Kainate Receptors, Circuit Imbalance and Mental Diseases

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Establishing the adequate receptor number and type at synapses is fundamentally important to fine tune neuronal communication and brain plasticity associated to learning and memory. Normally, we tend to think about mutations that alter protein function as a source of synaptic disruption that may lead to disease. However, the vulnerability of neurons to modest changes in levels of normal proteins provides a new way to understand pathogenesis. Indeed, pervasive brain pathologies can emerge because of variations in the dosage of certain genes that may result in loss or gain of protein function. This seems to be the case of kainate receptors (KARs) and we have addressed this problem in two cases. First, a *de novo* duplication of the chromosome 11q23.3–q24.1 locus in which the gene *GRIK4* lies has been identified in cases of autism and schizophrenia. We have evaluated mice overexpressing *Grik4* in principal cells of the forebrain. These animals display signs of depression, anxiety and social impairment, closely reflecting the human endophenotypes associated to autism and schizophrenia. We found that modest increases in GluK4 protein are associated with increased synaptic gain at selected synapses in the amygdala and the hippocampus, resulting in unbalanced circuit outputs and behavioural abnormalities common to these human diseases. Second, using a genetic strategy for dose normalization, we examined the contribution of *Grik1* over-dosage to Down syndrome (DS), where the chromosome 21, encompassing this gene, is triplicated. We found in a transgenic mouse model of DS that spatial memory and inhibitory activity are affected in the hippocampus due to the excess of GluK1 protein, with a redistributed inhibition along the somatodendritic axis of pyramidal cells. In summary, the synaptic effects of KAR genes overexpression produce anomalous circuit activity and recapitulate behavioural abnormalities in humans, which may be significant to understand the etiopathology of human disorders.