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FRAGILE X SYNDROME: RECENT RESEARCH REVIEWED

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CONTENTS

SUMMARY

Fragile X syndrome is an X-linked genetic disorder associated with abnormal trinucleotide repeat sequences in the fragile X mental retardation 1 (FMR1) gene. The resulting DNA expansions can cause varying degrees of developmental problems, including learning disabilities and cognitive impairment. Research into the molecular changes underlying behavioral/medical problems associated with fragile X syndrome has highlighted new avenues for pharmacotherapy, which will supplement educational/learning support. This article highlights current clinical focus in the field and summarizes the research underlying the rationale for targeting, among others, the cholinergic system, AMPA, NMDA and GABA receptor-mediated signaling.

INTRODUCTION

Fragile X syndrome is an inherited syndrome involving a range of developmental problems, including learning disabilities and cognitive impairment. Its name came about due to the identification of an associated "fragile" portion of the X chromosome in these patients, induced by a change or mutation in the fragile X mental retardation 1 (*FMR1*) gene on the X chromosome. While less than 60 cytosine, guanine and guanine (CGG) trinucleotide repeat sequences are commonly seen in unaffected subjects, those with 60-200 CGG repeats are said to have a "premutation" (carriers of an unstable *FMR1* mutation, and thus further expansion of the repeats in subsequent generations can cause the condition to occur more frequently or severely [1, 2]), and subjects with over 200 repeats are said to have a full mutation, which causes the fragile X syndrome (3, 4). The full mutation triggers methylation of a region of the *FMR1* gene and, as a consequence, an absence of functional fragile X mental retardation protein (FMRP), a protein that plays a role in synaptic development. The outcome is nervous system dysfunction and the signs and symptoms of fragile X syndrome: anxiety, hyperactivity, attention deficit disorder, seizures and autistic-like behavior (5, 6).

Population analyses have shown that males are more severely affected by this disorder than females, with additional physical characteristics such as a long, narrow face, prominent ears, jaw and forehead, unusually flexible fingers and enlarged testicles after puberty (7). Cognitive impairment is rare in those with a premutation; however, due to lower levels of FMRP, mild symptomatology is evident, e.g., prominent ears and emotional problems such as anxiety or depression. Approximately 20% of women with a premutation have premature ovarian failure, in which menstrual periods stop by age 40 (6, 8). Men, and some women, with a premutation have an increased risk of developing a disorder known as fragile X-associated tremor/ataxia syndrome (FXTAS) (9). As this is an "X-linked" condition, a woman with a premutation or full mutation has a 50% chance of passing on the X with the mutation in each pregnancy; as males only pass their Y chromosome onto their sons, premutation inheritance is only passed down to their daughters.

In terms of the worldwide prevalence of males and females born with the full mutation for fragile X syndrome, this has been reported to be approximately 1 in 3,600-4,000 males and 1 in 4,000-6,000 females, respectively. In comparison, worldwide, approximately 1 in 800 men and 1 in 260 women are carriers of the fragile X premutation (10).

While there is no cure for fragile X syndrome, quality of life can be enhanced by therapies for speech and language, behavior, cognitive development, sensory and social integration, and motor development. Research into the molecular changes underlying behavioral/medical problems associated with fragile X syndrome has highlighted new avenues for pharmacotherapy. This article will focus on new clinical advances in the pharmacotherapy of fragile X syndrome. Table I summarizes ongoing clinical research in this area.

RECENT RESEARCH

Cholinergic manipulation

Studies have shown that disruption of the cholinergic system may occur secondary to FMRP deficiency, contributing to cognitive impairment associated with fragile X syndrome. A 3-week, open-label pilot trial of donepezil, an acetylcholinesterase inhibitor (N =

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Table I. *Ongoing clinical studies investigating new treatments for fragile X syndrome.*

Phase	Drug	Investigators	Ref.
–	Minocycline	UC Davis MIND Institute The National Fragile X Foundation Fragile X Research Foundation of Canada	26 27
–	Memantine	University of California, Davis National Institute on Aging (NIA) Forest Laboratories	20
Phase II	Arbaclofen (STX-209)	Seaside Therapeutics, LLC	23
Phase II	AFQ-056	Novartis	16
Phase II	RO-4917523	Hoffmann-La Roche	15
Phase II	Donepezil	Stanford University	12
Phase I/II	Fenobam	Neuropharm	28

8), demonstrated that 5 mg/day significantly improved cognitive–behavioral function via improvements in Contingency Naming Task (CNT) scores (to measure working memory and mental flexibility), reductions in the Aberrant Behavior Checklist (ABC; a standardized rating scale developed to measure pharmacological effects on problem behaviors in individuals with mental retardation) and the Achenbach Child and Adult Behavior Checklists (CBCL, ABCL; to assess general cognitive–behavioral status), with additional improvements in hyperactivity and irritability (11). Researchers at Stanford University School of Medicine recently initiated a phase II trial of donepezil in a larger cohort (12).

Several lines of research have hypothesized that overactive signaling by group I metabotropic glutamate (mGlu) receptors could contribute to many of the psychiatric and neurological aspects of fragile X syndrome (13). Concerns about ataxia caused by $mGlu_1$ receptor blockers have opened the field for investigation of $mGlu_5$ receptors. An open-label trial of single-dose fenobam (50-150 mg p.o.), an $mGlu_5$ receptor antagonist, was carried out in 12 subjects with fragile X syndrome. Beneficial clinical effects were observed as ≥ 20% improvement in prepulse inhibition (a measure of sensorimotor gating) versus baseline in 50% of subjects, with a positive safety profile (14). More recently designed $mGlu_5$ receptor antagonists are also being tested in fragile X syndrome patients in phase I/II studies (Table I), i.e., RO-4917523 (15) and AFQ-056 (16).

Ampakines

Preclinical studies in *Fmr1* knockout mice have identified an associated reduction in AMPA receptors and AMPA-mediated long-term potentiation (LTP) (17). Subsequent to this, a 4-week, randomized, double-blind, placebo-controlled phase II trial investigated the potential of the Ampakine CX-516 to enhance AMPA receptor functioning and cognition in fragile X syndrome (N = 49). Despite the rationale for this study, no significant improvement in memory, language, attention/executive function, behavior and overall functioning was seen for CX-516-treated subjects versus placebo. However, it was suggested that the dosing strategy may have been inadequate for a therapeutic effect (18).

NMDA receptor antagonists

Preclinical studies in *Fmr1* knockout mice have also demonstrated an associated enhanced NMDA receptor-dependent LTP (19). In an attempt to correct this abnormality and potentially improve neurological impairment in fragile X syndrome, U.S. researchers are investigating memantine, an NMDA receptor antagonist (20).

GABA

Studies have demonstrated that increasing γ-aminobutyric acid $GABA_B$ receptor-mediated signaling may improve the behavioral and neurological phenotype of fragile X syndrome (21). Arbaclofen, the active enantiomer of racemic baclofen, a GABA derivative commonly used to treat spasticity, has been proposed to offer enhanced efficacy and tolerability versus baclofen (22) and is currently undergoing phase II investigation at Seaside Therapeutics (23).

Minocycline

The neuroprotective effects of minocycline (24), along with its ability to lower matrix metalloproteinase MMP-9 levels (25), are now being put to the test in clinical studies. Two studies, one in the U.S. and one in Canada, are testing whether minocycline can improve language, behavior and/or cognition in fragile X syndrome patients (26, 27).

The field of drug discovery for gene-based behavioral/neurological syndromes such as fragile X syndrome is expanding with deeper molecular research. Although the aim is for targeted treatments to "strengthen" synaptic functioning, it is essential that these treatments be combined with educational/learning support to address the cognitive deficits in fragile X syndrome.

DISCLOSURES

The author states no conflicts of interest.

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