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Effects of Cannabidiol on Audiogenic Seizures in the DBA/1 Mouse Model of Sudden Unexpected Death in Epilepsy (SUDEP)

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INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) is a major cause of mortality in epilepsy and the second leading cause of years of patient life lost among neurological disorders (Thurman et al 2014).

The DBA/1 mouse model of SUDEP displays generalized seizure-induced respiratory arrest (S-IRA) during audiogenic seizures (AGSz). Prompt respiratory support consistently reverses S-IRA and prevents seizure-induced death in these mice.

Terminal apnea is a critical factor in SUDEP in patients with epilepsy (Ryvlin et al 2013).

AGSz priming (3-4 daily AGSz at ~21 days of age) is required for consistent susceptibility to S-IRA in DBA/1 mice (Faingold et al., 2010; Faingold and Feng, 2023).

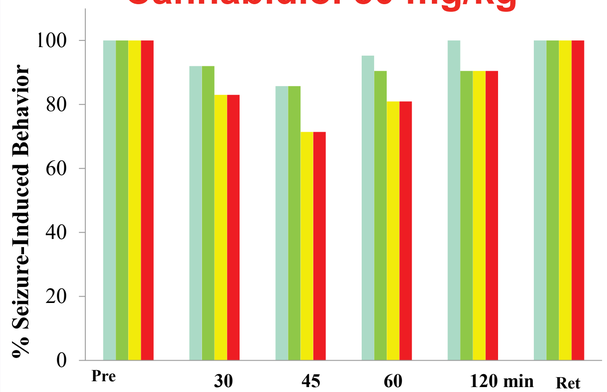
Cannabidiol (Epidiolex®) is an FDA-approved treatment for seizures associated with specific forms of epilepsy, including Dravet syndrome, a form of epilepsy that exhibits a high incidence of SUDEP (Sullivan et al., 2024).

Aim: evaluate the effect of CBD on seizure behavior and S-IRA in a mouse model of AGSz

METHODS

1. Male and female DBA/1 mice (22-28 days old) were subjected to priming, which consisted of 4 audiogenic seizures (AGSz) at daily intervals), using an electric bell (122 dB SPL for 60 sec) in a cylindrical chamber.
2. After priming all mice exhibited the full spectrum of seizure behaviors, including wild running (WR), clonic and tonic extension seizure behaviors and seizure-induced respiratory arrest (S-IRA).
3. When mice exhibited S-IRA they were resuscitated using a rodent respirator.
4. Effects of intraperitoneal (i.p.) plant-derived highly-purified CBD (Jazz Pharmaceuticals Research UK Ltd) in vehicle (1:1:18 Cremaphor : ethanol : 0.9% saline) at doses of 50, 100, and 200 mg/kg were evaluated at several time points following administration.
5. Separate groups of mice were used for each dose of CBD and each time point.
6. All seizures were video recorded, and changes in AGSz were evaluated for statistical significance using Chi square analysis.
7. Return of pre-drug AGSz behaviors were evaluated at 24 and / or 48 hours.

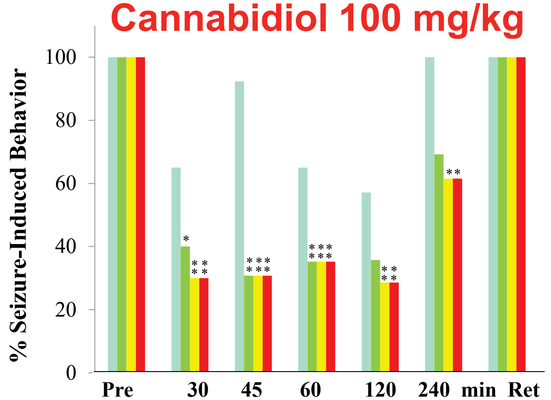
Cannabidiol 50 mg/kg



Effects of CBD 50 mg/kg i.p. on AGSz behaviors, including wild running (WR), clonus, tonic extension (Tonus), and seizure-induced respiratory arrest (S-IRA) in male and female DBA/1 mice and 24 hr prior to drug testing (Pre) (N=68). Each time point was evaluated in a separate group of mice. No statistically significant effect (Chi square test) was observed at 30 (N=14), 45 (N= 12), 60 (N=21) and 120 minutes (N=21). Return (Ret) to pre-drug seizure-induced behaviors was observed at 24 to 48 hr.

WR
Clonus
Tonus
S-IRA

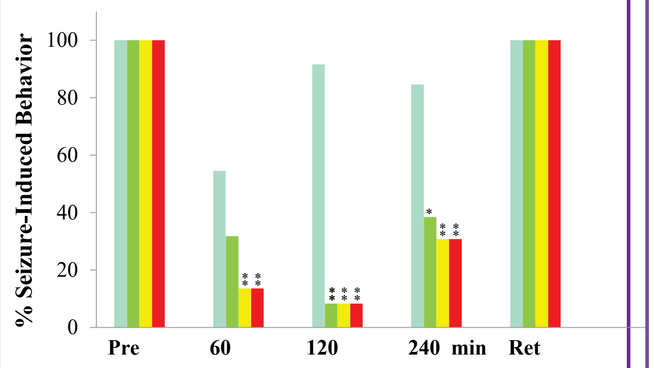
Cannabidiol 100 mg/kg



Effects of CBD 100 mg/kg i.p. on AGSz behaviors, including wild running (WR), clonus, tonic extension (Tonus), and seizure-induced respiratory arrest (S-IRA) in male and female DBA/1 mice and 24 hr prior to drug testing (control) (N=77). Each time point was evaluated in a separate group of mice. Statistically significant effect P< **0.001 and P<* 0.01 (Chi square test) was observed at 30 (N=20), 45 (N= 13), 60 (N=17), 120 (N=14) and at 240 minutes (N=13). Return (Ret) to pre-drug seizure-induced behaviors occurred at 24 to 48 hr after CBD administration (N=77).

WR
Clonus
Tonus
S-IRA

Cannabidiol 200 mg/kg



Effects of CBD 200 mg/kg i.p. on behaviors induced by AGSz, including wild running (WR), clonus, tonic extension (Tonus), and seizure-induced respiratory arrest (S-IRA) in male and female DBA/1 mice and 24 hr prior to drug testing (Pre) (N=47) . Each time point was evaluated in a separate group of mice. Statistically significant effects P< **0.001 and P< *0.01 (Chi square test) were observed at 60 (N=22),120 (N=12) and at 240 minutes (N=13). Return (Ret) to pre-drug seizure-induced behaviors occurred at 24-48 hr after CBD administration (N=47).

WR
Clonus
Tonus
S-IRA

REFERENCES

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Thurman et al., Epilepsia 2014

ABBREVIATIONS

AGSz	Audiogenic Seizures
CBD	Cannabidiol
i.p.	intraperitoneal
Pre	pre-drug control
Ret	Return to pre-drug AGSz at 24-48 hr
S-IRA	Seizure-induced Respiratory Arrest
SUDEP	Sudden Unexpected Death in Epilepsy

DISCLOSURES

All authors met the ICMJE authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship. JC & WH are employees of Jazz Pharmaceuticals, Inc.

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SUMMARY & CONCLUSIONS

Cannabidiol (100 mg/kg i.p.) significantly reduced AGSz behaviors at 30 min in male and female mice, and the effect was seen when testing was assessed in other animal groups up to 240 min. At 200 mg/kg cannabidiol exerted a greater degree of effect. However, the 50 mg/kg dose did not significantly reduce any AGSz behavior.
The return to susceptibility to all AGSz behaviors following CBD treatment occurred by 24-48 hours. The vehicle and lower CBD doses did not induce any change in AGSz behaviors.

Conclusions:

- These findings indicate that CBD is effective at reducing S-IRA in primed DBA/1 mice. This effect occurred in a dose-related manner in animals of both sexes.
- CBD has been established as being effective in treating seizures associated with Dravet syndrome.
- CBD reduced clonus, tonus and S-IRA in primed DBA/1 mice.
- The data presented in this study support further research to determine whether CBD may also be useful in preventing SUDEP.
- Experiments are ongoing to evaluate the PK / PD relationship in this SUDEP model at the doses evaluated in the current study.