of KiSS1/GPR54 signaling is also an early key event in serial, late-occurring reproductive dysfunctions in the delayed effect. Recently, our laboratory also identified that the rat neonatally exposed to various dose of EE showed the decreased FSH levels at PND14 and decreased ERα expression in the uterine epithelium at 10 weeks of age [44]. These early stage functional changes in the kisspeptin neuron, hormone balance and reproductive tissues might have the possibility to be the useful indicator for the delayed effects substitute for the abnormal estrous cycle occurred in later age, and may provide a new clue for the further investigation and risk identification of the delayed effect induced by the estrogenic chemicals like EDCs.

Interestingly, several investigations that focused on the perinatal development of kisspeptin neurons have revealed that KiSS1 mRNA-positive cells in the AVPV are first detected at PND 12 and that kisspeptin-expressing neurons progressively increase approximately from PND 25–35 until puberty onset in the mouse brain [26,45]. These results have provoked controversy over the question of what the direct target of the neonatal exposure to xenobiotic compounds in the delayed effect may be. Thus, the underlying target of estrogen exposure in the neonatal period that induces the delayed effect needs to be further elucidated.

5. Conclusion

In conclusion, we found attenuation and a delayed peak in the LH surge and depression of KiSS1 mRNA expression in the AVPV in both neonatal EE-exposed and middle-aged rats. These AVPV-specific changes indicate the disruption of the LH surge center that consequently may cause the early onset of abnormal estrous cycling in the delayed effect. Since these changes were observed in both of delayed effect and aging animals, the delayed effect may be relevant to reproductive aging. Furthermore, in light of the earlier occurrence of hypothalamic and hormonal changes than in abnormal estrous cycling, attenuation of the LH surge and KiSS1 mRNA expression have the possibility of being early stage toxicological indicators of the delayed effect, may provide the new clue for the risk assessment of estrogenic chemicals like EDCs.

Conflict of interest

The first author is an employee of Mochida Pharmaceutical Co., Ltd., but there is no conflict of interest to be declared for this publication. The company and funding organizations do not have control over the resulting publication.

Transparency document

The Transparency document associated with this article can be found in the online version.

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