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Rett Syndrome: Translate Medicine from Brain to Heart

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Abstract

Rett syndrome (RTT) is a neurodevelopmental disorder typically caused by mutations in *methyl-CpG–binding protein 2 (MECP2)*. 26% of deaths in RTT are sudden and of unknown cause. A recent study found prolongation of the corrected QT interval (QTc), a risk factor for unstable fatal cardiac rhythm, in both RTT patients and animal models. It further demonstrated that cardiac abnormalities in RTT are secondary to abnormal nervous system control, which leads to increased persistent sodium current, suggesting that treatment of RTT would be more effective if it can target the increased persistent sodium current to prevent lethal cardiac arrhythmias. This surprising finding of brain to heart connection will have profound implications for therapies of neurological diseases which are in the situation similar to RTT.

Rett syndrome (RTT) is a X-linked neurodevelopmental disorder that affects approximately 1 in 10,000 live female births and is characterized by delayed-onset loss of spoken language, loss of hand use, problems with ambulation, and the development of distinctive hand stereotypes [1-12]. RTT is typically caused by mutations in *methyl-CpG–binding protein 2 (MECP2)* [1,2,5,8-10,13,14], a gene encoding a protein involved in regulation of gene expression [3,13,15,16]. In addition to the cognitive and motor abnormalities, RTT patients also show autonomic dysfunction, with breathing and heart rate irregularities [17-20]. Boys with mutations in *MECP2* show more severe autonomic dysfunction, with marked breathing and heart rate abnormalities that usually result in death within the first year of life [21]. RTT patients have a high incidence of sudden unexpected deaths (26% of all deaths) [22], which are probably of cardiac origin. Previous studies have shown that some RTT patients have prolonged QT intervals (LQT) on electrocardiograms (ECGs) [23]. In patients with other diseases, LQT is a significant risk factor for sudden arrhythmic cardiac death [24]. However, so far the causes for LQT in RTT and its contribution to the high proportion of sudden death are still unknown. As reported recently in *Science Translational Medicine*, McCauley et al. [25] tested the hypothesis that these sudden deaths in RTT patients may be due to cardiac dysfunction.

In most cases, inherited LQT are caused by mutations in the voltage-gated potassium channels *KVLQT1* (LQT1) and *HERG* (LQT2) and in the voltage-gated sodium channel *SCN5A* (LQT3) [26-29]. Rare mutations in genes encoding other channel subunits and other cardiac proteins such as caveolin-3 [30], may also contribute to some cases of inherited LQT. Since RTT patients have *MeCP2* dysfunction, which causes the LQT phenotype, McCauley et al. [25] aimed at understanding whether (I) *MeCP2* dysfunction in mice can recapitulate the long QT phenotype and cause predisposition to arrhythmic-induced death after programmed electrical stimulation (PES); (II) neuronal tissue specific *MeCP2* dysfunction is sufficient to reproduce the LQT phenotype; and (III) alterations in the sodium current contribute to the LQT phenotype in this mouse model of RTT.

Firstly, McCauley et al. [25] examined ECGs in 379 female patients with typical RTT to define the prevalence of electrophysiological abnormalities in RTT. The authors found that 18.5% of these patients had long corrected QT interval (QTc), consistent with previous reports [23,31,32]. They thought that these 18.5% of affected individuals are likely at risk for sudden death since 26% of deaths in RTT are sudden and unexpected [24]. The authors then tried to identify electrophysiological abnormalities in mouse models of RTT. They found that hemizygous male *Mecp2*$^{Null/Y}$ mice have severe early-onset LQT and QRS prolongation, and heterozygous female *Mecp2*^{Null}/+ show prolongation of both parameters that becomes apparent at older ages. These data indicate that Long QTc, which is common in people with RTT, can be reproduced in the animal model of RTT.

Secondly, McCauley et al. [25] further tested whether these RTT mice are more susceptible to developing ventricular arrhythmias since there is the association between LQT and development of ventricular arrhythmias. The authors electrically stimulated the heart using PES to determine susceptibility toward cardiac arrhythmias. They found that male *Mecp2*$^{Null/Y}$ mice developed sustained ventricular tachycardia (VT) more often than did wild-type mice immediately after ventricular stimulation. The duration of any arrhythmia episodes was significantly longer in *Mecp2*$^{Null/Y}$ mice than in wild-type mice. The authors also noticed that only older female *Mecp2*$^{Null/+}$ mouse showed PES-induced ventricular arrhythmias, which is similar to the age-dependent nature of LQT in female *Mecp2*$^{Null/+}$ mice. Noteworthily, 29% (two of seven mice) of female *Mecp2*$^{Null/+}$ mice died of VT during ventricular stimulation, suggesting that older female *Mecp2*$^{Null/+}$ with LQT are at risk for arrhythmia-induced death. These data indicate that RTT mice do show increased susceptibility to induced ventricular tachycardia.

Thirdly, McCauley et al. [25] investigated whether loss of *MeCP2* function within the nervous system could result in LQT and increased susceptibility to ventricular arrhythmias, since loss of *MeCP2* function only in the nervous system was found to reproduce all the phenotypes of animals lacking *MeCP2* in all tissues, including premature death [33]. The authors generated a nervous system–specific conditional knockout (NKO) using the Nestin-Cre/loxP system, which restricts knockout of *MeCP2* to the nervous system [34,35]. In these NKO mice, *Mecp2* mRNA expression was absent in the brain in, but was unaffected in the heart. Their findings actually confirmed that neuronal deficiency of

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Mecp2 is sufficient to cause both LQT and pacing-induced arrhythmias and arrhythmia-induced death.

Fourthly, McCauley et al. [25] evaluated the effectiveness of different treatments and tried to find out the right medication for preventing arrhythmias in RTT, since current strategies to prevent sudden arrhythmic events in RTT are just empirical due to lack of knowledge of the exact etiology of LQT in RTT. The authors found that β-adrenergic receptor blocker (propranolol), which is currently a standard therapy to prevent arrhythmias in RTT, is actually not effective for the treatment of QT prolongation and arrhythmias in RTT mice. Since β-Adrenergic receptor blockers, are efficacious primarily in LQT1 and LQT2 syndromes, which are ascribed to potassium channelopathies, but not effective in primary sodium channelopathies such as LQT3 or Brugada syndrome [36], it is likely that LQT phenotype in RTT is caused by alteration in the voltage-gated sodium channel current. To test this, the authors performed patch clamping in isolated ventricular myocytes to measure the voltage-gated sodium channel current from male $Mecp2^{Null/Y}$ mice. They found that measurements of persistent sodium channel current (INa) showed a larger INa in $Mecp2^{Null/Y}$ mice versus wild-type. Isolated ventricular myocytes from NKO animals also showed an increased persistent I_{Na}. Since the β-adrenergic receptor blocker propranolol could not alter either QTc interval or arrhythmia incidence in $Mecp2^{Null/Y}$ mice, and a persistent late I_{Na} current existed in $Mecp2^{Null/Y}$ mice, the authors then evaluated the potential therapeutic effect of phenytoin (PHT), which blocks the persistent late I_{Na} and thus prevents cardiac arrhythmias and neurological epileptic seizures, in RTT mice. They found that PHT could reverse persistent late I_{Na} and completely abolished ventricular arrhythmias in $Mecp2^{Null/Y}$ mice. These data indicate that alteration in sodium current underlies LQT and the susceptibility to ventricular arrhythmia, and that PHT or drugs with similar pharmacology may reduce arrhythmia risk in RTT patients.

Thus, McCauley et al. [25] systemically determined LQT and the susceptibility to VT and sudden cardiac death in RTT. Their study eventually unveiled mechanisms underlying the lethal cardiac arrhythmias in RTT. A surprising finding in this study is that the cardiac arrhythmias present in the animals are the result of changes in *MeCP2* function within the nervous system. This was really unexpected because LQT usually reflects alteration in the repolarization property of cardiomyocytes themselves, and idiopathic LQT are directly resulted from mutations in genes that encode proteins within the cardiomyocytes that control the electrical properties of those cells. However, electrical properties of cardiomyocytes from both $Mecp2^{Null/Y}$ and NKO animals were indeed changed. It is reasonable that the alteration in the electrical properties in the cardiomyocytes is a response to alterations in the nervous system control of the heart. This study reveals a brain to heart connection which may have farreaching implication for therapies of RTT and other neurological disorders.

It has been known that neurological dysfunction could affect the control of cardiac rate and rhythm. Previous studies showed that repetitive seizures can induce remodeling of the potassium and sodium channels within the heart, leading to QTc prolongation and cardiac arrhythmias [37], and that autonomic neuropathies can prolong QTc interval in patients with primary central nervous system disease [38-42], autonomic neuropathy [43,44], and amyotrophic lateral sclerosis [45]. The exact mechanism by which altered nervous system control leads to cardiac arrhythmias in these cases is unknown. It has been suspected that sympathovagal imbalance in people with RTT may contribute to sudden cardiac death [23,46]. RTT patients often have recurrent seizures [47], and a similar situation may occur in patients with other neurogenetic disorders, such as fragile syndrome [48-50], Angelman syndrome [51-53] and Prader-Willi syndrome [54,55]. The authors hypothesized that nervous system abnormalities cause remodeling of the heart in RTT patients, including elevation of persistent sodium current, and suggested that sodium channel blockers, such as phenytoin, be tested as therapeutic agents.

In the 12 years since the identification of *MECP2* as the causal gene for RTT, progresses towards an understanding of the mechanisms behind RTT have been swift [3,5,56-64], with recent efforts at pharmaceutical interventions being particularly noteworthy [65-68]. But McCauley and colleagues' observation of the brain to heart connection in RTT is a reminder that we still have much to learn about this disorder at the systems levels. Given the similar situation in many other neurological disorders, the significance of this connection between brain and heart will definitely transcend the exact nature of RTT itself.

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