TBMH 5004
Fundamentals of TBMH

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Contents

1 TBMH Fundamentals Overview

For the purpose of this course and program, translational biology is the act or process of changing some aspects of knowledge about living organisms and vital processes. Notably, the translational element of this program does not specifically apply to either medicine or health.

1.1 Translational Research

Although the definition and stages of translational research vary, we will define it in five stages, broadly, as:

1. **T0** — The focus is on identifying problems, opportunities, and novel approaches to tackle those problems and opportunities. This is characterizes by the identification of approaches to relevant health problems with research beginning with a basic research question.
2. **T1** — Discovery or foundational research and development of treatments. This is translational research in which findings are moved from basic research to testing for clinical effect and/or applicability.
3. **T2** — Health application to assess efficacy of treatment. This research assesses the value of the treatment in a clinical trial (i.e., in Phase III clinical trials).
4. **T3** — Health practice; science of dissemination and implementation. This attempts to move evidence-based guidelines into health practice (analogous to Phase IV clinical trials).
5. **T4** — Evaluation of health impact on real-world populations. This is, broadly, outcomes research that monitors the morbidity, mortality, benefits, and risks in the population of the treatment.

Specifically, this is an iterative process with each stage building on and informing every other.

1.2 Clinical Trials

The phases of clinical trials are as follow (via the NIH):

1. **Phase I** — Researchers test a new drug or treatment in a small group for the first time to evaluate its safety, determine its dosage range, and identify side effects.
2. **Phase II** — The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.
3. **Phase III** — The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly-used treatments, and collect information that will allow the drug to be used safely.
4. **Phase IV** — Studies done after the drug is places on the market to gather information on its effect in varied populations and any side effects associated with long-term use.

2 Fragile X Syndrome

2.1 Overview

Fragile X Syndrome (also known as Martin-Bell syndrome, or Escalante's syndrome) is a sex-linked genetic disorder causing mental retardation and one of the largest single-gene causes of autism among children.

Specifically, Fragile X Syndrome (FX) is most often caused by a simple CGG repeat in the FMR1 gene on the X chromosome. This, in turn, causes an underexpression of the Fragile X mental retardation protein (FMRP). The amount of FRMP present is demonstrated to affect synaptic plasticity (with an abundance correlating to increased plasticity), and thereby to affect learning. As such, when the protein is absent, there is reduced plasticity in the individual, yielding mental retardation. The degree of retardation is inversely proportional to the amount of FMRP present in the individual.

Moreover, research has indicated in mouse models that there is a functional opposition between FMRP and certain metabotropic glutamate receptors (mGluRs), and specifically mGluR5. FMRP and mGluR5 both appear to regulate mRNA translation at the synapse, with mGluR5 inhibiting translation and FMRP promoting it. As such, in the absence of FMRP, mRNA translation at the synapse is highly downregulated, resulting in the observed mental retardation.

In neonates, long-term potentiation (LTP) appears to be important for retaining newly-formed synapses and long-term depression (LTD) for activity-guided synapse elimination. Further, post-synaptic group 1 mGluR activation is responsible in many parts of the brain for LTD. However, for this to occur, there must be a rapid translation of preëxisting mRNA in the postsynaptic dendrites. Given that FMRP mRNA is found in dendrites and that FMRP binds mRNA, it is perhaps unsurprising that in the absence of FMRP (in *Fmr1* knockout mice), exaggerated protein-synthesis-dependent LTD has been observed.

"According to this model, mGluR activation normally stimulates synthesis of proteins involved in stabilization of LTD and, in addition, FMRP. The FMRP functions to inhibit further synthesis (an example of end-product inhibition), and puts a brake on LTD" (Bear, Huber, & Warren). That is, in a typical individual, FMRP acts as a negative feedback to LTD, thus promoting normal growth. When it is absent, however, LTD is allowed to continue unimpeded, resulting in excessive activity-guided synapse elimination. This interaction between FMRP and mGluRs may thus result both in an insufficient number of synaptic interconnections at birth (via synaptic pruning) and an inability to effectively form these connections throughout life (via reduced synaptic plasticity resulting from mGluR-induced LTD).

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