

Altered circuit function and plasticity in the hippocampus and prefrontal cortex of an animal model of treatment-resistant depression

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INTRODUCTION

The Wistar-Kyoto rat exhibits several behavioral deficits (e.g., despair, anhedonia, and cognitive deficits) and has been shown to be insensitive to treatment with selective serotonin reuptake inhibitors. Additionally, molecular and cellular abnormalities, such as decreased N-methyl-D-aspartate (NMDA) function in the prefrontal cortex (PFC) and increased gamma-aminobutyric acid-A (GABA_A) function in the hippocampus (HPC), have also been demonstrated in Wistar-Kyoto rats. Despite this, very little is known about potential circuit dysfunctions in this animal model. Since there is increasing evidence suggesting that synaptic plasticity plays an important role in the etiology and treatment of depression, we sought to characterize circuit function and plasticity in the HPC and PFC of Wistar-Kyoto rats.

METHODS

Wistar Kyoto, Wistar, and Sprague Dawley rats (male, 6-9 weeks old) were obtained from Charles River (Kingston, RI, USA and Quebec). WIS and SD rats were chosen as control strains since both strains are used in the literature. On the day of recording, slices (400 μm thick) of the dHPC, vHPC, or PFC were prepared for *in vitro* testing. Field excitatory postsynaptic potentials (fEPSPs) were recorded from either the stratum radiatum of the CA1 region of hippocampal slices or layer V of PFC slices. Input/output (I/O) curves and paired-pulse facilitation (PPF) ratios were generated prior to and after induction of long-term potentiation (LTP). Analysis on I/O curves, PPF and LTP was performed using pClamp software and unpaired t-test or two-way and one-way ANOVA's with Bonferroni's *post hoc* tests for multiple comparisons ($\alpha=0.05$) using Microsoft Excel or Graphpad Prism Software.

CONCLUSIONS

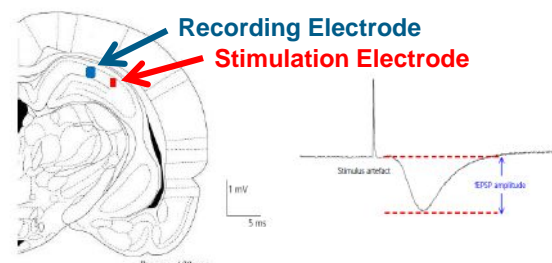
- These data demonstrate alterations in circuit function and plasticity in Wistar-Kyoto rats in brain areas central to many of the behavioral and cognitive dysfunctions observed in clinically depressed populations.
- Interestingly, these data highlight both basal decreases in synaptic strength in HPC and impaired plasticity in PFC, each of which may be underlying mechanisms of the augmented responses to stress and cognitive functions observed in Wistar-Kyoto rats.
- Given the potential utility of the Wistar-Kyoto rat as an SSRI insensitive animal model that mimics some neurophysiological aspects of depression, it is of considerable interest to further define the underlying mechanisms of impaired hippocampal circuit connectivity and plasticity in the prefrontal cortex, and whether these deficits may be uniquely augmented by non-standard antidepressant therapies.

DISCLOSURES

- CBP and CS are employees of Alkermes, Inc.
- AW, JSW, and SO are employees of Cerebrasol, which was contracted to perform these experiments

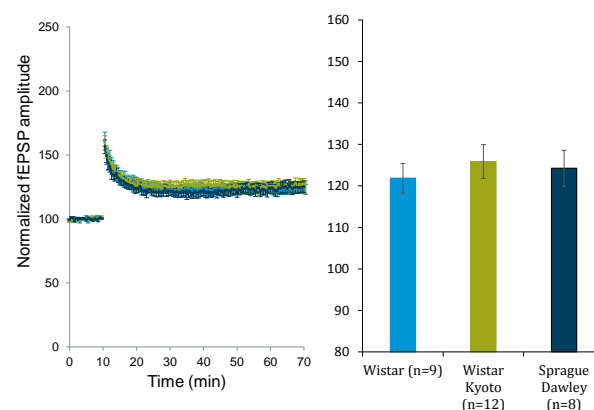
RESULTS

FIGURE 1
Dorsal Hippocampus
(CA3 → CA1)

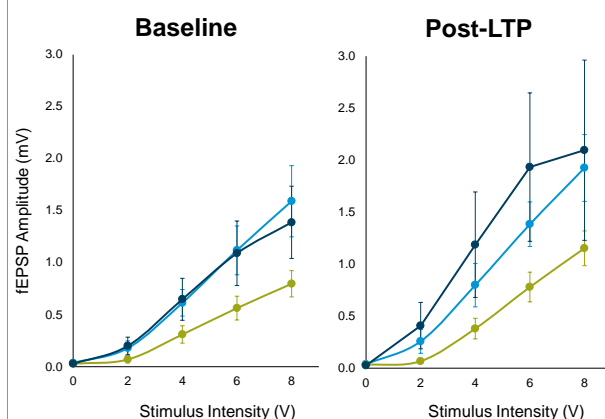


● Sprague Dawley ● Wistar ● Wistar-Kyoto

Long-Term Plasticity (LTP)



Synaptic Connectivity



Pre-Synaptic Short-Term Plasticity

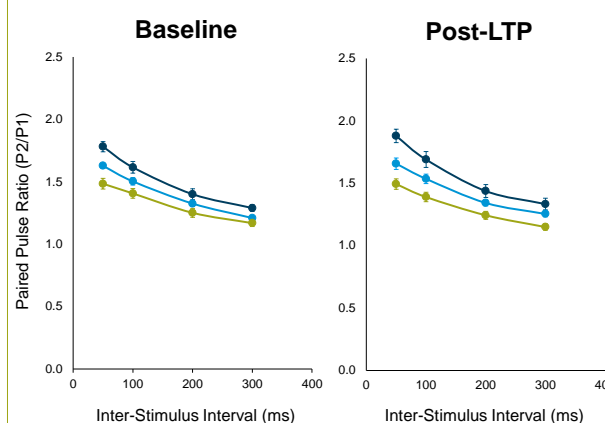
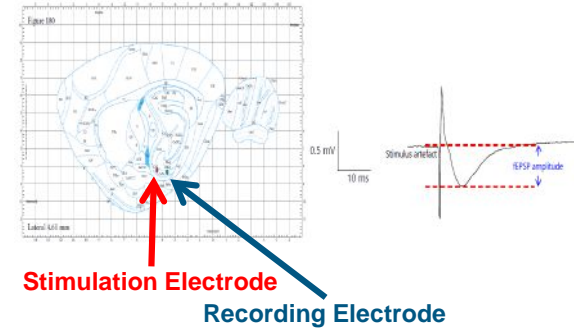
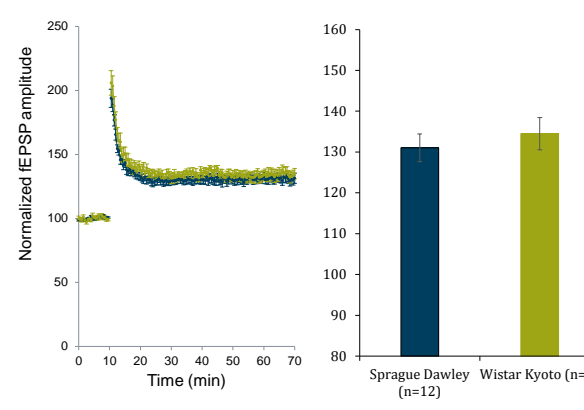


FIGURE 2
Ventral Hippocampus
(CA3 → CA1)

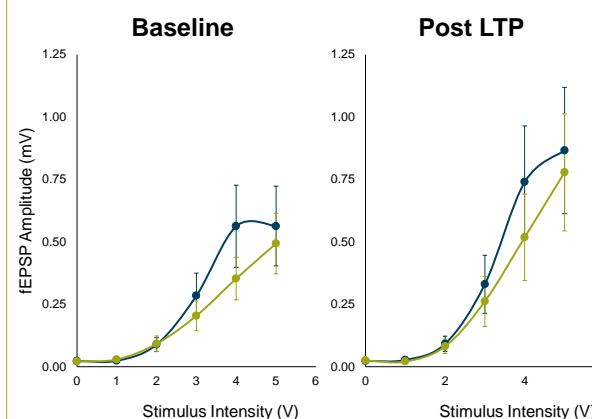


● Sprague Dawley ● Wistar ● Wistar-Kyoto

Long-Term Plasticity (LTP)



Synaptic Connectivity



Pre-Synaptic Short-Term Plasticity

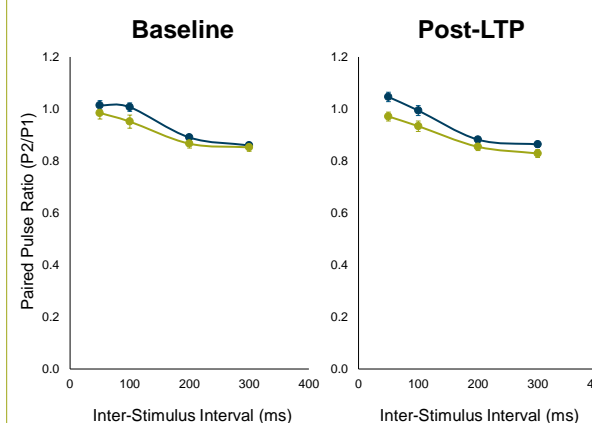
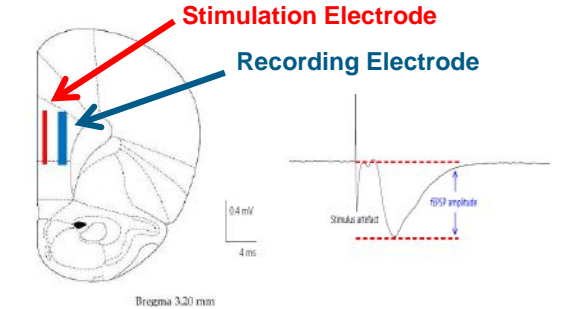
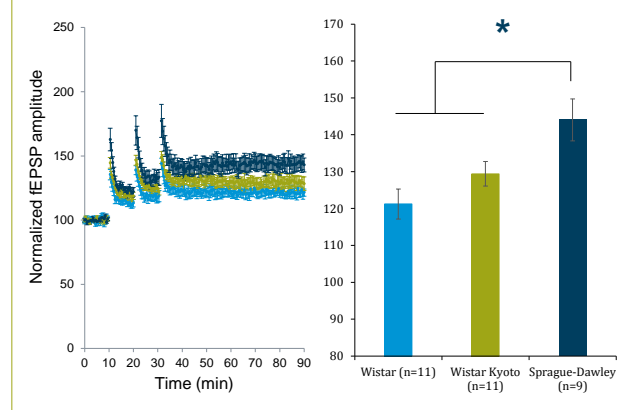


FIGURE 3
Medial Prefrontal Cortex
(LII-III → LV)

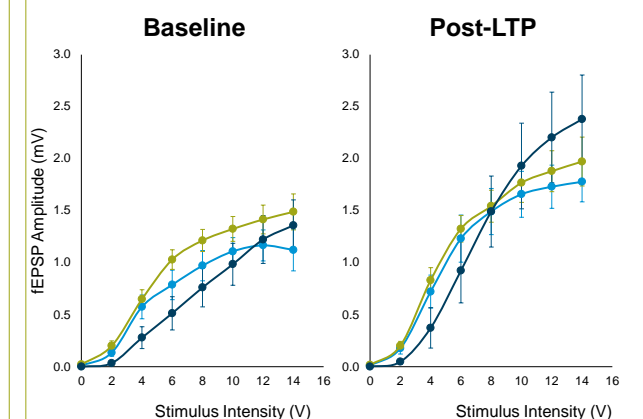


● Sprague Dawley ● Wistar ● Wistar-Kyoto

Long-Term Plasticity (LTP)



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