The Effects of Perinatal or Peripubertal Exposure to Tetrahydrocannabinol on Developmental Milestones, Motor Behavior, and Somatosensation in Rats.

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BACKGROUND

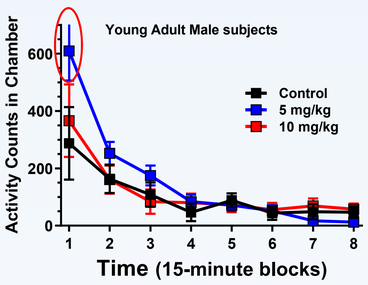
Tetrahydrocannabinol (THC) is the primary psychoactive component in marijuana, one of the most frequently used recreational drugs. The longitudinal effects of chronic or gestational use of THC are poorly understood. As legalization of marijuana becomes prominent across the United States, it is important to understand the mechanisms of THC and its possible effects on the developing fetal and adolescent brain. Both pregnant and nursing mothers who ingest THC, expose their offspring through the placenta or breastmilk, which can promote structural and motor effects at birth or a considerable amount of time after birth. Adolescents are another group of cannabis users where compromised brain development is a concern. THC exposure during gestation and/or adolescence could alter psychomotor behavior through direct actions on cannabinoid receptors or secondarily, because of downstream effects on the other neurotransmitters regulated by cannabinoid receptors.

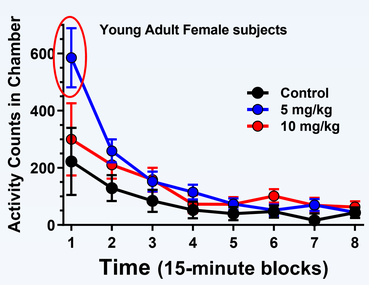
The current study used a rat model to examine THC's effects on early development and long-term sensory and motor behavior. Cohort one featured prenatal THC exposure where pregnant rats were administered THC from gestational day 1 to postnatal day 21. Cohort two consisted of juvenile exposure where pups were directly administered THC from postnatal day 22-40.

METHODS

- Dose Groups: control, low (2 mg/kg), medium (5mg/kg), high (10mg/kg)
- Perinatal Cohort: dosed Gestational Day (GD) 1 to Postnatal Day (PND) 21
- Developmental Milestone Tests
  - -Righting Reflex: pup is placed on side and timed to determine how long it takes to return to upright posture
  - -Eye-opening: to determine the age when both eyes unseal
- Somatosensory
  - -Tail Flick latency: a heat stimulus is directed at the rat's tail and timed to determine latency until tail is moved
- Juvenile Cohort: dosed PND 22-40
- 2-hour Locomotor: Animals are introduced to an operant chamber for 2 hours. Their locomotor activity levels are recorded during this time.
- Maternal THC Levels:
- Blood samples were collected from dams in early postnatal period to measure THC and metabolite levels
- Frozen samples were shipped to TVMDL for analysis via a LC-MS/MS procedure with protein precipitation.

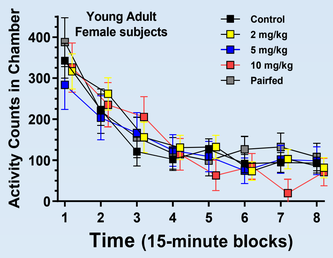
Juvenile Cohort

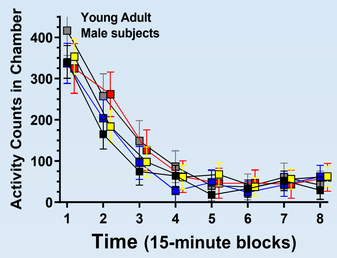


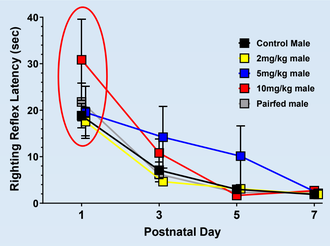


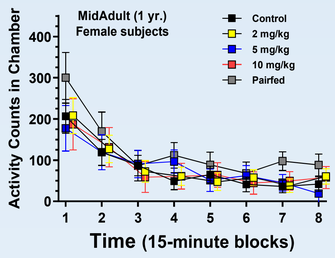
FIGURES

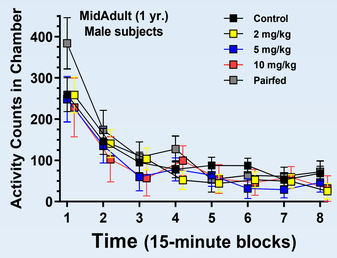
Perinatal Cohort

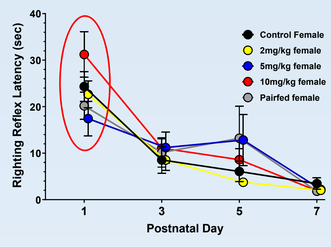


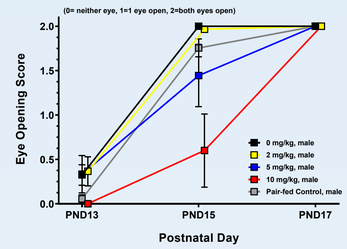


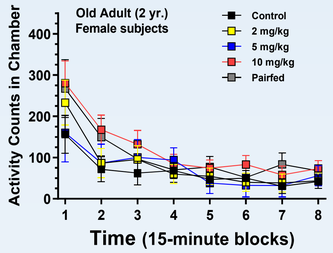


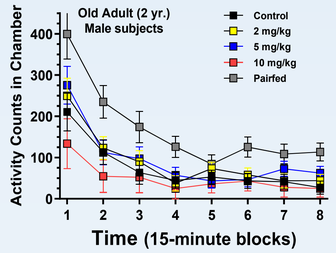


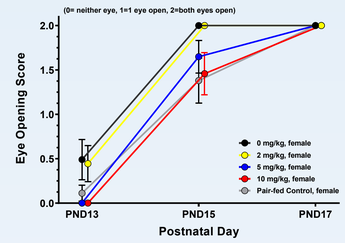


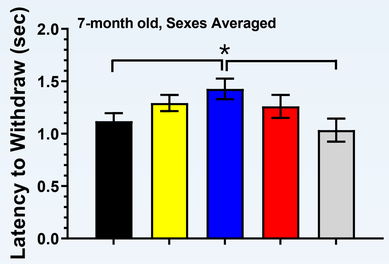


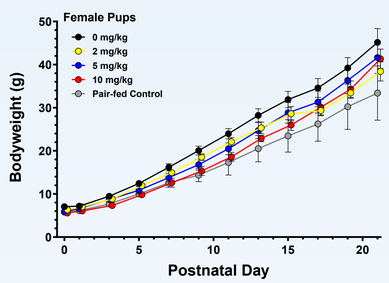


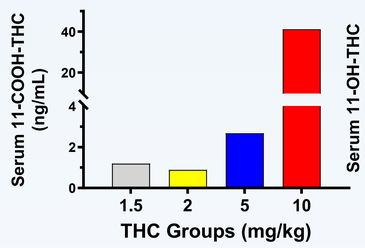


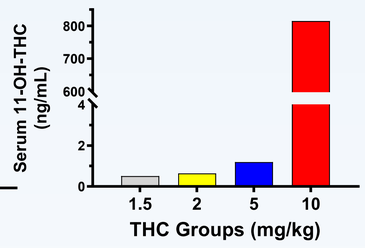


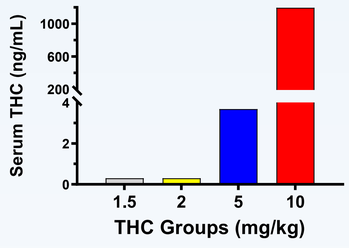












RESULTS

Pup Development

- No significant effect of Bodyweight and Crown-Rump Length, but controls were always bigger and heavier than dosed groups
- High Dose groups took the longest to return to their stomach for righting reflex
- There was a significant effect on Eye opening, control animals had both eyes open by PND15 but dosed groups did not

Maternal Blood levels suggest that a threshold exists between the 5 and 10mg/kg dose group where dams can no longer metabolize THC between consecutive doses.

Somatosensory: the 5mg/kg group was slower to react than other dose groups

Locomotor

- No THC effect in the perinatal cohort
- Juvenile cohort shows an effect within the first 15 minutes with the 5mg/kg groups being more active.

CONCLUSION

The current results represent only a portion of the data that our lab has collected over the past 5 years. Assessment of the juvenile cohort is ongoing. These developmental and somatomotor data will be used to help interpret the cognitive analyses that we are also conducting.

It is apparent from the current data that THC can produce "non-monotonic" dose-response effects. For example, the 5 mg/kg group had the slowest tail flick withdraw latency, even though the 10 mg/kg group had greater milestone delays (eye opening and righting reflex). It is also apparent that the age of THC exposure influences the behavioral consequences. For example, there were no locomotor activity effects in the perinatal cohort but there was a THC effect in the juvenile cohort.

It is also worth noting that the dams that were dosed daily with 10mg/kg THC displayed dramatic bioaccumulation. This dose was well in excess of their ability to metabolize and excrete and might account for some of the diminished maternal care we reported previously.

Support

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