

UAMS



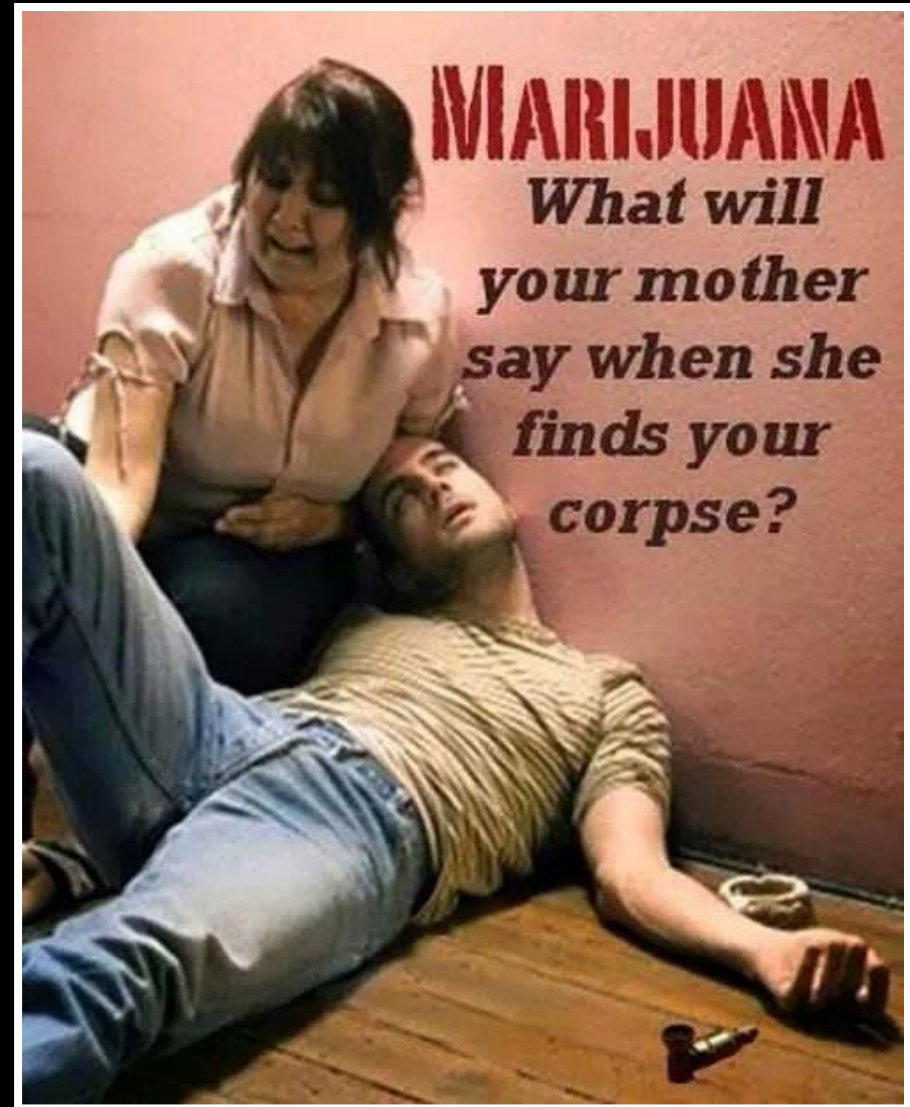
COLLEGE OF MEDICINE
DEPARTMENT OF
PHARMACOLOGY & TOXICOLOGY

William E. Fantegrossi, Ph.D.

Pharmacodynamic and pharmacokinetic factors impacting the *in vivo* pharmacology and toxicology of K2 synthetic marijuana

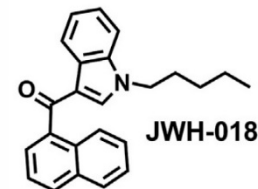
Synthetic Cannabinoids

- Recent normalization of marijuana use is based to some extent on its well-known safety profile and relatively low toxicity risk.
- References to high-efficacy synthetic cannabinoids as “fake marijuana” have hampered efforts to educate the public about potential toxic effects of these substances.

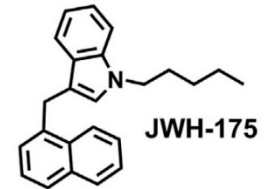


Synthetic Cannabinoids

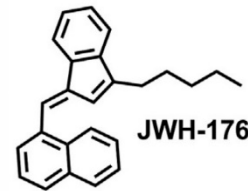
- High degree of structural diversity among compounds.
- Not unusual to find 2 or more compounds in the same sample.
- All compounds typically possess higher affinity for and efficacy at CB1 receptors as compared to Δ^9 -THC, and are usually more potent *in vivo*.



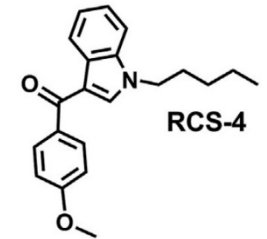
Naphthoylindole



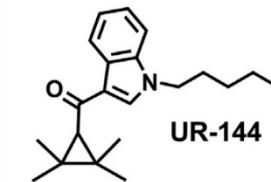
Naphthylmethylindole



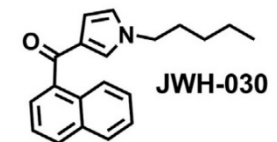
Naphthylmethylindene



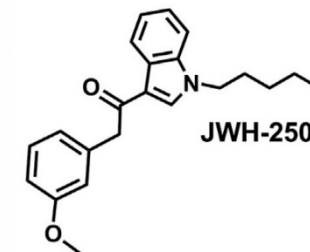
Benzyolindole



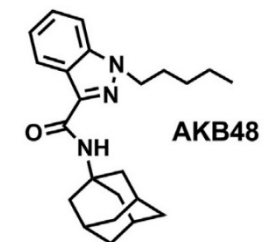
Tetramethylcyclopropylindole



Naphthoylpyrrole



Phenylacetylindole



Adamantoylindole

Synthetic Cannabinoids



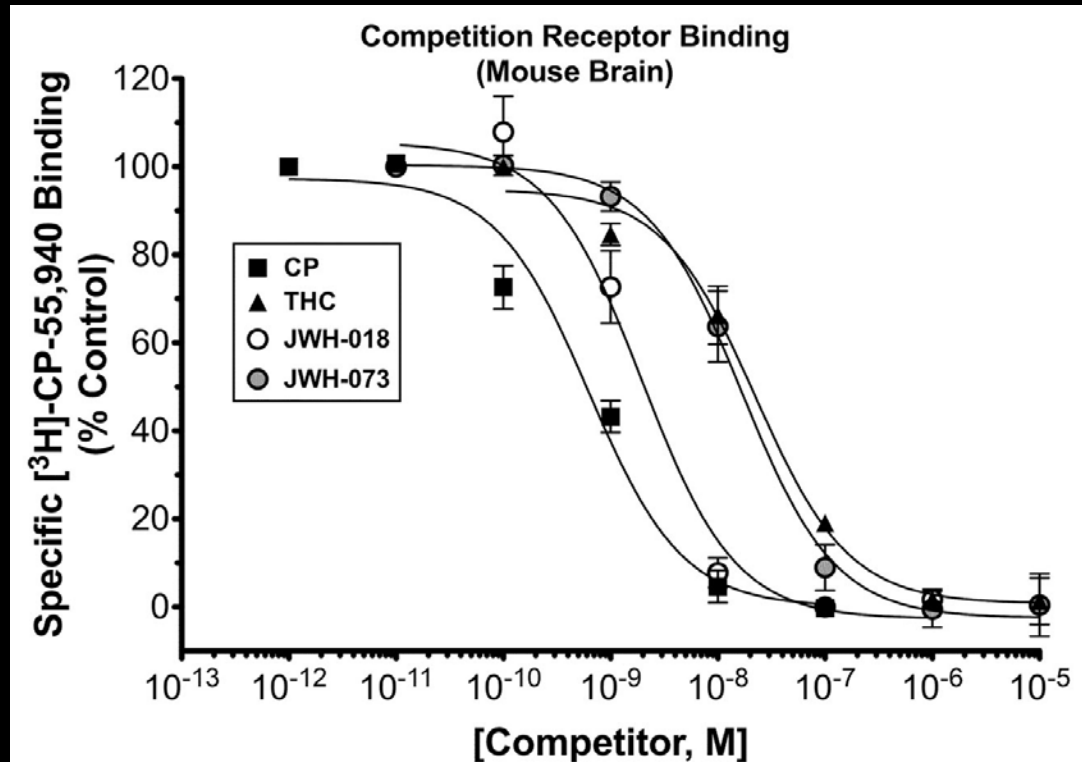
R – butyl = JWH-073

R – pentyl = JWH-018

Etc.

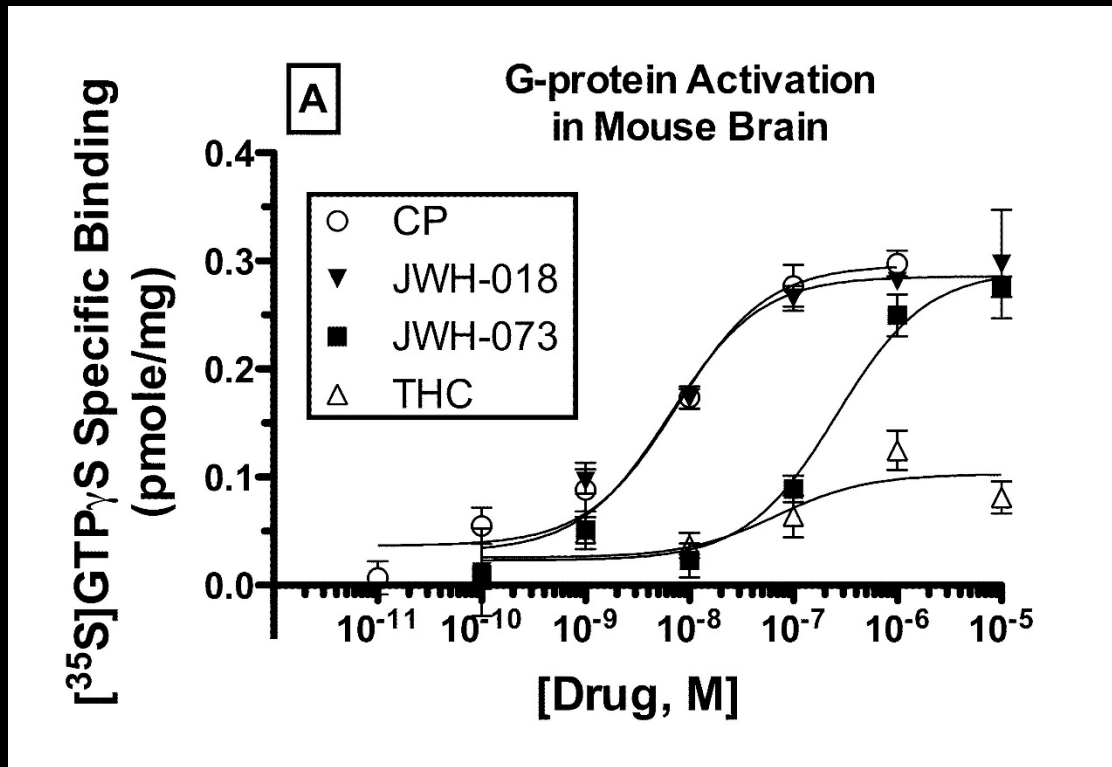
- In 1992, John W. Huffman (Clemson U) began synthesizing a series of several hundred compounds for SAR studies designed to tease out physiological function of CBR subtypes.

Synthetic Cannabinoids



- Synthetics have higher (JWH-018) or comparable (JWH-073) affinity to Δ^9 -THC.

Synthetic Cannabinoids



- Synthetics are full CB1 agonists, while Δ^9 -THC is a partial CB1 agonist.

Synthetic Cannabinoids

- Essentially all preclinical studies with these compounds involve systemic injection, but the preferred route of administration in human users is via smoking.

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Short communication

A survey study to characterize use of Spice products (synthetic cannabinoids)

Ryan Vandrey^{a,*}, Kelly E. Dunn^a, Jeannie A. Fry^a, Elizabeth R. Girling^{a,b}

^a Johns Hopkins University School of Medicine, Baltimore, MD 21224, United States

^b Towson University, Towson, MD 21252, United States

products were primarily smoked (via pipe, cigarette, blunt, or water pipe/bong), though administration via vaporization, oral ingestion, and rectal ingestion were also reported.

Synthetic Cannabinoids

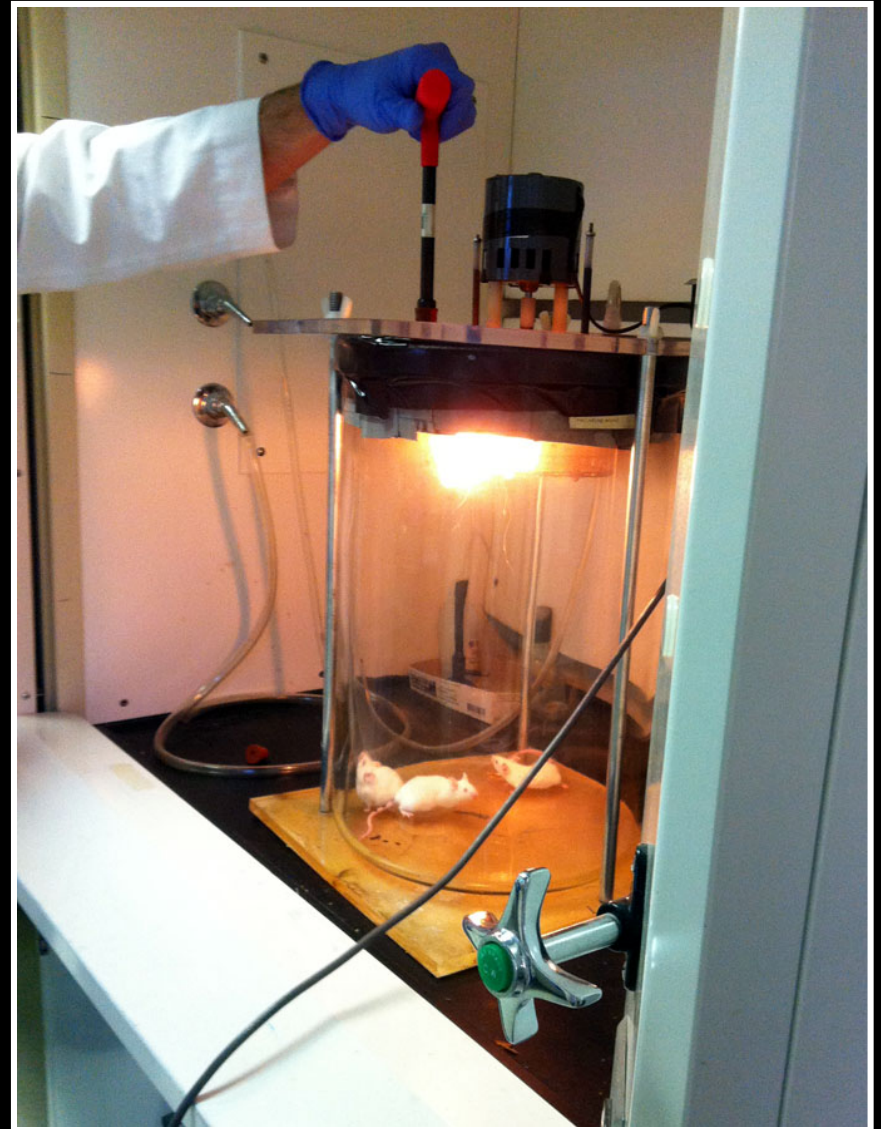
A background image of a city skyline at night with illuminated buildings and a bridge.

- **Formation of Phase I metabolites is probably maximized when drugs are administered orally or via IP injection, and likely minimized when drugs are smoked. ¹**
- **Thus, systemic injection of SCBs in laboratory animals may overestimate biological effects due to contribution of active hydroxylated metabolites.**
- **We therefore compared a range of doses of Δ^9 -THC, JWH-018 and JWH-073 in several in vivo assays after IP injection or inhalation of volatilized compound.**

¹ Pond SM and Tozer TN (1984) First-pass elimination. Basic concepts and clinical consequences. *Clin Pharmacokinet* 9(1):1-25

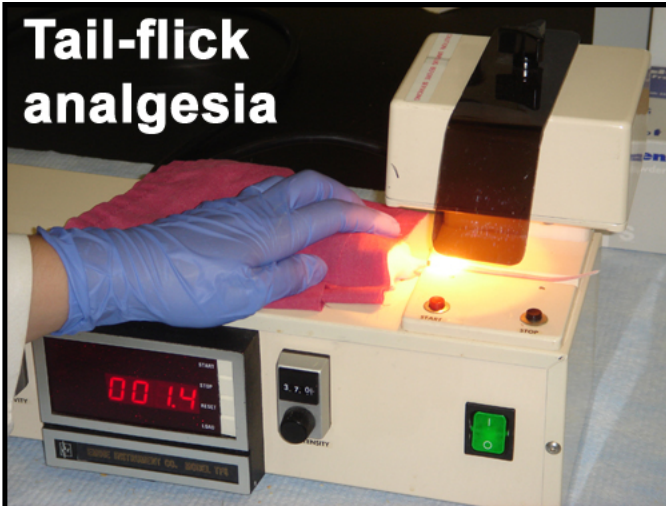
Synthetic Cannabinoids

- Apparatus for whole-body exposure to volatilized drugs.
- Mice exposed 3 at a time.
- 10 min exposure, with room air added 5 min into exposure for 60 seconds.



Synthetic Cannabinoids

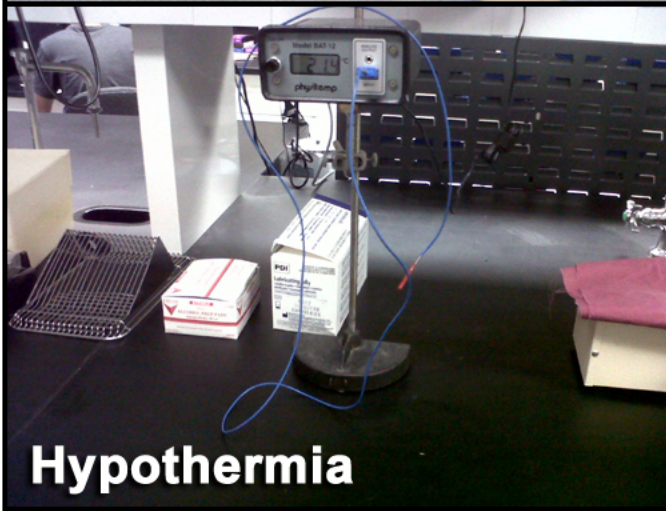
**Tail-flick
analgesia**



**Horizontal bar
catalepsy**



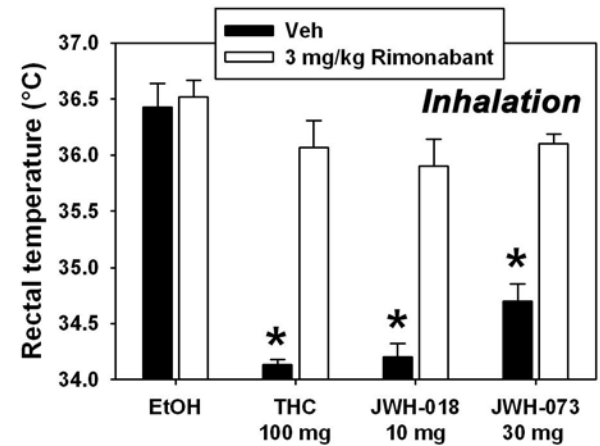
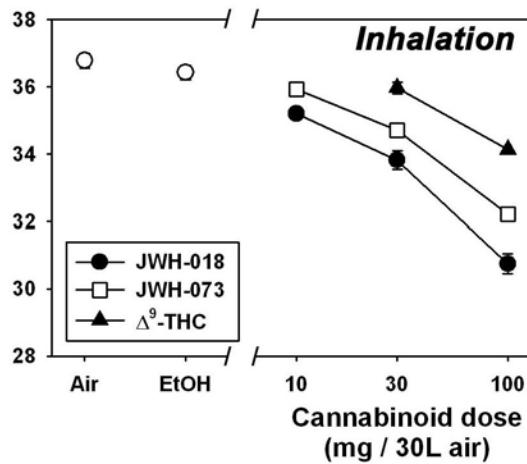
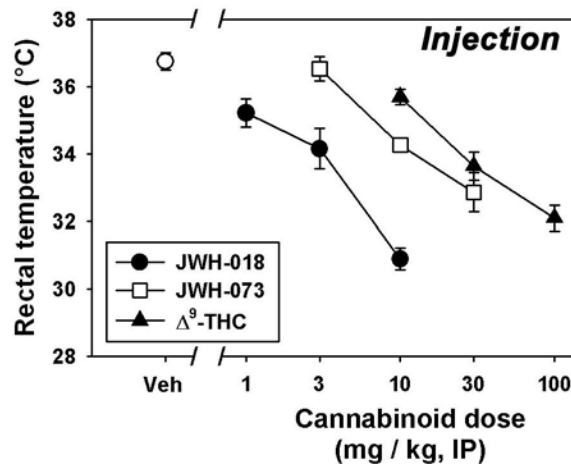
Hypothermia



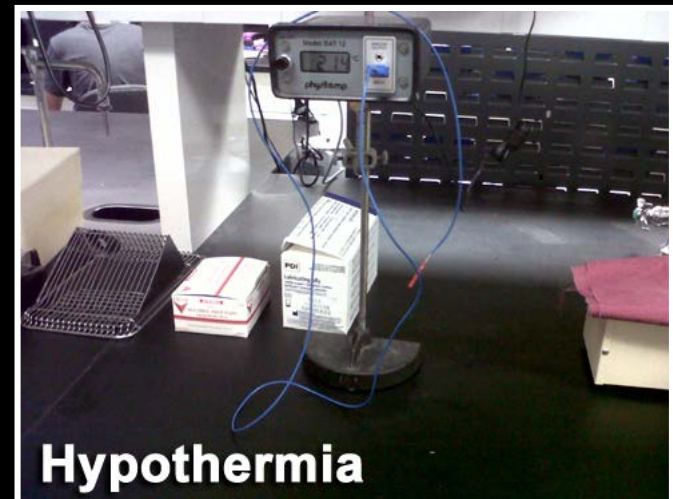
Locomotor suppression



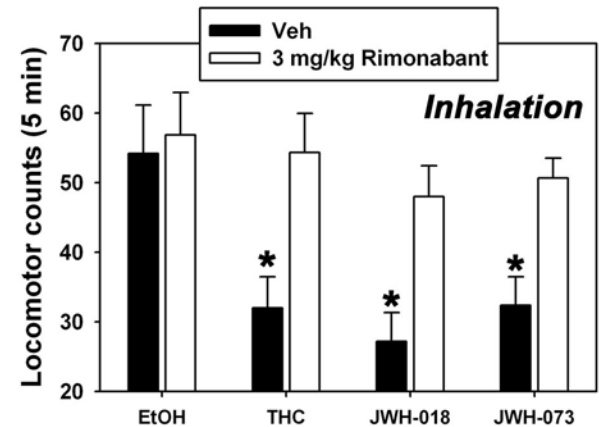
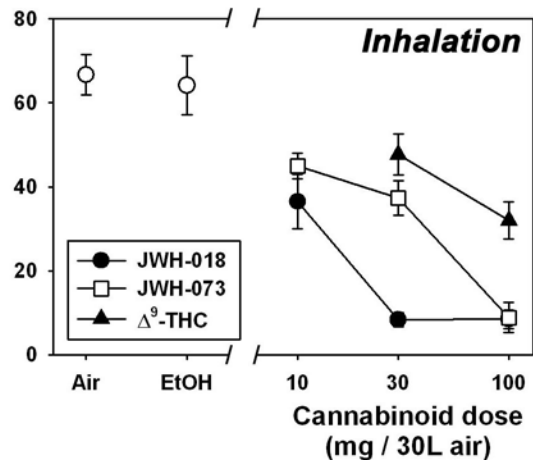
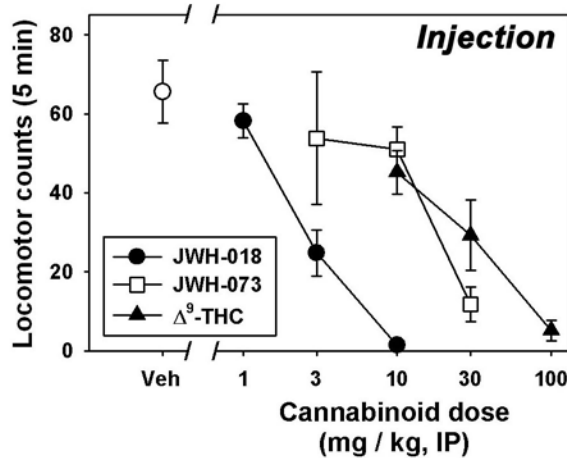
Synthetic Cannabinoids



- Similar hypothermic effects across routes, and same order of potency.
- Hypothermic effects of inhaled CBs were attenuated by rimonabant pretreatment.



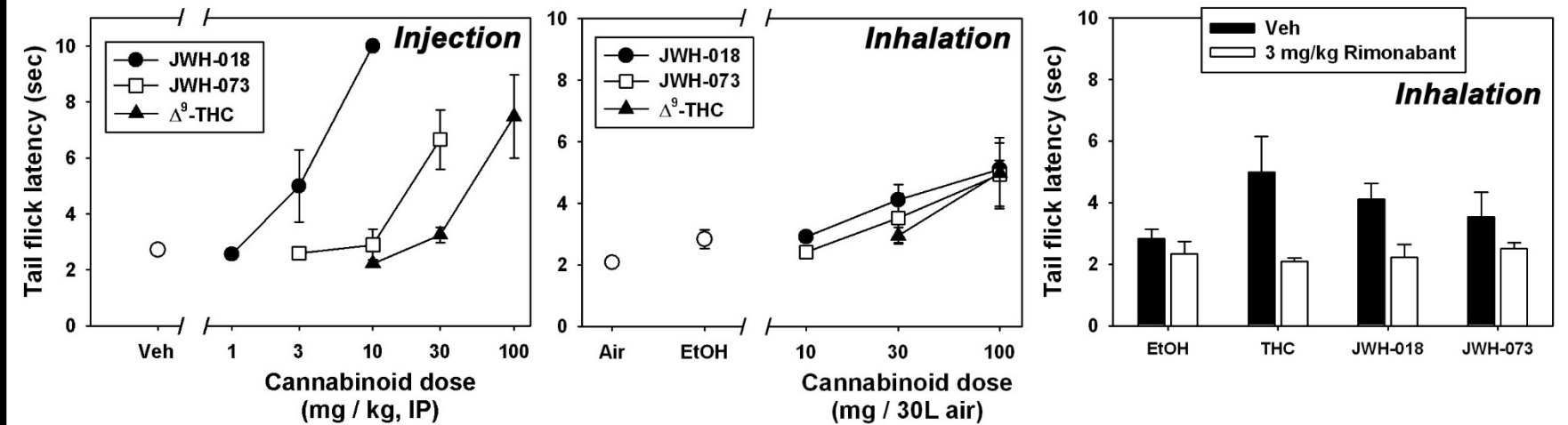
Synthetic Cannabinoids



- Similar locomotor effects across routes, and same order of potency.
- Locomotor effects of inhaled CBs were attenuated by rimonabant pretreatment.



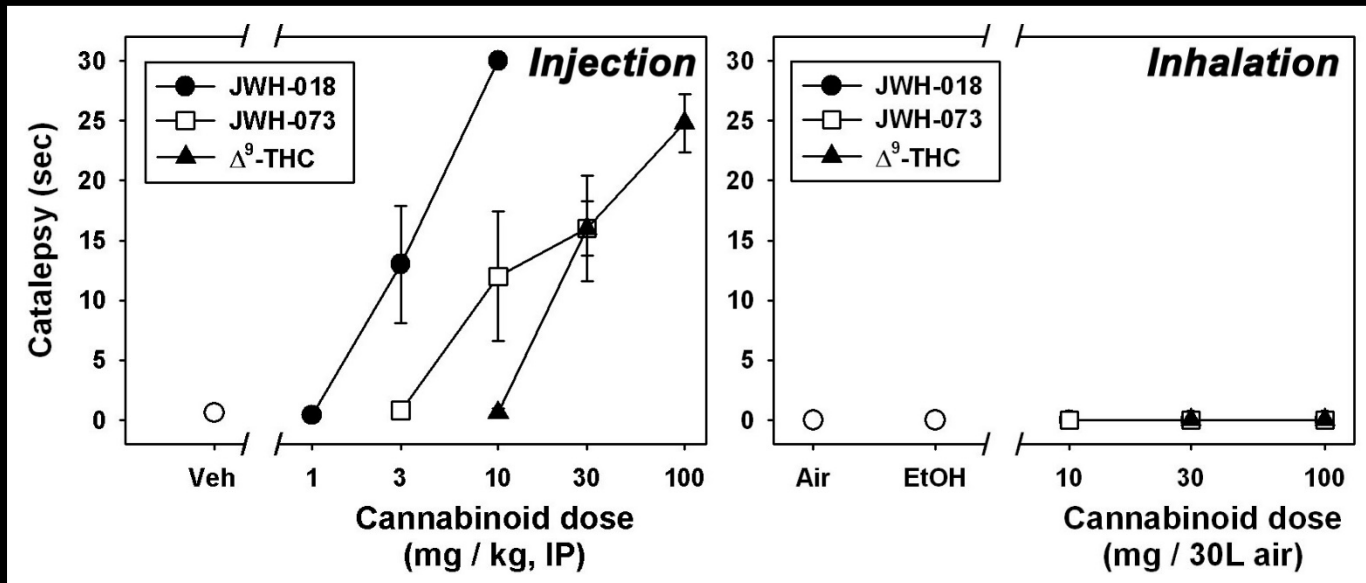
Synthetic Cannabinoids



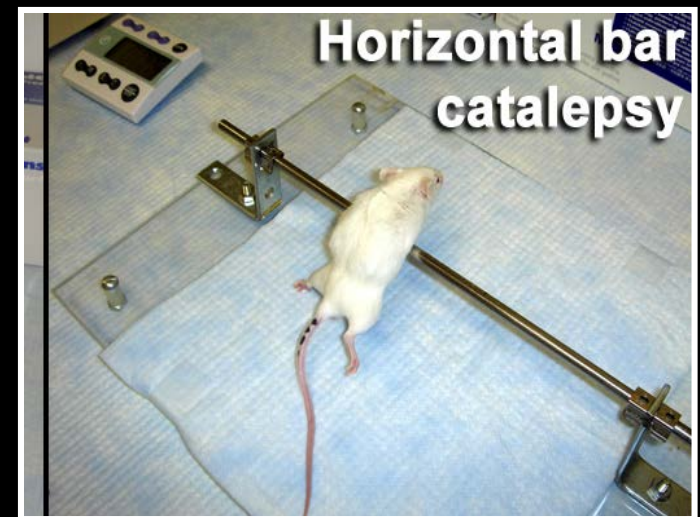
- Weaker analgesic effects after inhalation, but same order of potency.
- Effects not really big enough to block with rimonabant.



Synthetic Cannabinoids

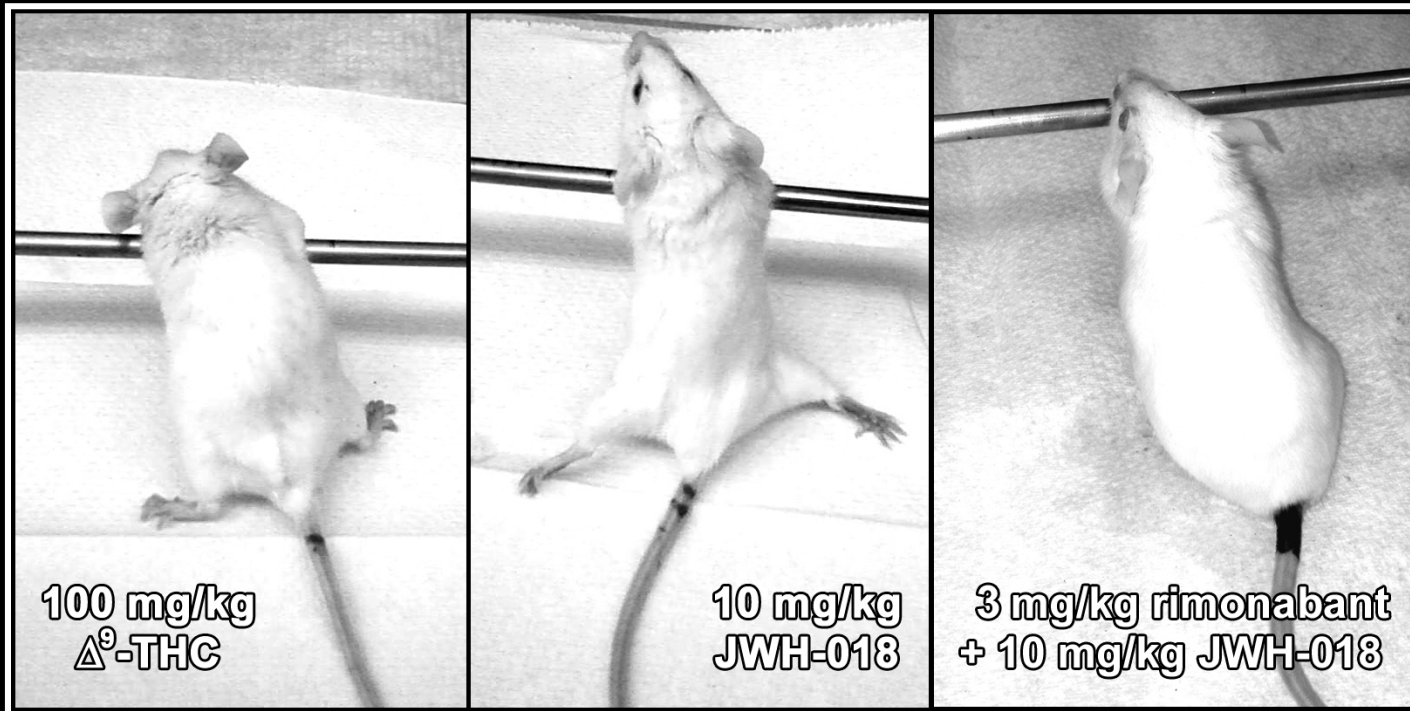


- Cataleptic effects were not observed after inhalation.
- Interesting qualitative differences between Δ^9 -THC and SCBs...



Synthetic Cannabinoids

IP administration



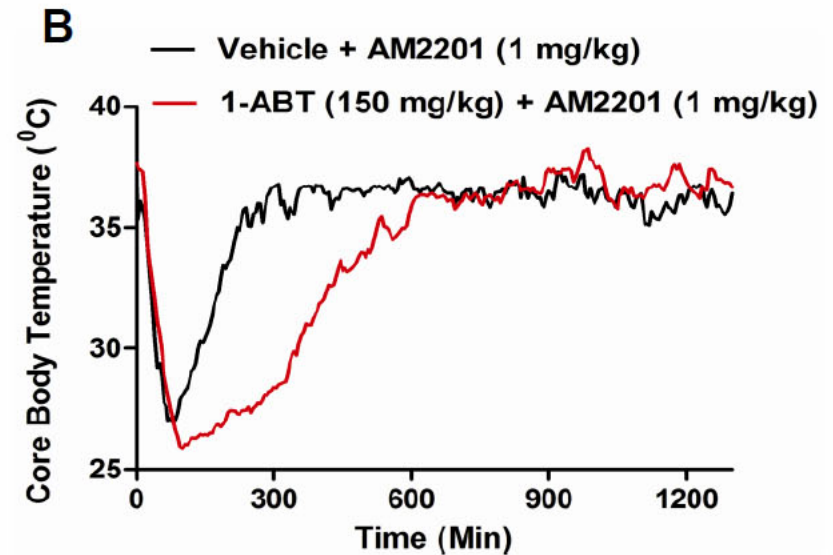
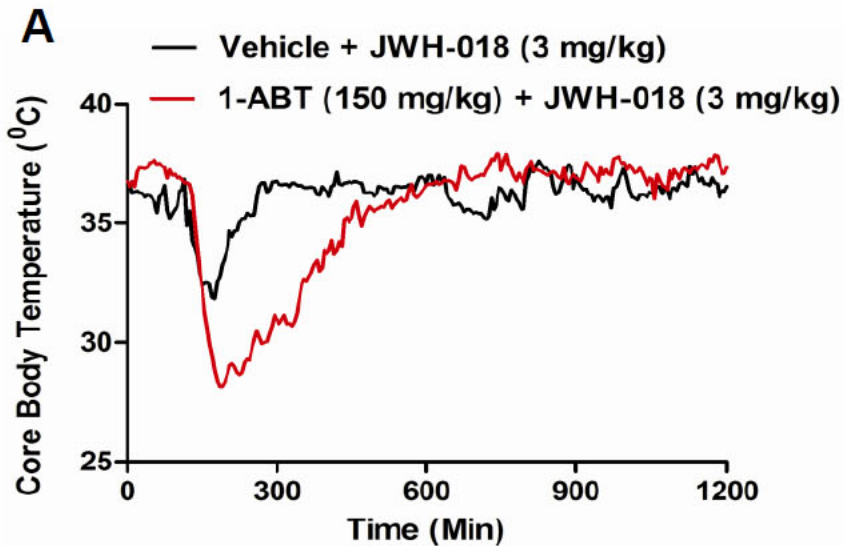
- Leg splay, full-body jerks, and handling-induced convulsions observed with JWH-018, but not with Δ^9 -THC, were blocked by rimonabant.

Synthetic Cannabinoids



- Convulsions do not occur unless animals are disturbed.
- Convulsions are CB1-mediated, and are completely blocked by rimonabant.

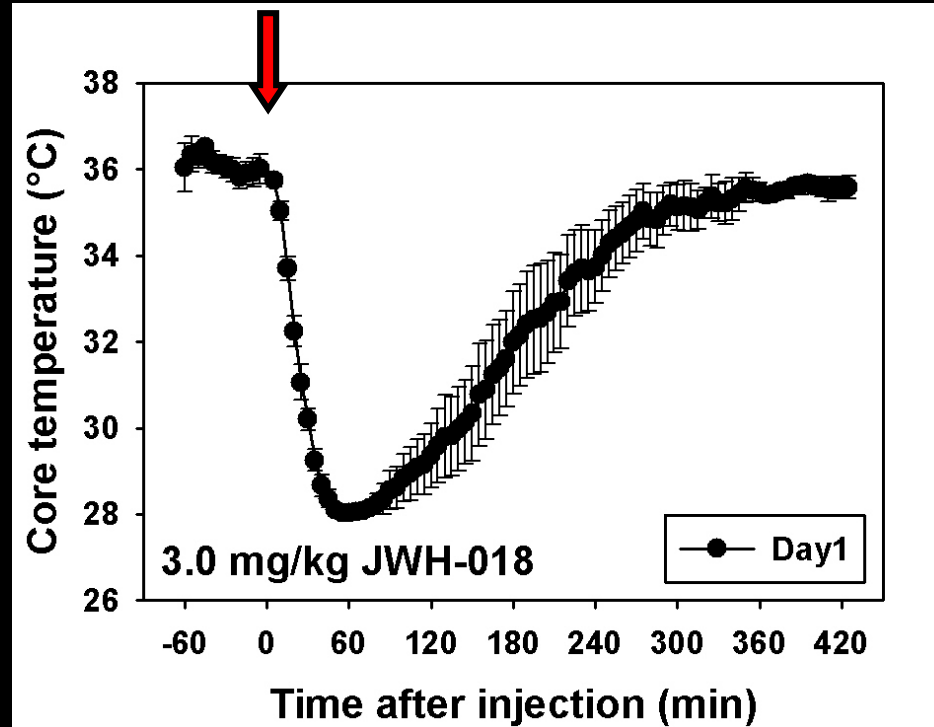
Synthetic Cannabinoids



- Pretreatment with 150 mg/kg of the global P450-enzyme inhibitor 1-aminobenzotriazole (1-ABT) potentiates hypothermic effects of SCBs – **consistent with detoxification?**

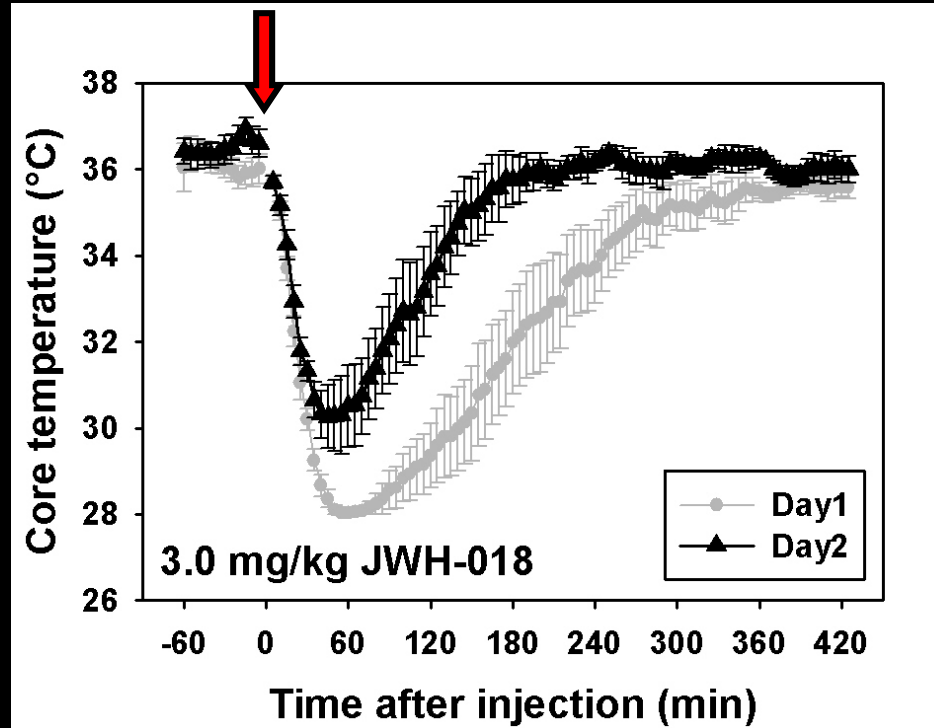


Synthetic Cannabinoids



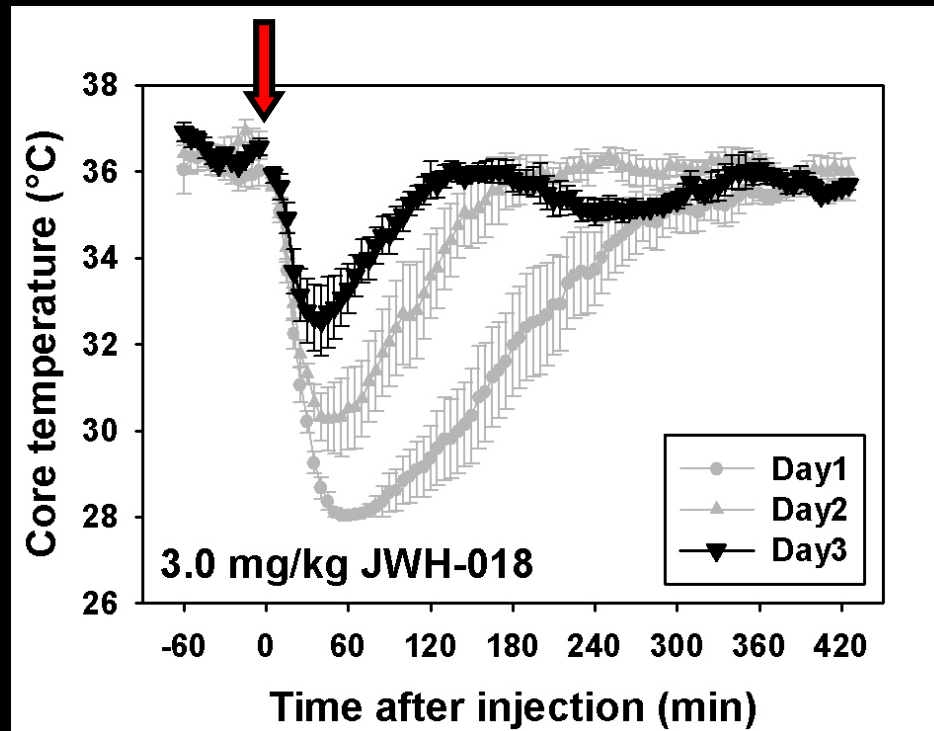
- Profound tolerance develops to the hypothermic effects of JWH-018

Synthetic Cannabinoids



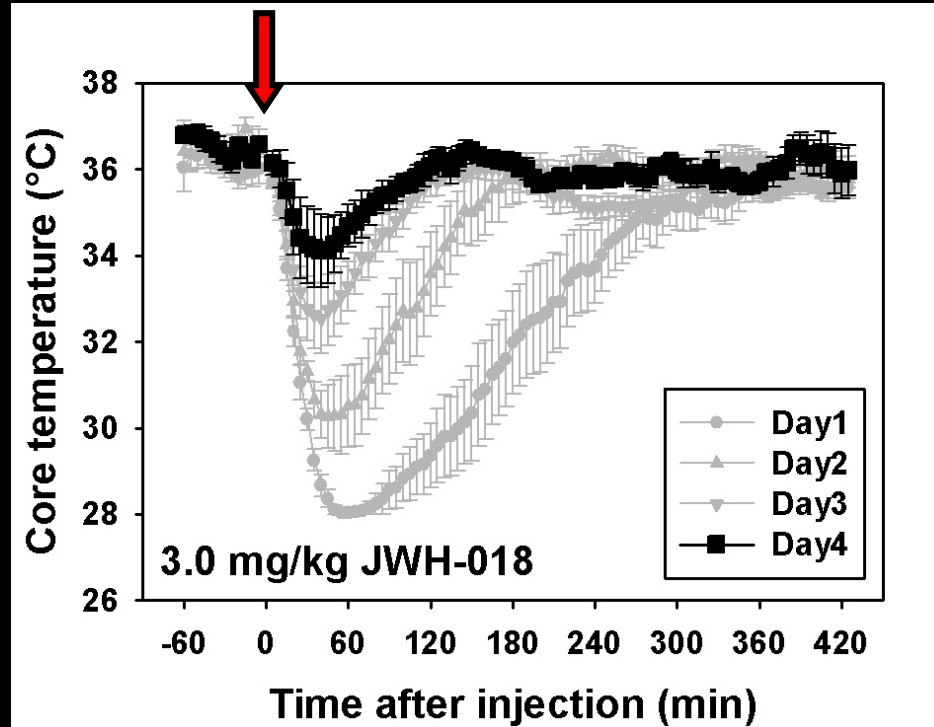
- Profound tolerance develops to the hypothermic effects of JWH-018

Synthetic Cannabinoids



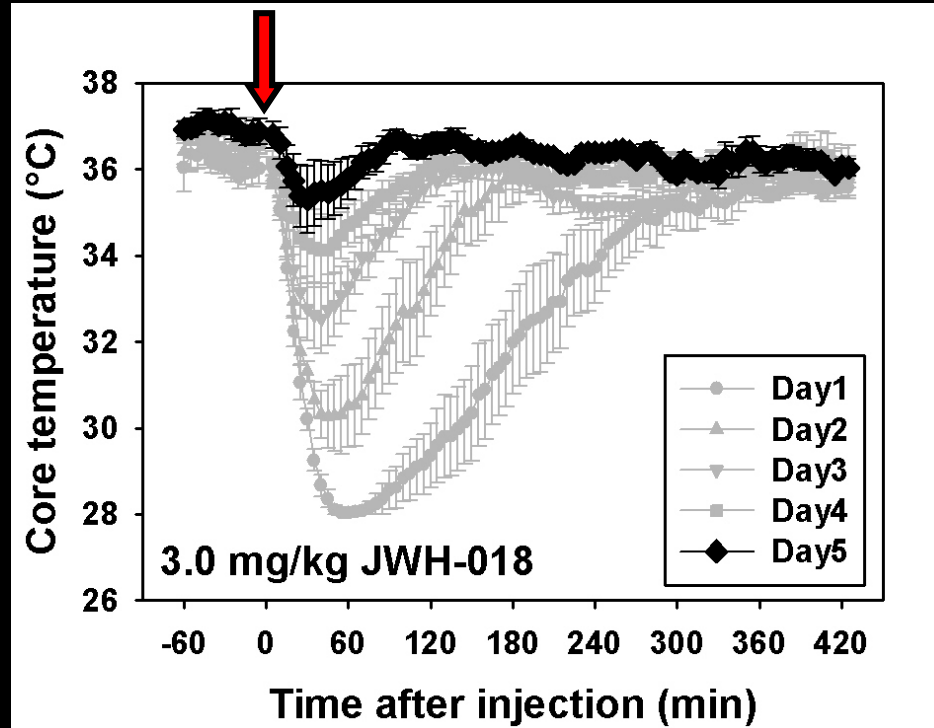
- Profound tolerance develops to the hypothermic effects of JWH-018

Synthetic Cannabinoids



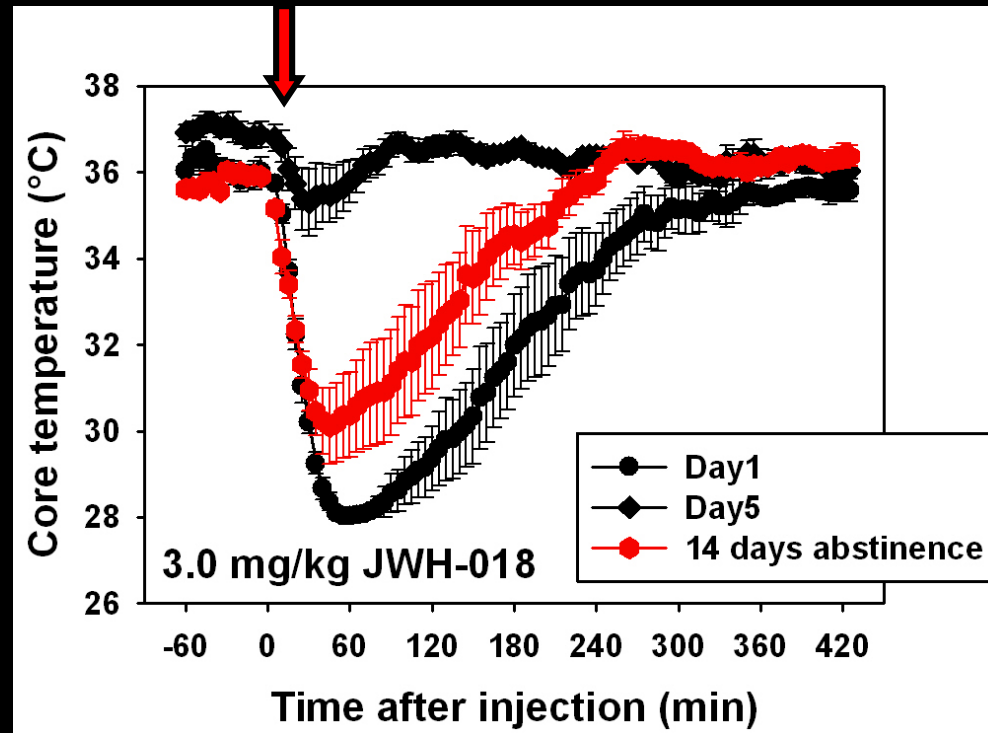
- Profound tolerance develops to the hypothermic effects of JWH-018

Synthetic Cannabinoids



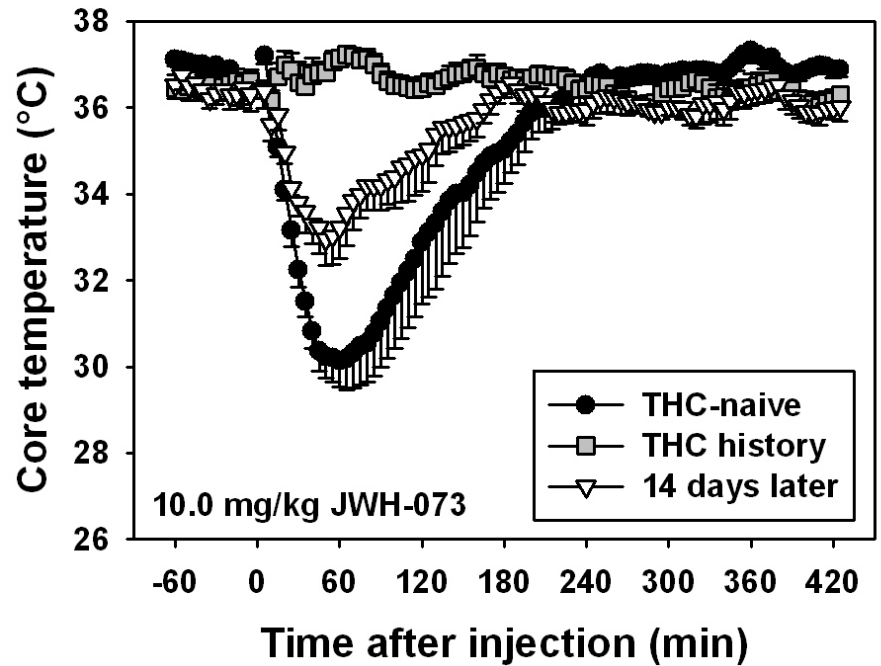
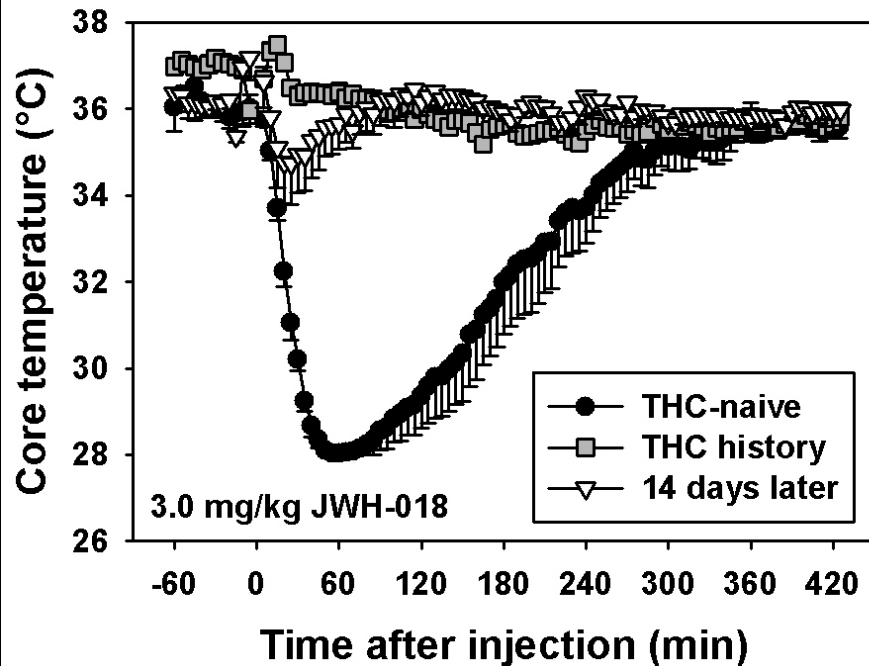
- Profound tolerance develops to the hypothermic effects of JWH-018

Synthetic Cannabinoids



- Tolerance is still evident in mice injected again 14 days after last drug dose.

Synthetic Cannabinoids



- Mice made tolerant to THC (30 mg/kg/day x 4 days) show cross-tolerance to synthetics.
- Greater efficacy does not overcome tolerance?



Conclusions

- **SCBs induce Δ^9 -THC-like effects in mice when administered IP or by inhalation (except for catalepsy.)**
- **Order of potency remains the same, and effects are blocked by CB1 antagonist rimonabant.**
- **Dramatic handling-induced convulsant effects with high doses of SCBs after IP injection, but never observed with Δ^9 -THC. These effects are CB1-mediated.**
- **Inhibition of CYP450 enzymes increases effectiveness and duration of action of SCBs, implying that phase I metabolism is involved in detoxification of these compounds.**

Conclusions

- Tolerance and cross-tolerance among THC and the synthetics suggests that marijuana users and first-time users will differ greatly in sensitivity to SCBs.





Acknowledgements

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- **UAMS: Sherrica Tai, Brenda Gannon, Bill Hyatt, Brad Gray, Ramey Marshall, Krishna Chimalakonda**
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