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Editorial

The role of red blood cells in cardiovascular disease

Many chronic illnesses show a sex difference, not only in the incidence but also in the severity of these diseases. For example, women, especially before menopause, have a significantly lower risk of cardiovascular disease (CVD) and chronic kidney disease than men.[1] However, to date, there is uncertainty as to why sex differences influence physiological, pathological, and pathophysiological changes, partly because these chronic illnesses are complex diseases of multifactorial origin.[2] In addition, an interaction between each other might slow down or accelerate the processes of these diseases. Among these factors, sex hormones are considered of critical importance. Therefore, attention recently has been focused on understanding the features of sex hormones relevant to the physiological, pathological, and pathophysiological features of various kinds of systems, including Taskin et al's[3] study in this issue.

Evidence has shown that oral contraceptives (OCs) might induce extremely rare CVD and venous thromboembolism in young healthy women, however, the risk of CVD was dramatically and significantly increased in smoking and/or older women (≥35 years).[4] Although the underlying mechanism of the increased risk in smoking and/or older women is unknown, it might involve female sex hormones and smoking, and their interaction, which affect the metabolism and possibly impair homeostasis of coagulation.[4]

The carbonic anhydrase (CA) enzymes play an important role in CO_2 influx and efflux by red blood cells.[5] The reason for briefly considering the history of modeling CO_2/HCO_3^- equilibrium under physiological conditions is that the effects of CA enzymes, by their nature, depend on time and space.[5] This CO_2/HCO_3^- buffer system is critical to maintain cellular function, because it regulates intracellular pH, which is also important for metabolism and homeostasis.[6] However, the term *metabolon* should be introduced, because CA enzymes work as a metabolon. A metabolon is described as a complex of enzyme systems that catalyze a series of reactions in a metabolic pathway.[5] A product of one enzyme is a substrate of the next; therefore, the *channeling* of intermediates increases their effective concentrations, permitting the overall process to proceed with a much higher efficiency than if the enzymes were spatially dispersed.[5] In addition, mammalian cells express 16 isoforms of CA, found in the cytosol (CAI, CAII, CAIII, CAVII, CAXIII), membrane-associated (CAIV, CAIX, CAXII, CAXIV, CAXV), in the mitochondria (CAV), and secreted into saliva and milk (CAVI).[6]

We do not know the rationale of Taskin et al's[3] study, because we wonder why they studied CA enzymes activity of red blood cells (RBC) in women with/without smoking. Taskin et al[3] found that smoking might significantly increase CAI and CAII enzyme activity of RBC, and female sex hormones had a strongly inhibitory effect on CA enzyme activity; and this inhibitory effect was much more apparent in smoking women. However, the authors also found that the inhibitory effect of female sex hormones on CA enzyme activity was varied by different types of female sex hormones and this inhibitory effect of female sex hormones was also varied by different subtypes of CA enzymes. This study is interesting, because it explains why some kinds of OCs contributed to a higher risk of CVD, even in those women who believed that they were not contraindicated to receive OC treatment. In addition, the risk of CVD was dramatically increased in smoking women, and even when these women used the *comparatively* safe OCs. However, is it true that CA enzyme activity involves the risk of CVD? More evidence might be needed. One report published in 2007, showed that CA might be mediated by the hypertrophic response of cardiac myocytes to phenylephrine, suggesting that CA inhibition may represent an effective therapeutic approach toward mitigation of the hypertrophic phenotype.[7] If female sex hormones function as CA inhibitors, and CA inhibitions in the RBC contribute to a lower risk of CVD, such as cardiac hypertrophy, this may well explain why women, especially before menopause, have a significantly lower risk of CVD. These premenopausal women indeed have higher levels of female sex hormones than age-matched men,[8] suggesting that these endogenous female sex hormones which are beneficial in protection against the occurrence of CVD, may be significantly mediated by decreasing CA enzyme activity of RBC. In addition, smoking can elevate CA enzyme activity of RBC in these women significantly. It provides an acceptable answer to respond to why smoking has a significantly higher risk of CVD. By contrast, Taskin et al's[3] study showed that exogenous and supraphysiologically high levels of female sex hormones used in younger women and the effects of these female sex hormones still function as CA enzyme inhibitors. Moreover, CA enzyme inhibition was female sex hormone dose dependent. Why does the CVD risk

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paradoxically increase in these younger women? This result makes the audience confused about the role of CA enzyme activity of RBC in the risk of CVD. Is it a hero or villain?

In conclusion, CVD is a complex disease, and it is difficult to use a limited number of factors to explain its complicated features. However, we still believe that this article provided by Taskin et al[3] is of value, because RBC (containing CA enzyme) might be a potential target in place of platelets for the prevention of CVD, if Taskin et al's[3] findings could be further and clearly explored.

Conflicts of interest

The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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