Consumption of Methamphetamine Decreases in a Two-Bottle Choice Drinking Paradigm

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AIMS

1. **To investigate methamphetamine (MTA) self-administration using a two-bottle choice drinking paradigm.**
2. **To investigate the effect of melatonin (MLT) on methamphetamine self-administration.**

Background

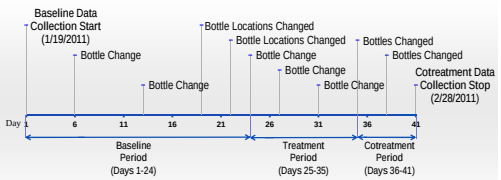
- **Melatonin is a hormone made at night by the pineal gland in mammals. It plays a role in their circadian rhythm through its broad biochemical effects on the body.**
- **Animal models of addiction have shown diurnal differences in behavioral sensitization to psychostimulants.[1]**
- **Diurnal behavioral differences in models of addiction can be explained by diurnal rhythms of dopamine transmission in the mesolimbic-dopamine system.[2]**
- **Melatonin receptors have a diurnal rhythm of expression in parts of the mesolimbic pathway, [3] and may influence the diurnal rhythms in dopamine transmission.[4]**
- **Studies in our laboratory indicate that melatonin increases the magnitude of methamphetamine induced locomotor sensitization in C3H-HeN mice.**

Hypothesis

Melatonin will amplify the rewarding properties of methamphetamine, thus increasing self-administration of methamphetamine in C3H-HeN mice.

Methods

Approach: To test this hypothesis, sixteen C3H-HeN mice were tested in a two drinking bottle paradigm.



All bottles were weighed when they were changed in order to calculate average daily consumption. Their locations were also changed to prevent a place-preference.

Treatment Given to Groups Based on Period

Group	Baseline Period (24 Days)		Treatment Period (11 Days)		Cotreatment Period (6 Days)	
	Bottle I (200mL)	Bottle II (50mL)	Bottle I (200mL)	Bottle II (50mL)	Bottle I (200mL)	Bottle II (50mL)
Group A (4 mice)	Water	Water	VEH	VEH	VEH	VEH
Group B (4 mice)	Water	Water	VEH	VEH	VEH	MLT 20 µg/mL in VEH
Group C (4 mice)	Water	Water	VEH	MTA	VEH	MTA
Group D (4 mice)	Water	Water	VEH 0.01% ethanol in water v/v	MTA 0.005% w/v in VEH	VEH	MTA+MLT

Acknowledgements

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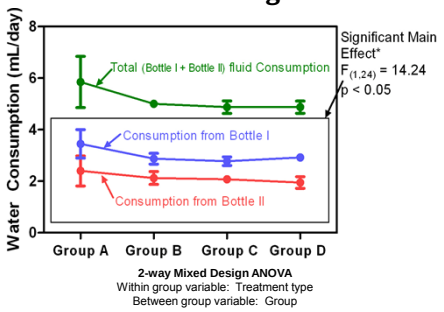
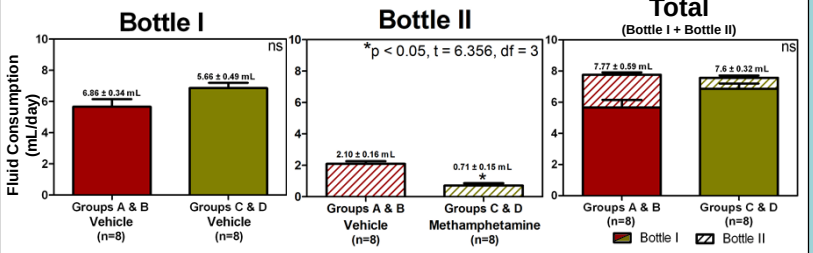
Baseline Drinking Behavior



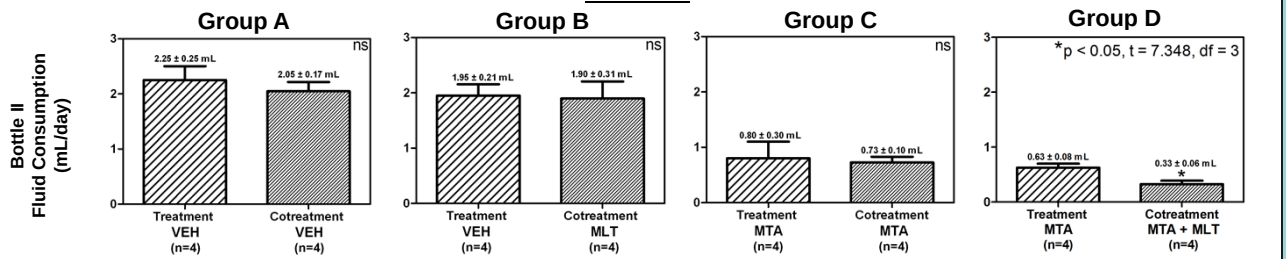
2-way Mixed Design ANOVA
Within group variable: Treatment type
Between group variable: Group

Presence of MTA Decreases Consumption in 2-Bottle Choice Test

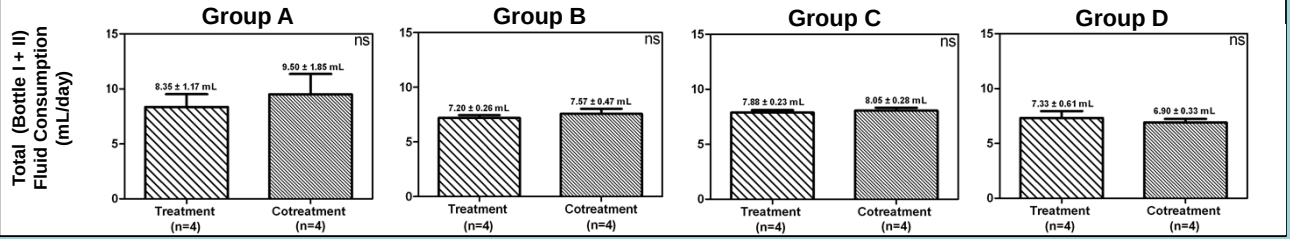


Melatonin Cotreatment Further Decreases MTA Consumption in 2-Bottle Choice Test

Bottle II



Total (Bottle I + Bottle II)



Summary

1. **There was no significant difference in the mean daily total drinking behavior between the four groups.**
2. **The mice successfully utilized both bottles in the two-bottle choice drinking paradigm, although there was significantly more water consumption from the Bottle I than Bottle II ($p < 0.05$).**
3. **There was no significant difference in total fluid (Bottle I + Bottle II) consumption between the MTA and VEH ($p > 0.05$) treated groups. However, consumption from Bottle II in the MTA treated group was significantly less than in the VEH treated group ($p < 0.05$).**
4. **There was a significant difference in Bottle II fluid consumption between the treatment and cotreatment ($p < 0.05$) periods for Group D, and there was not for group B ($p > 0.05$). There was also no significant difference in the total fluid consumption between the periods for either group.**

Conclusions

1. **The mice began the experiment with similar total drinking behavior.**
2. **The two-bottle drinking choice paradigm is a viable way of presenting a choice in fluid consumption, although using our current setup mice developed a preference for the larger bottle (Bottle I).**
3. **Decreased fluid consumption from Bottle II containing methamphetamine is potentially caused by the development of a taste aversion to methamphetamine.**
4. **The decrease observed in methamphetamine consumption following melatonin co-treatment is likely due to either:**
   - **An attenuation of the reward associated with methamphetamine self-administration.**
   - **Strengthening of the conditioned taste aversion.**

References

[1] Abarca, C., Albrecht, U., & Spanagel, R. (2002). Cocaine sensitization and reward are under the influence of circadian genes and rhythm. *Proceedings of the National Academy of Sciences*, *99*(13), 9026-9030. doi: 10.1073/pna s . 1 42039099.

[2] Falcon, E., & McClung, C.A. (2009). A role for the circadian genes in drug addiction. *Neuropharmacology*, *56*, 91-96. doi: 10.1016/j.neuropharm.2008.06.054.

[3] Uz, T., Arstan, A.D., Kurtuncu, M., Imbesi, M., Akhisaroglu, M., Dwivedi, Y., Pandey, G.N., & Manev, H. (2005). The regional and cellular expression profile of the melatonin receptor MT1 in the central dopaminergic system. *Molecular Brain Research*, *136*(1-2), 45-53. doi: 10.1016/j.molbrainres. 2005.01.002.

[4] McClung, C.A. (2007). Circadian rhythms, the mesolimbic dopaminergic circuit, and drug addiction. *The Scientific World Journal 7*, 194-202. doi: 10.1100/tsw.2007.213.