Neurons originating from the raphe nuclei of the brainstem are the exclusive source of serotonin (5-HT) to the cortex. Their serotonergic phenotype is specified by the transcriptional regulator Pet-1, which is also necessary for maintaining their neurotransmitter identity across development. Transgenic mice in which the Pet-1 gene is genetically knocked out (KO), show a dramatic reduction (ca. 80%) in forebrain 5-HT levels, yet no investigations have been carried out to assess the impact of such severe 5-HT depletion on the function of target cortical circuits. Using whole-cell patch clamp techniques, 2-D electrode arrays, morphological reconstructions of cortical neurons, and animal behavior, we investigated the impact of 5-HT depletion on cortical cell-intrinsic and network excitability. We found significant changes in several parameters of cell-intrinsic excitability in cortical pyramidal cells, as well as an increase in spontaneous synaptic excitation through 5-HT3 receptors. These changes are associated with increased cortical network excitability and oscillatory activity in a 5-HT2 receptor-dependent manner, consistent with previously reported hypersensitivity of cortical 5-HT2 receptors in mutant mice. In contrast, recordings of network activity with 2-D arrays (120 electrodes; 100 um pitch) revealed that neuronal activity propagates less and more slowly in the neocortex of Pet-1 KO mice than in wild-type controls. A possible, mechanistic explanation for these results is
provided by the analysis of pyramidal cell morphology, which reveals a significant reduction in the complexity of their dendritic arbors. This likely leads to reduced network connectivity, acting as a compensatory mechanism for increased excitability at the single-cell level. Consistent with this interpretation, when we carried out experiments with convulsant-induced seizures to assess cortical excitability in vivo, we observed no significant differences in seizure parameters between wild-type and Pet-1 KO mice. Our findings provide the first evidence for functional changes in neuronal and network excitability in target structures of serotonergic neurons in mice lacking the Pet-1 gene.

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