Promoting the formation of sound-specific auditory memories using epigenetic interventions

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Epigenetic mechanisms, which regulate gene expression necessary for memory consolidation, have recently emerged as powerful modulators of learning-induced neural plasticity and concomitantly, the formation of long-term memories (Stefanko et al., 2009; McQuown et al., 2011; Gervain et al., 2013; Bieszczad et al., 2015; Rotondo & Bieszczad, 2020). The present work in a rodent model of auditory appetitive associative learning demonstrates that inhibition of the epigenetic regulator histone deacetylase 3 (HDAC3), which releases HDAC3-mediated constraints on gene expression by facilitating activity-dependent epigenetic "writing", promotes long-term memory formation that is highly sound-specific for sound. Long-term behavioral effects are accompanied by an enhancement in learning-dependent auditory neuroplasticity that appears in both in vivo auditory cortical and brainstem neurophysiological responses. Changes in sound-evoked activity mediated by HDAC3 are unusually selective for behaviorally relevant spectral (acoustic frequency) or temporal (amplitude modulation rate) features of sound (Bieszczad et al., 2015; Rotondo & Bieszczad, 2020; Rotondo & Bieszczad, 2021). Animals with increasing behavioral specificity to acoustic frequency is correlated with greater frequency-specific narrowing of auditory cortical tuning bandwidth and enhanced response amplitude in the auditory brainstem (ABR). Animals with increasing behavioral specificity to amplitude modulation (AM) rate is correlated with AM rate-specific enhancements phase-locking revealed in auditory cortical responses and in the frequency following response (FFR), which reflects cortical and subcortical auditory sources. Collectively, these findings reveal novel auditory neural substrates of sound cue-specific memory revealed behaviorally. In addition, they demonstrate novel effects of HDAC3 inhibition, including on both rate and temporal coding and localized to both the cortical and subcortical auditory system. A major implication is that HDAC3 inhibition enhances memory specificity by facilitating the development of sound-specific auditory plasticity in the relevant representation of behaviorally-significant sound features. All together, these findings are consistent with the ability of HDAC3-inhibition to facilitate memory for spectro-temporally complex vocalizations in birds (Phan et al., 2017) and promote the hypothesis that epigenetic manipulations enhance discriminability of sensory cues encoded into auditory long-term memory (c.f., Day & Sweatt 2011; Biergans et al., 2012), which has important implications for promoting memory for sounds typical of human voices and

speech.