Palmitoylethanolamide (PEA) causes a dose-dependent decrease in thalamocortical brain activity: A functional MRI study in awake rats

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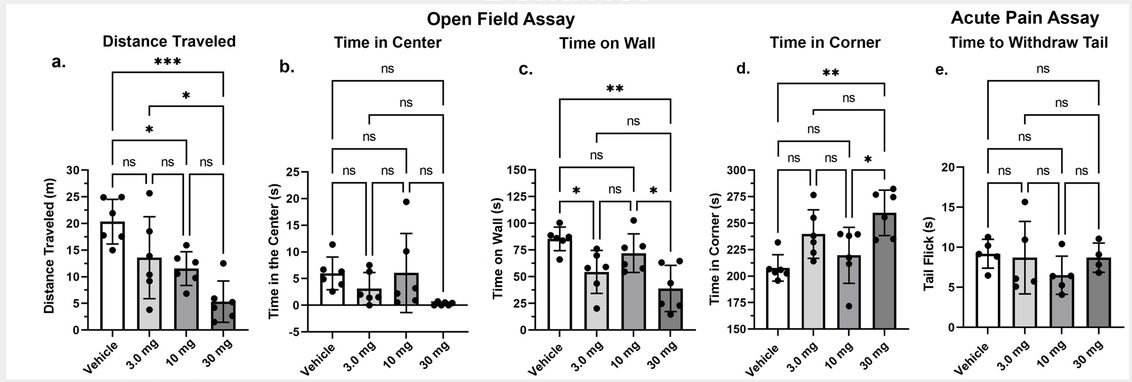
Background, Rationale & Approach

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide, belonging to a class of lipid signaling molecules, the N-acylethanolamines (NAEs) that includes the endogenous cannabinoid anandamide (AEA). There are numerous preclinical studies showing PEA is an effective analgesic, anti-inflammatory agent and anticonvulsant in different rodent models. The actual mechanism of action for PEA, i.e., molecular targets, and neural circuits, is unknown. PEA is a promiscuous molecule that impacts multiple signaling pathways. It is thought to have an "entourage effect ", enhancing the levels of AEA by indirectly competing with FAAH the primary enzyme for degrading both NAEs. Functional magnetic resonance imaging in awake animals provides a mean of evaluating the effect of exogenous PEA on global brain activity. Specifically, pharmacological MRI (phMRI) provides a view of the integrated neural circuits that respond in a dose-dependent manner to a test compound. When combined with resting state functional connectivity (rsFC) the key nodes and connections in these circuits can be identified. The present studies were undertaken to characterize or "fingerprint" the functional activity of exogenous PEA on brain activity in awake rats using BOLD imaging.

Experimental Design

Rats were randomly assigned to one of five experimental groups: 1) controls without vehicle, n=5; 2) gum Arabic vehicle, n=4; 3) 3.0 mg PEA, n=6; 4) 10 mg PEA, n=5; and 5) 30 mg PEA, n=6. Images were registered to, and analyzed, using a 3D MRI rat atlas providing site-specific data on 173 different brain areas. All experiments were conducted under dim red illumination between 10:00 hrs and 18:00 hrs to avoid the transitions between the L-D dark cycles. Rats were acclimated to the awake imaging protocol for five days before imaging. Imaging was conducted on a 7T small animal scanner

Behavior



Shown are dot (subjects) and bar graphs for the motor activity and anxiety in the open field assay and pain in the tail flick assay for the different doses of PEA. High dose PEA significantly reduces motor behavior as noted in distance traveled. The enhanced time in the corner with high dose PEA maybe a consequence of reduced motor activity or resting in a 'safe space" There was no effect of on acute pain as assessed by time to withdraw of the tail.

Summary and Speculation

Given the reported behavioral effects of PEA, we hypothesized it would interact with neural circuitry associated with pain, as identified in other awake imaging studies on rodents and key nodes associated with the genesis of clonic-tonic seizures. PEA affected these neural circuits, but to our surprise the drug showed a negative BOLD, inverse dose response with the lowest dose (1mg/kg) having the greatest increase on negative BOLD. This response is interpreted as a decrease in brain activity and would require future studies using measurements of cerebral blood flow and EEG to help in this interpretation. Also, surprisingly was the decrease in motor activity as noted in the open field and the significant time in the corner. Is this a soporific effect of PEA? It would make sense to rest in a "safe space." However, high dose PEA increased functional connectivity in basal ganglia, cortex, thalamus, amygdala, pons, olfactory system and cerebellum. The cerebellum communicates to the brain through the three deep cerebellar nuclei. The dramatic increases in connectivity to the cerebral cortex, olfactory system and key brainstem nuclei e.g., solitary tract n. and locus coeruleus suggest cerebellar influence over perception, sensory/motor integration and behavior

Acknowledgement

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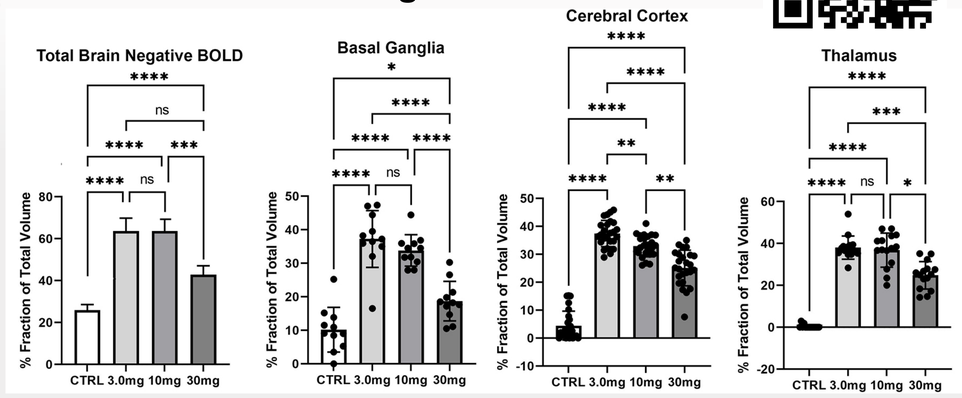
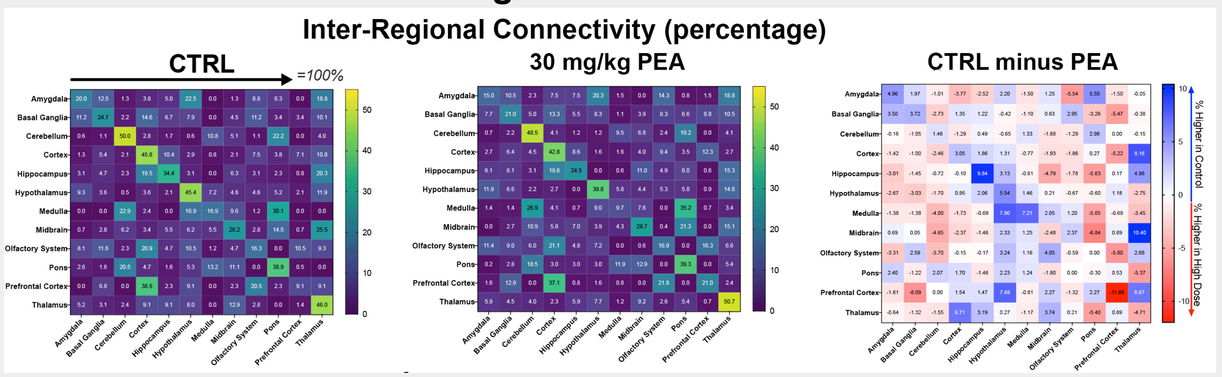
Results

BOLD Pharmacological Functional MRI

Shown are the changes in the precent fraction of the total volume of activation (voxel numbers) for the whole brain and different brain regions. Note the dose-dependent decrease in negative BOLD across all areas. The changes in positive BOLD were minimal but did increase with the 30 mg/kg dose of PEA.

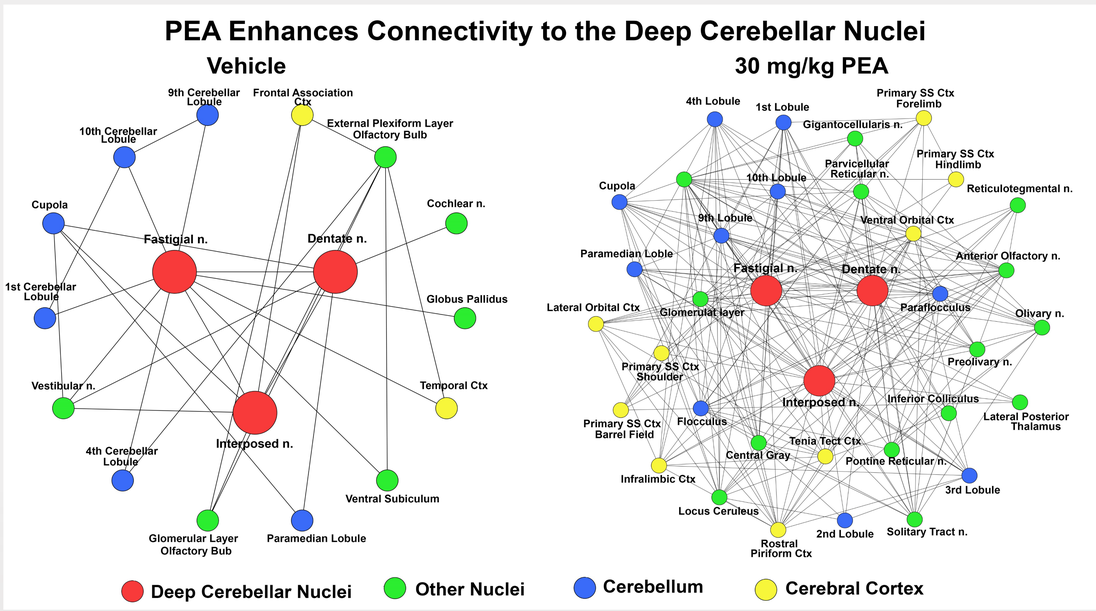


BOLD Resting State Functional MRI



There were significant changes in connectivity with the 30mg/kg dose of PEA as compared to vehicle. Shown are heat maps showing the connectivity between major brain areas as a percentage.

PEA Enhances Connectivity to the Deep Cerebellar Nuclei



Shown are lines (degrees) connecting the three deep cerebellar nuclei (red) to different brains areas (nodes) following vehicle and PEA treatment.