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·Minireview·

Fragile X syndrome and epilepsy

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Abstract: Fragile X syndrome (FXS) is one of the most prevalent mental retardations. It is mainly caused by the loss of fragile X mental retardation protein (FMRP). FMRP is an RNA binding protein and can regulate the translation of its binding RNA, thus regulate several signaling pathways. Many FXS patients show high susceptibility to epilepsy. Epilepsy is a chronic neurological disorder which is characterized by the recurrent appearance of spontaneous seizures due to neuronal hyperactivity in the brain. Both the abnormal activation of several signaling pathway and morphological abnormality that are caused by the loss of FMRP can lead to a high susceptibility to epilepsy. Combining with the research progresses on both FXS and epilepsy, we outlined the possible mechanisms of high susceptibility to epilepsy in FXS and tried to give a prospect on the future research on the mechanism of epilepsy that happened in other mental retardations.

Keywords: epilepsy; fragile X mental retardation protein; metabotropic glutamate receptor; γ-aminobutyric acid; dendritic spines

1 Introduction

Fragile X syndrome (FXS), one of the most common genetic diseases, is an X-linked mental retardation with a conservative prevalence of 1 in 4000 males and 1 in 8000 females. The main symptoms of FXS include facial abnormality, macroorchidism, mental retardation and high susceptibility to epilepsy, and so on. As one of the most common symptoms of FXS, epilepsy has stepped into the highlight of research recent years. Epileptic seizure is a disorder of recurrent, spontaneous episodes of aberrant synchronization in neural networks, which has a prevalence of 1%. Seizures occur in 22% of fragile X patients[1]. The occurrence of epilepsy has brought a great of pain to the patients and their families. However, there is still no appropriate therapy to cure it. Here, we try to give a review on the mechanism of high susceptibility to epilepsy in FXS based on both our own researches and some of the recent works done by others on this topic.

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2 Fragile X syndrome

Studies on FXS in the late 1970s and 1980s led to the current clinical picture of FXS. The primary attributes of an affected male are moderate to severe mental retardation[2], macroorchidism[3], and a connective tissue dysplasia leading to a characteristic yet mild physical appearance of a long, narrow face and large ears[4]. Other clinical signs, presumably due to the connective tissue disorder, include velvet-like skin, finger-joint hyperextensibility, and aortic root dilatation. Patients often display autistic features ranging from shyness, poor eye contact, and social anxiety in less affected individuals to hyperactivity, hand flapping, hand biting, and perserverative speech in the severely affected[5]. Additionally, epilepsy is reported to occur in 20% to 25% of individuals with FXS and paroxysmal EEG abnormalities are present in about 50% of prepubescent boys with FXS[6,7].

FXS is a disease caused by unstable trinucleotide expansion in the 5' regulatory sequence of the gene *Fmr1*, causing hypermethylation and subsequent transcriptional silencing of *Fmr1*. FXS can also arise from point mutations or deletions in coding sequence, demonstrating that loss of function is causative. The protein encoded by *Fmr1*, the fragile X mental retardation protein (FMRP), associates with FXR1P, FXR2P and other proteins and mRNAs to form a messenger ribonucleoprotein (mRNP)[8]. In general, the N-terminal a third of FMRP interacts with proteins, whereas the C-terminal two-thirds of FMRP binds to RNA. FMRP contains nuclear localization signals (NLS) and nuclear export signals (NES) and four putative RNA-binding motifs: an N-terminal domain (NDF), two K homology domains (KH1 and KH2) and an RGG box (a cluster of arginine and glycine residues)[9]. In mammals, FMRP function is regulated by phosphorylation at three conserved serine sites. This phosphorylation is associated with stalled polyribosomes and, so, is believed to modulate translation regulation of target mRNAs. At steady state, FMRP is predominantly localized in the cytoplasm, associated with translating polyribosomes in many types of cells and function as a translational suppressor[10,11]. Through interactions with Kinesin, FMRP is able to travel between distal neurites and the soma of neurons and thereby regulate protein synthesis locally within specific cellular compartments[12].

3 Epilepsy

Epilepsy is a chronic neurological disorder, with a prevalence of about 1%, which is characterized by the recurrent appearance of spontaneous seizures due to neuronal hyperactivity in the brain. Epilepsy is not a single disorder but a group of disorders. In approximately 30% of cases, epilepsy is caused by such events as head trauma, tumor, stroke, or infection. In those cases for which there are unknown causes, recent evidence suggests there may be genetic predisposition to developing the disease.

In general, epileptic seizure can remain local, spread to other sites, or engage all cortical regions simultaneously. Cortical or hippocampal circuits are always activated during an epileptic seizure; synaptically linked downstream regions are recruited in ways that serve to amplify or limit the discharge in time and space[13]. A number of factors can be involved into the mechanisms of epileptogenesis. It can be produced by an imbalance between neuronal excitation and inhibition, where glutamate and γ-aminobutyric acid (GABA), respectively, play important roles. Furthermore, chronic experimental models of epilepsy and the phenomenon of kindling have provided abundant evidence that neural circuits undergo long-term progressive structural and functional alterations in response to seizures which maybe in turn leads to further epileptogenesis[14,15]. There is also considerable effort directed to the molecular changes that occur during epileptogenesis. Unfortunately, it will probably still be the case that many of these changes are simply correlates with the epileptic state but have no causal relationship to it. To work out the critical mechanisms underlying the development of the epileptic state, key findings needs to be explored from unexpected sources.

4 Pathogenesis of epilepsy susceptibility in FXS

A frequent seizure/EEG pattern in FXS appears to resemble that of benign focal epilepsy of childhood (BFEC). However, in the *Fmr*1 knockout mice, the susceptibility to seizures appears age dependent, with older mice showing a higher susceptibility.

Hyperactivity of fragile X mice to auditory stimulus was indicated in the prepulse inhibition paradigm. A moderately intense prepulse tone, that can suppress startle response to a strong auditory stimulus, elicited a significantly stronger effect in fragile X mice than in control mice. Moreover, sensory hyperactivity of fragile X mice was demonstrated by a high seizure susceptibility to auditory stimulation. However, three different chemical convulsants (kainic acid, bicuculline and pentylenetetrazole) elicited similar effects in fragile X mice and wild-type mice[16]. So, whether or not the loss of FMRP can directly lead to a high susceptibility to epilepsy, and what is the causal trigger is still unknown. These questions have stepped into the spotlight of researchers. Here we try to clear out some clues from the function of FMRP and its link to epileptogenesis pathology.

4.1 Altered expression of FMRP's target mRNAs may exert a pro-effect on epileptogenesis FMRP acts at several points in RNA metabolism and has been recently shown to associate with components of the RNA interference pathway. Microarray studies suggest that FMRP has hundreds of putative RNA targets (432 in mouse)[12] and a mass of protein interactors. However, only a handful of the encoded pro-

teins have been demonstrated to be regulated *in vivo*, including the myelin basic protein[17,18], cytoskeletal proteins Arc/Arg3.1 and MAP1B[19], and the kinase α-CaMKII. R*ac1* mRNA is also a dFMRP target, while Rac1 protein cooperates with dFMRP in regulating dendrite arborization[20] as well as synaptic morphology via its interaction with CYFIP/Sra[21]. The single characterized *Drosophila* CPEB, Orb, is a germline specific RNA binding protein that mediates translation activation in oocytes. Costa *et al.* showed that dFMRP negatively regulated Orb translation[22]. What is more complex is that the temporal/spatial role of FMRP in translation regulation appears dependent on interaction with a number of different mRNA binding proteins. To identify additional dFMRP-interacting genes, Zarnescu *et al*. conducted a saturating genetic screen for suppressors of a rough eye phenotype induced by dFMRP overexpression[23]. Of the genes hit multiple times, highest hit rate (19/109 suppressors) was the lethal large *larvae* (*Lg*l) gene. Lgl is a RNA binding, cytoskeletal protein implicated in cell polarity and transport, and may be involved in axon reorganization in epileptogenesis.

It seems that the abnormal regulation of FMRP's mRNA target and/or the altered function of FMRP's associated protein can lead to high epilepsy susceptibility in several ways. α-CaMKII, who appears to modulate neurotransmitter biosynthesis and release, is overexpressed in synaptoneurosomes in *Fmr1* knockout mice. α-CaMKII, located both pre- and postsynaptically, is critical for synaptic plasticity and morphology genesis. It has been reported that the expression of CaMKII mRNA is increased after kindling and status epilepsy. Neurochondrin conditional knockout mice show up-regulated activity of CaMKII and high susceptibility to epilepsy[24]. A*rc/Arg3.1* is one of the immediate early genes that are evoked by epilepsy. However, whether or not these correlated molecule can function as a trigger factor in epileptogenesis in FXS still needs to be proved.

4.2 Abnormal activation of metabotropic glutamate receptor Many of the diverse functional consequences of activating group 1 metabotropic glutamate receptors (Gp1 mGluRs) require translation of pre-existing mRNA near synapses[25,26,27]. FMRP normally functions as a subcellular regulator on the translation of specific mRNAs, which indicate that FMRP may play an important role in Gp1 mGluRs signaling pathway. Actually, many functional consequences of Gp1 mGluR-dependent protein synthesis might be exaggerated in the absence of FMRP. These consequences include epilepsy, cognitive impairment, developmental delay, an increased density of long, thin dendritic spines, and loss of motor coordination. It has been reported that loss of FMRP enhanced Gp1 mGluR dependent LTD (which requires rapid protein synthesis of the preexisted mRNAs) in mouse hippocampus while had no effect on NMDA dependent LTD[28]. Also, prolonged treatment of hippocampal neurons with DHPG could increase the proportion of long, thin dendritic spines, which could commonly be found in FXS; the GluR5-specific antagonist, 2-methyl-6-phenylethynyl-pyridine (MPEP), was anticonvulsant and raised the threshold for audiogenic seizure in sensitive strains of mice[29], while enhanced sensitivity to audiogenic seizures was a robust phenotype in *Fmr1* knockout mice in several genetic backgrounds[30,31]. On the other hand, many effects induced by the loss of FMRP can be reversed by the antagonist of Gp1 mGluR. It is found that fruit flies lacking *dfmr1*, the *Drosophila* homolog of human *fmr*1, exhibited altered courtship behavior, decreased memory and alterations in the structure of the brain (the mushroom bodies). All these defects could be rescued by the antagonist of mGluR MPEP[32].

The functions of mGluR in epilepsy had long been investigated. The mGluR1 antagonism blocked hippocampal kindling while producing little or no effect on the triggered discharge. Chuang *et al.* had found that epileptiform discharges in the CA3 region of hippocampal slices from *Fmr1* knockout mice after $GABA_A$ receptor blockade was prolonged compared to the wild type (WT) mice. This prolonged epileptic discharges was blocked by MPEP, the antagonist of Gp1 mGluR[33]. It had also been reported that activity induced expression and subcellulor location could also be blocked by Gp1 mGluR's antagonist. More importantly, 2 to 5 min application of DHPG (Gp1 mGluR's agonist) could significantly increase the expression of FMRP[34]. However, a decreased expression of mGlu5 receptor on membrane was reported recently, which made the issue more complicated[35].

4.3 Abnormal alterations in GABA-mediated inhibition Western blot analysis revealed that the expression of the $GABA_A$ receptor β subunit ($GABA_{A\beta}$), which is required for receptor function, was reduced in the cortex, hippocampus, diencephalon and brainstem in adult male fragile X mice[36]. Immunohistochemical analysis of brain sections indicated a reduction in $GABA_{A\beta}$ immunoreactivity. They also found an

increased expression of glutamic acid decarboxylase, the enzyme responsible for GABA synthesis, in the same regions that showed $GABA_{A\beta}$ reduction. Chuang *et al*. had found that epileptiform discharges in the CA3 region of hippocampal slices from *Fmr1* knockout mice after $GABA_A$ receptor blockade was prolonged compared to the WT, which indicate an abnormal function of inhibitory system in *Fmr1* knockout mice[33].

The importance of GABA systems in the control of neural activity and the suppression of epileptiform discharge is well established. K^+-evoked, Ca^{2+}- dependent GABA release was increased in hippocampal slices one day after kindling[37]. This increase was found to be persistent in CA1[38] and amygdala[39] slices. Meantime, repeated intra-amygdala application of the selective $GABA_A$ receptor antagonist picrotoxin[40] or bicuculline[41] produces a kindling-like response. It has been found that amygdale kindling can be reliably retarded by selective $GABA_A$ agonists. These $GABA_A$ receptor agonists also have potent anticonvulsant effects on seizures in animals that were previously kindled in the amygdala. However, these drugs seems have no effects on the development of spontaneous seizures. It is likely that the relatively less $GABA_A$ receptor in *Fmr1* knockout mice leads to a reduced function of the inhibitory system, which may in turn cause the epilepsy.

4.4 Morphological factors Similar to the early development, morphology changes are critical in epilepsy. It is now clear that axonal growth and synaptogenesis can be induced by epilepsy. If the new circuits are functional, they could contribute to the generation of epileptiform discharge by creating recurrent excitatory loops or by simply amplifying the response of the affected region. While, longer and immature dendritic spines were observed in FXS patients. Golgi-impregnated mature cerebral cortex from fragile X patient exhibited long, thin, tortuous postsynaptic spines resembling spines observed during normal early neocortical development[42,43,44]. Consistent phenomenon was also observed in knockout mice and mutant *Drosophila*. It is found that loss of dFMRP converts unipolar neurons into multipolar neurons in all neuronal classes. Loss of dFMRP causes increased structural complexity throughout the entire neuron, including the extension of additional processes from neuronal soma, overbranching and overgrowth of both the dendritic field and axon processes, and consequent defects in projection[45].

There are also data which can indicate a direct functional role of FMRP in cytoskeleton dynamics. Zarnescu *et al.* show that *lgl* is a dominant enhancer of the *dfmr1* mutant neural-muscular junction (NMJ) structural overgrowth phenotype, with a 2-fold increase in synaptic bouton number in the double heterozygote. Both aPKC-zeta and PAR-6 interact with dFMRP, either alone or in complex with LGL[23].

Thus, a decidedly different circuit, which has been influenced both by the initial genetic perturbation and by incoming stimuli, built and continued to drive the developmental pathoprocess. This abnormal circuit will definitely contribute to an increase of epileptogenesis.

5 An underground river between mental retardation and epilepsy—the dawn of understanding our mysterious brain

FXS is not the only mental retardation (MR) in which epilepsy is an obvious feature. In fact, epilepsy is often associated with MR and vice versa. This holds true for MR with mutation on genes *Ophn1*, *Mecp2*, *Slc6a8*, *Pina*, *Arx*, *Phf6*, *Syn1*, *Atp6ap2*, *Smcx*, respectively. Even in some syndromes such as ISSX, where MR and epilepsy are combined, provides compelling evidence for the association between MR and epilepsy.

However, it is not easy to find out the linkage between the two major mental diseases. The genes whose dysfunctions lead to both MR and epilepsy usually have distinct sometimes opposite functions. GDI1 mutations have been shown to reduce the concentration of several Rab GTPases resulting in a reduction of the synaptic vesicle pool[46,47]. IL1RAPL1 functions as a negative regulator of dense-core granule exocytosis[48]. What's more, the progression of epilepsy from trigger to endpoint involves second messengers, kinases, immediate early genes, transcription factors, protein synthesis and receptor changes.

But when we try to search some common things among MR, we are likely to see a dawn to untie this knot. Morphological abnormality has been reported in several X-linked MR. LGI1 have been identified as the cause of autosomal-dominant partial epilepsy with auditory features. The LGI1 molecules act as adhesion molecules and may modulate cell-to-cell communication. Until a few years ago, it is found that many of the *XLMR* genes that had been identified were functionally related to the formation and deconstruction of the

actin cytoskeleton and to the control of neurite outgrowth[49-51]. This holds true for *Ophn1*[52], *Pak3*[53] and *Arhgef6*[54] (three of the few genes involved in NS-XLMR that were identified before the year 2000) and for FGD1[55,56]. These morphological abnormalities in MR seems bidirectional, include increased or reduced spine density, prolonged or shortened spine length, disguided and delayed axonal outgrowth, increased or reduced axon and dendrites branches. Dysfunction of the signaling pathway and/or neuronal morphogenesis may be a potential mechanism of epilepsy in MR.

The continuing advances in understanding the fundamental property of activity-dependent plasticity in neurons and neural circuits offer substantial new opportunities to gain insights into the neurobiology of progressive features of epileptic syndromes, which goes far beyond what has been possible from clinical and epidemiological analysis. Genetic background has already provided a surprisingly rich and unanticipated series of observations about the remarkable capacities of neurons and neural circuits to undergo modifications potentially influencing progression in both epileptic syndromes and individual patients. Translating these findings on MR into greater insight of both neuronal development and adult-onset mental disorders, like epilepsy, may greatly benefit the definition of the mechanisms of both MR and epilepsy.

References:

[1] Hagerman RJ. Physical and behavioral phenotype. In: Hagerman RJ, Hagerman PJ Ed. Fragile X syndrome: diagnosis, treatment and research. 3rd ed. Baltimore: Johns Hopkins University Press, 2002, 3-109.

[2] Bennetto L, Pennington BF. The neuropsychology of fragile X syndrome. In: Hagerman RJ, Cronister Ed. Fragile X syndrome: diagnosis, treatment and research. 2nd ed. Baltimore: Johns Hopkins University Press, 1996, 210-248.

[3] Turner G, Daniel A, Frost M. X-linked mental retardation, macroorchidism, and the Xq27 fragile site. J Pediatr 1980, 96: 837-841.

[4] Opitz JM, Westphal JM, Daniel A. Discovery of a connective tissue dysplasia in the Martin-Bell syndrome. Am J Med Genet 1984, 17: 101-109.

[5] Merenstein SA, Sobesky WE, Taylor AK, Riddle JE, Tran HX, Hagerman RJ. Molecular-clinical correlations in males with an expanded FMR1 mutation. Am J Med Genet 1996, 64: 388-394.

[6] Musumeci SA, Hagerman RJ, Ferri R, Bosco P, Dalla Bernardina B, Tassinari CA, *et al*. Epilepsy and EEG findings in males with fragile X syndrome. Epilepsia 1999, 40: 1092-1099.

[7] Sabaratnam M, Vroegop PG, Gangadharan SK. Epilepsy and EEG findings in 18 males with fragile X syndrome. Seizure 2001, 10: 60-63.

[8] O'Donnell WT, Warren ST. A decade of molecular studies of fragile X syndrome. Annu Rev Neurosci 2002, 25: 315-338.

[9] Ashley CT Jr, Wilkinson KD, Reines D, Warren ST. FMR1 protein: conserved RNP family domains and selective RNA binding. Science 1993, 262: 563-566.

[10] Brown V, Jin P, Ceman S, Darnell JC, O'Donnell WT, Tenenbaum SA, *et al*. Microarray identification of FMRP-associated brain mRNAs and altered mRNA translational profiles in fragile X syndrome. Cell 2001, 107: 477-487.

[11] Miyashiro KY, Beckel-Mitchener A, Purk TP, Becker KG, Barret T, Liu L, *et al*. RNA cargoes associating with FMRP reveal deficits in cellular functioning in Fmr1 null mice. Neuron 2003, 37: 417-431.

[12] Davidovic L, Jaglin XH, Lepagnol-Bestel AM, Tremblay S, Simonneau M, Bardoni B, *et al*. The fragile X mental retardation protein is a molecular adaptor between the neurospecific KIF3C kinesin and dendritic RNA granules. Hum Mol Genet 2007, 16: 3047-3058.

[13] Sutula TP. Mechanisms of epilepsy progression: current theories and perspectives from neuroplasticity in adulthood and development. Epilepsy Res 2004, 60: 161-171.

[14] Morimoto K, Fahnestock M, Racine RJ. Kindling and status epilepticus models of epilepsy: rewiring the brain. Prog Neurobiol 2004, 73: 1-60.

[15] Shi XY, Wang JW, Lei GF, Sun RP. Morphological and behavioral consequences of recurrent seizures in neonatal rats are associated with glucocorticoid levels. Neurosci Bull 2007, 23: 83-91.

[16] Chen L, Toth M. Fragile X mice develop sensory hyperreactivity to auditory stimuli. Neuroscience 2001, 103: 1043-1050.

[17] Li Z, Zhang Y, Ku L, Wilkinson KD, Warren ST, Feng Y. The fragile X mental retardation protein inhibits translation via interacting with mRNA. Nucleic Acids Res 2001, 29: 2276-2283.

[18] Hummel T, Krukkert K, Roos J, Davis G, Klämbt C. *Drosophila* Futsch/22C10 is a MAP1B-like protein required for dendritic and axonal development. Neuron 2000, 26: 357-370.

[19] Wei ZX, Yi YH, Sun WW, Wang R, Su T, Bai YJ, *et al*. Expression changes of microtubule associated protein 1B in the brain of Fmr1 knockout mice. Neurosci Bull 2007, 23: 203-208.

[20] Lee A, Li W, Xu K, Bogert BA, Su K, Gao FB. Control of dendritic development by the *Drosophila* fragile X-related gene involves the small GTPase Rac1.Development 2003, 130: 5543-5552.

[21] Schenck A, Bardoni B, Langmann C, Harden N, Mandel JL, Giangrande A. CYFIP/Sra-1 controls neuronal connectivity in *Drosophila* and links the Rac1 GTPase pathway to the fragile X protein. Neuron 2003, 38: 887-898.

[22] Costa A, Wang Y, Dockendorff TC, Erdjument-Bromage H, Tempst P, Schedl P, *et al*. The *Drosophila* fragile X protein functions as a negative regulator in the orb autoregulatory pathway. Dev Cell 2005, 8: 331-342.

[23] Zarnescu DC, Jin P, Betschinger J, Nakamoto M, Wang Y, Dockendorff TC, *et al*. Fragile X protein functions with lgl and the par complex in flies and mice. Dev Cell 2005, 8: 43-52.

[24] Dateki M, Horii T, Kasuya Y, Mochizuki R, Nagao Y, Ishida J, *et al*. Neurochondrin negatively regulates CaMKII phosphorylation, and nervous system-specific gene disruption results in epileptic seizure. J Biol Chem 2005, 280: 20503-20508.

[25] Hou L, Antion MD, Hu D, Spencer CM, Paylor R, Klann E. Dynamic translational and proteasomal regulation of fragile X mental retardation protein controls mGluR-dependent long-term depression. Neuron 2006, 51: 441-454.

[26] Nosyreva ED, Huber KM. Metabotropic receptor-dependent long-term depression persists in the absence of protein synthesis in the mouse model of fragile X syndrome. J Neurophysiol 2006, 95: 3291-3295.

[27] Ronesi JA, Huber KM. Metabotropic glutamate receptors and fragile X mental retardation protein: partners in translational regulation at the synapse. Sci Signal 2008, 1: pe6.

[28] Huber KM, Gallagher SM, Warren ST, Bear MF. Altered synaptic plasticity in a mouse model of fragile X mental retardation. Proc Natl Acad Sci USA 2002, 99: 7746-7750.

[29] Chapman AG, Nanan K, Williams M, Meldrum BS. Anticonvulsant activity of two metabotropic glutamate group I antagonists selective for the mGlu5 receptor: 2-methyl-6-(phenylethynyl)-pyridine (MPEP), and (E)-6-methyl-2-styryl-pyridine (SIB 1893). Neuropharmacology 2000, 39: 1567-1574.

[30] Musumeci SA, Bosco P, Calabrese G, Bakker C, De Sarro GB, Elia M, *et al*. Audiogenic seizures susceptibility in transgenic mice with fragile X syndrome. Epilepsia 2000, 41: 19-23.

[31] Chen L, Toth M. Fragile X mice develop sensory hyperactivity to auditory stimuli. Neuroscience 2001, 103: 1043-1050.

[32] Dockendorff TC, Su HS, McBride SM, Yang Z, Choi CH, Siwicki KK, *et al*. *Drosophila* lacking dfmr1 activity show defects in circadian output and fail to maintain courtship interest. Neuron 2002, 34: 973-984.

[33] Chuang SC, Zhao W, Bauchwitz R, Yan Q, Bianchi R, Wong RK. Prolonged epileptiform discharges induced by altered group I metabotropic glutamate receptor-mediated synaptic responses in hippocampal slices of a fragile X mouse model. J Neurosci 2005, 25: 8048-8055.

[34] Weiler IJ, Irwin SA, Klintsova AY, Spencer CM, Brazelton AD, Miyashiro K, *et al*. Fragile X mental retardation protein is translated near synapses in response to neurotransmitter activation. Proc Natl Acad Sci U S A 1997, 94: 5395-5400.

[35] Giuffrida R, Catania MV. A reduced number of metabotropic glutamate subtype 5 receptors are associated with constitutive homer proteins in a mouse model of fragile X Syndrome. J Neurosci 2005, 25: 8908-8916.

[36] El Idrissi A, Ding XH, Scalia J, Trenkner E, Brown WT, Dobkin C. Decreased GABAA receptor expression in the seizure-prone fragile X mouse. Neurosci Lett 2005, 377: 141-146.

[37] Liebowitz NR, Pedley TA, Cutler RW. Release of gamma-aminobutyric acid from hippocampal slices of the rat following generalized seizures induced by daily electrical stimulation of entorhinal cortex. Brain Res 1977, 138: 369-373.

[38] Kamphuis W, Huisman E, Dreijer AM, Ghijsen WE. Kindling increases the K^+-evoked. Ca^{2+}-dependent release of endogenous GABA in area CA1 of rat hippocampus. Brain Res 1990, 511: 63-70.

[39] Kaura S, Bradford HF, Young AM, Croucher MJ, Hughes PD. Effect of amygdaloid kindling on the content and release of amino acids from the amygdaloid complex: *in vivo* and *in vitro* studies. J Neurochem 1995, 65: 1240-1249.

[40] Cain DP. Kindling by repeated intraperitoneal or intracerebral injection of picrotoxin transfers to electrical kindling. Exp Neurol 1987, 97: 243-254.

[41] Uemura S, Kimura H. Amygdaloid kindling with bicuculline methiodide in rats. Exp Neurol 1988, 102: 346-353.

[42] Reiss AL, Lee J, Freund L. Neuroanatomy of fragile X syndrome: the temporal lobe. Neurology 1994, 44: 1317-1324.

[43] Hinton, VJ, Brown WT, Wisniewski K, Rudelli RD. Analysis of neocortex in three males with the fragile X syndrome. Am J Med Genet 1991, 41: 289-294.

[44] Irwin SA, Galvez R, Greenough WT. Dendritic spine structural anomalies in fragile-X mental retardation syndrome. Cereb Cortex 2000, 10: 1038-1044.

[45] Pan L, Zhang YQ, Woodruff E, Broadie K. The *Drosophila* fragile X gene negatively regulates neuronal elaboration and synaptic differentiation. Curr Biol 2004, 14: 1863-1870.

[46] D'Adamo P, Menegon A, Lo Nigro C, Grasso M, Gulisano M, Tamanini F, *et al*. Mutations in GDI1 are responsible for X-linked non-specific mental retardation. Nat Genet 1998, 19: 134-139.

[47] D'Adamo P, Welzl H, Papadimitriou S, Raffaele di Barletta M, Tiveron C, Tatangelo L, *et al*. Deletion of the mental retardation gene Gdi1 impairs associative memory and alters social behavior in mice. Hum Mol Genet 2002, 11: 2567-2580.

[48] Ferrante MI, Ghiani M, Bulfone A, Franco B. IL1RAPL2 maps to Xq22 and is specifically expressed in the central nervous system. Gene 2001, 275: 217-221.

[49] Chelly J, Mandel JL. Monogenic causes of X-linked mental retardation. Nat Rev Genet 2001, 2: 669-680.

[50] Chelly J. Breakthroughs in molecular and cellular mechanisms underlying X-linked mental retardation. Hum Mol Genet 1999, 8: 1833-1838.

[51] Ramakers GJ. Rho proteins, mental retardation and the cellular basis of cognition. Trends Neurosci 2002, 25: 191-199.

[52] Billuart P, Bienvenu T, Ronce N, des Portes V, Vinet MC, Zemni R,

et al. Oligophrenin-1 encodes a rhoGAP protein involved in X-linked mental retardation. Nature 1998, 392: 923-926.

[53] Allen KM, Gleeson JG, Bagrodia S, Partington MW, MacMillan JC, Cerione RA, *et al*. PAK3 mutation in nonsyndromic X-linked mental retardation. Nat Genet 1998, 20: 25-30.

[54] Kutsche K, Yntema H, Brandt A, Jantke I, Nothwang HG, Orth U, *et al*. Mutations in ARHGEF6, encoding a guanine nucleotide exchange factor for Rho GTPases, in patients with X-linked mental retardation. Nat Genet 2000, 26: 247-250.

[55] Lebel RR, May M, Pouls S, Lubs HA, Stevenson RE, Schwartz CE. Non-syndromic X-linked mental retardation associated with a missense mutation (P312L) in the FGD1 gene. Clin Genet 2002, 61: 139-145.

[56] Pasteris NG, Cadle A, Logie LJ, Porteous ME, Schwartz CE, Stevenson RE, *et al*. Isolation and analysis of the faciogenital dysplasia (Aarskog-Scott syndrome) gene: a putative, rho/rac guanine nucleotide exchange factor. Cell 1994, 79: 669-678.

脆性 X 综合征与癫痫

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摘要 脆性X综合征(fragile X syndrome, FXS) 是一种最常见的遗传性智力障碍。这种智力障碍疾病主要是由于脆性X智力低下蛋白 (fragile X mental retardation protein, FMRP)的缺失引起。FMRP是一种RNA结合蛋白，通过调节与其结合的信使RNA的翻译而调节神经元内的信号传导。很多FXS病人表现出较高的癫痫发作易感性。癫痫是一种慢性神经系统疾病。它的主要症状是反复的癫痫发作。癫痫发作是由大脑神经元的异常高兴奋性和同步放电引起的。FMRP缺失引起的神经元形态异常和神经元内信号传导的异常均可导致癫痫发作。本文结合在FXS和癫痫病两方面上取得研究结果综合分析，探讨FXS病人癫痫高易感性的发病机理，并对其他智力障碍疾病中的癫痫高易感性的机制的研究做一展望。

关键词：癫痫；脆性X智力低下蛋白；代谢性谷氨酸受体；γ-氨基丁酸；树突突触