in men and women, I readily accepted this concept and realized its importance. The problem of gender imbalance in clinical research has long been recognized; in fact, as early as 1993, the National Institutes of Health (NIH) enacted a policy ensuring that women and minorities are included in all human research and that an adequate number of participants are recruited to analyze gender differences in phase III clinical trials [3]. However, preclinical animal research is still mainly performed on male animals. Sometimes researchers do not perform sex-based analyses in experiments using both sexes, or even do not mention the sex of the experimental animals in the manuscript [4].

Personal Experiences with Sex-related Issues in Preclinical Studies

I am a gastroenterologist, but as a clinician with experience in basic experimental research and

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Fig. 1. (A) Species and sex distribution (%) of experimental animals in preclinical research published in the *Journal of Neurogastroenterology and Motility* from 1994 to 2016. (B) Comparison of the sex distribution (%) of experimental animals between the domestic (1994 to 2009) and international (2010 to 2016) periods of this journal.

a section editor of basic research for the *Journal of Neurogastroenterology and Motility* (JNM), I have become particularly interested in sex bias in preclinical research. When I first started exploring sex- and gender-related issues, I and Professor Moon Young Lee, of the Department of Physiology of my university, had coincidentally just completed an experiment investigating the effects of a high-fat diet and stress on inflammation and colonic motility using both male and female rats. Surprisingly, we found that a high-fat diet and stress induced very different effects according to sex. We presented this result at the Gender Summit 2015 in Seoul and had a chance to discuss it with foreign experts [5]. I then wondered about the distribution of the sex of the animals in the basic experiments published in JNM. JNM was a Korean domestic journal published from 1994 to 2009 and became an international journal in January 2010 as a joint official journal of several Asian neurogastroenterology societies. As expected, most studies used male animals and some did not report the sex of the animals at all [6]. Moreover, these problems were not resolved even after JNM became an international journal, which means that foreign researchers, as well as Korean researchers, did not pay attention to the sex of experimental animals (Fig. 1) [7].

Guidelines for Sex and Gender Equity in Western Journals and Funding Agencies

As I became more familiar with gender issues, I learned that guidelines for sex balance in animal testing have been already introduced, starting several years ago, by journals, funding agencies, and other biomedical science organizations, including the International Committee of Medical Journal Editors (ICMJE). The ICMJE presented “Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals” and it has been updated through 2017

[8]. These guidelines emphasized that the terms “sex” and “gender” should be used correctly according to the aim of the study, and that appropriate-gender participants should be obtained at the study planning stage. In addition, authors should report the sex and/or gender of study participants, the sex of animals, and the sex of origin of in vitro cell lines, primary cells, and stem cells. Additionally, if the study was performed in only 1 sex, authors should explain the reason. The most important statement of the ICMJE guidelines is that analyses according to sex and gender should be performed routinely. Other guidelines, such as the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines, also contain a statement regarding the importance of reporting the sex of animals used [9].

However, there are many obstacles to performing sex-related analysis in all animal experiments. The biggest problem is that researchers may avoid using both sexes in their experiments due to the additional costs and complexity of the design. To solve this problem, it is necessary for funding agencies to actively provide additional financial support for using both sexes, and at the same time, the journals that publish the studies should show an interest in sex- and gender-related issues and present their own guidelines. These 2 strategies have already been implemented by Western scientific societies. Major funding agencies, including the NIH, the Canadian Institutes of Health Research, and the European Commission, have presented guidelines for gender equity; in particular, the NIH has officially encouraged researchers to consider sex as a biological variable in NIH-funded research, and researchers should explain “how relevant biological variables, such as sex, are factored into research designs and analyses for studies in vertebrate animals and humans” when they submit research grant applications, since 2015 [10].

In addition to funding policies, the NIH held a joint work-

shop in June 2014 with over 30 basic and preclinical journals, including *Nature* and *Science*, to discuss principles and guidelines for reporting preclinical research in the biomedical field in a manner that facilitates reproducibility, rigor, transparency, and independent verification of the scientific experiments [11]. They recommended describing biological materials with sufficient information, including the source, species, sex, age, husbandry, inbred status, and strain of animals, and these recommendations are reflected in many Western journals [12]. There is no doubt that journals and their editors play a crucial role as funding agencies in enabling researchers to realize that sex- and gender-based analyses are important and must be carried out.

Current Status in Biomedical Science in Korea: Taking the First Step

What about the situation in Korea? Unfortunately, most researchers, reviewers, and editors in Korea seem to be unaware of the importance of sex bias in preclinical research. Alternately, some of them may already be aware of these issues, but they may not be able to act accordingly due to various restrictions. I was a representative example of the former category. Despite having done experiments on sex-related effects in rats, I was embarrassed that the difference between the sexes seemed to be too great. Only after learning about sex bias issues in animal experiments, I was able to properly interpret these results and realized that the differences were probably natural. Nonetheless, I did not think that I should include sex bias issues in the authors' guidelines of JNM until I learned that major journals in the West had guidelines for reporting sex/gender differences. Perhaps many researchers and members of the editorial boards of journals in Korea and other Asian countries are in a similar situation.

Fortunately, a meaningful forum about how to apply gendered innovations in biomedical journals in Korea, organized by the Korean Federation of Science and Technology Societies and Center for Gendered Innovations in Science and Technology Research, was held in November 2017. I presented to editors of several Korean journals on the sex and gender-related guidelines of leading Western biomedical journals and then they discussed the current situation of Korean journals and how to implement such guidelines. I expect that gendered innovations will take place soon in Korean journals. Journals from Asia, including Korea, are growing rapidly, but it is time for qualitative growth to be more important than quantitative growth in the future [13]. In this regard, addressing sex and gender issues will be an important factor in improving the quality of journals in terms of reproducibility, rigor, and transparency. However, not only should journals implement chang-

es, but institutes that manage research grants should also pay attention to these issues and reflect them in their budgets so that actual gendered innovation can happen in biomedical science in Korea. In addition, universities, which employ most biomedical researchers, should educate their students about sex- and gender-related issues [14]. Finally, it is important to note that sex- and gender-related issues in biomedical science in Korea have been raised externally, not by biomedical experts themselves. In order to make the suitable improvements, researchers and editors in biomedical science, based on their expertise, should play a leading role in addressing this issue through research and journal policies.

Conclusion

Sex and gender issues are very important, especially in biomedical science and research. We should remember that not paying attention to this issue could result in harming human health. Moreover, we may lose the opportunity to make new discoveries and chances to cure disease. At this point, when members of Korean biomedical societies, including researchers and the editorial boards of journals, are beginning to recognize the importance of sex- and gender-related issues, a relevant quote from Leonardo da Vinci comes to mind. "I have been impressed with the urgency of doing. Knowing is not enough; we must apply. Being willing is not enough; we must do."

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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