mitochondrial membrane in the presynaptic terminal of monoamine projection neurons and in astrocytes, where they are positioned to regulate the amount of intracellular substrate available for release and the degree of monoamine inactivation [53]. While MAOB primarily metabolized dopamine, MAOA also metabolizes serotonin and norepinephrine. Therefore, genetic variation in the MAOA gene may cause disruption at serotonergic synapses. Although Brunner syndrome is rare, many common polymorphic variants have been identified in the MAOA gene region. Among them, a variable number of tandem repeat (VNTR) polymorphisms located in the promoter region of the gene have been the most widely studied. The MAOA upstream VNTR comprises a 30-bp sequence that is repeated 2, 3, 3.5, 4, or 5 times [55]. Higher expression linked to 3.5 or 4 repeats is referred to as MAOA-H, and is related to normal enzymatic activity, while 3 repeats or less are referred to as MAOA-L and is associated with reduced MAOA activity [56].

A wealth of evidence in animal research suggests that MAOA is an important biological regulator of aggressive behavior. MAOA knockout mice exhibited frequent reactive aggression [57]. Serotonin concentration was increased up to nine times in the brains of isolated transgenic mice in which transgene integration caused a deletion of the gene encoding MAOA [58]. Additionally, MAOA knockout mice lack the characteristic barrel-like clustering of layer IV neurons in the primary somatosensory cortex [59]. It is likely that some change in serotonin function occurs in the MAOA gene-deficient mice [46]. Intriguingly, with early administration of a serotonin-synthesis inhibitor, the mice restored the formation [59]. This result suggests that the impact of genetic risk might be mitigated during critical periods in youth and early adolescence [53]. This lends credence to the importance of gene-environment interactions in modulating aggressive behavior, and shows the potential benefits of early intervention for at-risk subjects.

The MAOA-L gene has been linked to aggressive behavior in humans [60]. A meta-analysis showed that MAOA-L was significantly associated with antisocial behaviors [61]. The importance of MAOA genetic variation in determining aggressive behavior is consistent with the fact that most violent criminals are male. Because the MAOA gene is linked to the X chromosome, men only need one copy of the MAOA-L gene to be affected, while women are affected only if both alleles contain the abnormal MAOA gene [60]. The relationship between MAOA gene variations and aggression in women is still controversial [62].

Few studies investigating the MAOA gene definitively distinguish reactive aggression from proactive aggression [63]. Evidence suggests MAOA-L is associated with aggressive reactions in highly provocative situations [63, 64]. In contrast, no evidence decisively indicates that proactive aggression is dominant in subjects with MAOA-L. MAOA gene variation may therefore be associated with impulsivity rather than antisocial behavior itself.

Supporting evidence comes from investigating what happens in brains of male carriers of the MAOA-L gene. The subjects showed a pattern of enhanced AMG activation and lower cortical volume [65, 66]. Dorsal anterior cingulate cortex, which is associated with rejection-related distress, is activated in MAOA-L individuals [67, 68]. It is highly likely that this imbalance within the corticolimbic circuit is the cause of disrupted emotion regulation. Recently, the interaction between the MAOA gene and the environment has become a hot topic. Maltreated children with an MAOA-L genotype were more likely to develop antisocial behavior [69] than those who were not maltreated. This finding was replicated by several studies [70] and substantiated by two meta-analyses [71, 72]. Successful visualization of altered brain structure and function in maltreated children with MAOA-L should be the next step in studying this issue, as well as assessing interventions that might reduce their risk of developing aggressive tendencies [67].

Conclusion

Reactive aggression has been attracting attention of many professionals in not only forensic science and criminal justice, but behavioral biology. Among recent studies, the results regarding the MAOA gene and gene-environment relationship greatlycontributed to the deep understanding of this antisocial, but originally functional phenomenon. In the near future, it is expected to apply these findings to the treatment setting. For example, children identified as high-risk may be educationally intervened in the early stage so that subsequent aggressive behaviors would be prevented. On the other hand, the clarification of the biological basis of reactive aggression is possible to visualize the effect of behavioral therapy, leading to further development of the psychological interventional technique. Collaboration of professionals with several backgrounds can reduce the victims of violence through utilizing the scientific research.

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