INTRODUCTION

FMRP: fragile X mental retardation protein

Fragile X syndrome (FXS) is the most common form of inherited intellectual disability, affecting 1:5,000 males and 1:6,000 females worldwide (1). FXS is caused by a CGG repeat expansion in the promoter region of fragile X mental retardation gene, *FMR1*. More than 200 repeats of CGG lead to hypermethylation and silencing of the gene, causing the loss of fragile X mental retardation protein (FMRP). In <1% of FXS individuals, absence of FMRP is caused by mutations in the coding region of *FMR1* (1). Males with FXS display intellectual disability (IQ ranging between 20 and 70) and a broad spectrum of symptoms including physical abnormalities (macroorchidism, prominent ears, elongated face and hyperextensible finger joints), and behavioral (anxiety, social avoidance and hand clapping), cognitive (executive functioning, visual-spatial processing and developmental delay), and neurological (epilepsy and disrupted sleep patterns) deficits (**Table 1**). Because the disease is X-linked, females with a full mutation are less affected than males, with an average IQ of 75–80 (1). Several animal models of FXS have been developed, including *Drosophila*, mouse, and rat (**Table 1**; see sidebar titled Animal Models of Fragile X Syndrome for details). In recent years, numerous preclinical and clinical studies have been carried out to develop and test novel therapeutics for FXS (2). In this review, we describe the latest advances in understanding the molecular basis of the disease pathogenesis and highlight the emerging therapeutic potential of the antidiabetic drug metformin.

FRAGILE X SYNDROME AND TRANSLATIONAL CONTROL

Many neuropsychiatric symptoms of FXS are thought to be a consequence of dysregulated protein synthesis at the synapse (3). FMRP is an RNA-binding protein, targeting a subpopulation of neuronal mRNAs (1, 4). The cardinal function of FMRP is repression of translation, mainly of genes encoding synaptic plasticity-related proteins (1, 4). The absence of FMRP leads to

Table 1 Overlapping phenotypes and the effects of metformin in humans with fragile X syndrome (FXS) and in FXS animal models[a]

Impaired phenotypes in FXS	*Drosophila* (references)	Mouse (references)	Rat (references)	Human (references)
Social interaction	Yes (101)	Yes (12, 15, 35, 91)	Yes (99, 100)	Yes (1, 2, 34)
Repetitive behavior	Yes (101)	Yes (15, 35, 91, 95)	No (100)	Yes (1, 2, 34)
Speech/ultrasonic vocalization	Not applicable	Yes (95)	No (100)	Yes (1, 2, 34)
Memory	Yes (33, 100)	Yes (12, 35, 90, 91, 95)	Yes (98, 99)	Yes (1, 2)
Hyperactivity	Yes (101)	Yes (15, 35, 90, 95)	No (100)	Yes (1, 2, 34)
Seizures	Not reported	Yes (15, 35, 90, 95)	Not reported	Yes (1, 2)
Sleep disorder	Yes (101)	Yes (91, 95)	Not reported	Yes (1, 2)
Circadian rhythm	Yes (33, 101)	Yes (91, 95)	Not reported	Yes (1, 2)
Long-term depression	Not applicable	Yes (12, 15, 35, 91, 93, 94)	Yes (98, 99)	Not applicable
Dendritic/synaptic morphology	Yes (101)	Yes (15, 35, 91, 92, 95)	Yes (98)	Yes (1, 2)
General protein synthesis	Not reported	Yes (12, 15, 35)	Yes (98)	Yes (3, 4)
Hyperactivation of mTOR	Not reported	Yes (12, 35)	Not reported	Yes (3, 4, 13)
Hyperactivation of ERK	Not reported	Yes (14, 35)	Not reported	Yes (3, 4, 13)
Macroorchidism	Yes (101)	Yes (12, 35)	Yes (99)	Yes (1, 2)

[a]Red text indicates phenotypes corrected by metformin.