

Decoupling of the cAMP activity and cerebral hemodynamic responses to cocaine challenge in adult and adolescent rat



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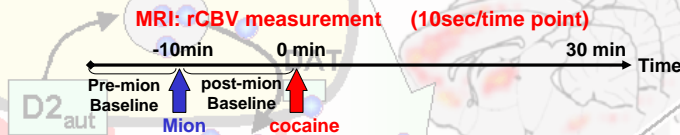
Introduction

- During adolescence, the dopaminergic system in the brain is undergoing dramatic changes that include synaptic pruning and alterations in dopaminergic receptor numbers. Here we used a multimodal approach to probe the age differences in the dopaminergic response to cocaine challenge.
- pHMRI was used to map the neuronal responses to acute cocaine challenge in P22 (postnatal 22 days) and adult rats.
- Microdialysis was used to measure the dopamine concentration to cocaine challenge in the caudate/putamen (CPU) in P22 and adult rats.
- cAMP activity was used to invest the post-synaptic activity in response to cocaine challenge in P22 and adult rats.

Method

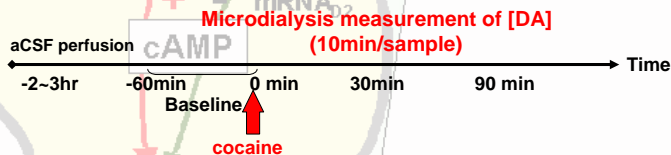
MRI (rCBV response)

- **Subjects** P22 (22 days old, n=7) and adult (>60 days old, n=6) SD rats.
- **Anesthesia** 1% halothane in 1:1 O₂ & N₂O.
- **Cocaine** 0.5mg/kg, iv (Sigma).
- **MRI measurement** Gradient echo EPI sequence (16 segments, TR/TE 625/6ms) using IRON method at a Bruker 9.4T scanner.



Microdialysis (synaptic DA concentration)

- **Subjects** P22 (22 days old, n=5) and adult (>60 days old, n=4) SD rats.
- **Anesthesia** 1% halothane in 1:1 O₂ & N₂O.
- **Probe coordinates in CPU** Based on the Paxino's atlas, and anatomically scaled down to fit the brain size for P22 rats. Final coordinates: P22 [AP 0.35 ML 2.7 DV 5.8]; Adults [AP 0.48 ML 3.2 DV 7.4].



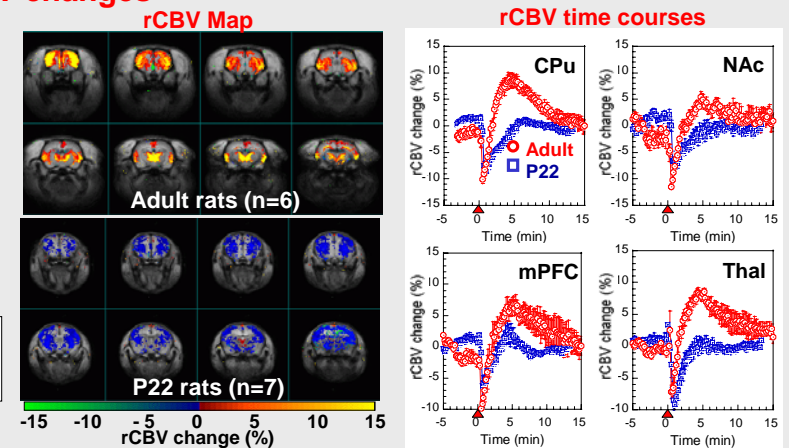
cAMP activity

- **Subjects** P22 (22 days old, n=6) and adult (>60 days old, n=4) SD rats.
- **Cocaine** 0.5mg/kg, iv (Sigma), brain samples obtained 6 min post injection.
- **Measurement** cAMP Biotrak Enzymeimmunoassay (Amersham).
- **Region** CPU, Thalamus, Medial Prefrontal Cortex and Nucleus Accumbens.

Cocaine induced rCBV changes

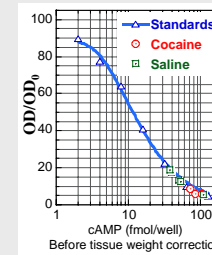
Adult rats cocaine induced bi-phasic rCBV changes (negative followed by positive rCBV changes) in the CPU, NAc, mPFC, and thalamus.
P22 rats have a longer negative rCBV component but lack the positive rCBV component.

CPu: Caudate/putamen
 NAc: Nucleus accumbens
 mPFC: Medial prefrontal cortex
 Thal: Thalamus

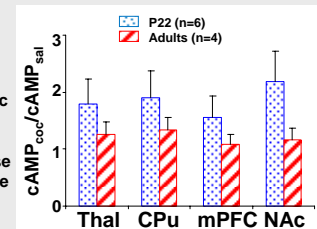


cAMP activity

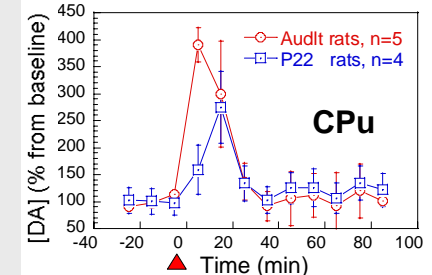
- cAMP concentration was measured by relative optical density @450nm.
- cAMP concentration for each brain sample was determined by the calibration curve (obtained from standard cAMP solutions at various concentrations).



- The cocaine-induced cAMP activity was stronger in P22 than adult rats.
- This set of data indicates a stronger excitatory post-synaptic state in the P22 rats.
- Since an increased cAMP activity could potentially increase rCBV, this data thus excludes the postsynaptic contribution to the rCBV responses in the P22 rats.



Cocaine induced [DA] changes



- Both age groups showed a cocaine-induced DA increase in CPU.
- DA concentration in the first post-cocaine dialysate was greater in adult than in P22 rats.
- This set of data indicates that the synaptic dopamine concentration (increases) was not responsible for the rCBV pattern differences at different ages.

Summary & Discussion

- In contrast to the biphasic rCBV response, P22 has a prolonged rCBV decrease to cocaine challenge.
- This rCBV decrease in P22 rats is decoupled to cAMP activity and synaptic dopamine concentration.
- We hypothesize that the absence of the positive rCBV component in the P22 rats may be due to
 1. a faster feedback mechanism in the dopamine release;
 2. a stronger vasoconstriction via D2/D3 receptors on vessel-bound glia cells; or
 3. immature expression of D1/D5 receptors in the microvessels of the P22 animals.

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