1521-0103/385/S3/supplement: ASPET 2023 Annual Meeting Abstracts
The Journal of Pharmacology and Experimental Therapeutics

dx.doi.org/10.1124/jpet.122.286940
J Pharmacol Exp Ther 385: June 2023

Pharmacology of Memory Dysfunction in Alzheimer's Disease (AD)

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Abstract ID 28694 **Poster Board 70**

The biological basis for memory continues to be actively investigated yet, as contrasted with cardiovascular pharmacology, an overarching pharmacological theory for the modulation of memory in healthy and diseased states remains largely unknown. To address this need for developing a platform for the interrogation of memory by probe drugs, we have focused on developing a paradigm for within subject interrogation of memory circuitry *in vivo* in awake ambulating animals as a basis for future discovery in a precision medicine approach to neurotherapeutics.

The hippocampal trisynaptic circuit (HTC) is formed by synapses between neurons in the entorhinal cortex (EC) synapsing on dentate granule cells (DC) that synapse upon pyramidal cells in the CA3 pyramidal neurons (Ca3 Pyr), which then synapse upon CA1 pyramidal neurons (CA1 Pyr): EC $>$ DC $>$ CA3 Pyr $>$ CA1 PyR which is recognized as a core module in mammalian memory systems function. Disorders of aging such as mild cognitive impairment and AD are associated with HTC hyperactivity (Wilson et al., 2006; Yassa et al., 2010; Baker et al., 2015; Robitsek et al., 2015; Sosulinaet al., 2021). We demonstrated that acute systemic administration of low dose levetiracetam + valproic acid reduced HTC hyperactivity and increased the spatial information content encoded by HTC place cells (Robitsek et al., 2015). We have also shown that the dose-dependent ripple band response to administration of an orally bioavailable negative allosteric modulator of alpha5-type GABA-A receptors (alpha 5IA) is attenuated or eliminated in awake immobile TgF344-AD rats with elevated plasma AB42 and AB40 (Ratner et al., 2021).

Here, we ask whether Abeta42 that is produced in a transgenic rat model of AD (TgF344-AD) disrupts synchronously firing of subsets of CA1 PyR that comprise sharp wave ripples (SPW-Rs) at 140 - 200 Hz. SPW-Rs are likely a functional elementary process in memory consolidation (Buzsaki 2015). Epsilon band (90 to 130 Hz) oscillations are smaller in amplitude than SPW-Rs and both emanate from CA3 Pyr oscillations. The boundary between these two frequency bands is defined by a characteristic dip between 130 and 150 Hz in power spectral density plots, surrounded by distinct peaks at 170–180 and 110 Hz. We have shown that this type of synchronous high frequency circuitry activity is disrupted in awake immobile TgF344-AD rats (Ratner et al., 2021).

We now show that administration of alpha5IA differentially modulates these two high frequency bands. In WT F344 CA1, alpha5IA dramatically potentiates SPW-Rs but has little effect on epsilon. Moreover, in TgF344-AD rats, where alpha5IA now fails to enhance the SPW-Rs, epsilon is largely unaffected by the overexpression of Abeta 42 and 40 and its sensitivity to alpha 5IA is not measurable in this respect like the ripple band. These observations suggest alpha-5 subunit-containing $GABA_A$ receptors, which are highly expressed in CA1 Pyr neurons play a role SPW-R modulation but not high frequency oscillations in the adjacent epsilon band. The results demonstrate that alpha5IA modulation can be used to differentiate between high frequency oscillations in the ripple band from those in the epsilon band. Further research will explore the relevance of this preferential modulatory effect in terms of the behaviorally demonstrated nootropic effects of alpha 5IA.

David H Farb was supported by National Institute on Aging

(R21AG056947, P01AG9973).

Marcia H. Ratner was supported by National Institute on Aging

(T32AG00115).