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Extracellular matrix balances principal cell excitability and synaptic plasticity

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The extracellular matrix (ECM) regulates both physiological and pathophysiological processes in the brain. Paradoxically, ECM attenuation is reported either to enhance or to impair synaptic plasticity. Here, we uncover molecular mechanisms behind this dualism. We demonstrate that enzymatic attenuation of ECM by chondroitinase ABC (ChABC) decreased CA1 pyramidal cell excitability and thus restrained long-term potentiation (LTP) in CA3-CA1 synapses. This effect was mediated by a loss of ECM proteoglycan brevican, triggering increased cell surface expression of small conductance (SK) Ca2+-activated K+ channels through a mechanism involving metabotropic glutamate receptors group III (mGlu7) and protein kinase A. Blocking this mechanism restored principal cell excitability and LTP in brevican knockout mice, and led to supranormal LTP through β1 integrins and NR2B after enzymatic attenuation of ECM. Thus, ECM attenuation counterbalances the augmented predisposition of synapses to undergo modifications by reduced cell excitability. This homeostatic regulation may protect neurons from excessive potentiation/saturation of synaptic inputs.