Fluoxetine, a selective 5-HT reuptake inhibitor, can prevent S-IRA in DBA/1 mice by activating 5-HT4 receptors.6,7 Fenfluramine (FFA), which enhances 5-HT release in the brain, has been reported to have antiseizure activity as an add-on therapy in patients with Dravet syndrome,14,15 and is able to block AGSz and S-IRA in DBA/1 mice in a dose- and time-dependent manner. The 5-HT1A receptors, known to be expressed in brainstem cardiorespiratory networks, are involved in modulating respiration.11 The present study examined the role of specific 5-HT receptor subtypes in mediating FFA’s prevention of S-IRA by treating DBA/1 mice with specific 5-HT antagonists and evaluating changes in the effect of FFA on seizure and S-IRA susceptibility.

The DBA/1 mouse model is widely used and recapitulates many aspects of human SUDEP. DBA/1 mice exhibit increased susceptibility to seizure and seizure-induced respiratory arrest (S-IRA) and death in response to electroconvulsive shock, high-frequency hypercapnia, convulsant drugs, and intense acoustic stimulation (audiogenic seizures [AGSz]).5 The AGSz in DBA/1 mice are comprised of GTC followed by S-IRA during post-ictal behavioral depression. Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter released during Pd that modulates respiration.11-12

**ABBREVIATIONS / DRUGS**

5-HT | 5-hydroxytryptamine
---|---
AEDs | Anti-epileptic drugs
AGSz | Audiogenic seizures
FFA | Fenfluramine
S-IRA | Seizure-induced respiratory arrest

**METHODS**

1. DBA/1 mice (25-26 days) were subjected to AGSz priming involving 3-4 daily seizures by presenting 122 dB SPL (re: 0.0002 dyne/cm2) broadband acoustic stimulus for 1 min.

2. Mice that showed S-IRA were resuscitated by placing the inhalation tube of a rodent respirator (200 strokes/min) over their noses.

3. At least 24 h after the final priming seizure, the consistent S-IRA susceptible mice were given an intraperitoneal (i.p.) injection of FFA or vehicle (saline).

4. The experimental paradigms used to determine the 5-HT receptors that mediate the protective effect of FFA involved:
   a. Determination of dose and time at which FFA-treated mice showed the lowest incidence of S-IRA following tonic seizures: Mice were tested at 8-h intervals after receiving FFA (5-20 mg/kg, i.p.) for 24 h to determine the selective S-IRA blocking effect. The mice that did not show a return of S-IRA susceptibility were tested again at 24-h intervals.
   b. Determination of 5-HT receptors that mediate S-IRA. 5-HT receptors are critical in the ability of FFA to prevent S-IRA and exert anticonvulsant effects. To determine the selective S-IRA blocking effect, 5-HT receptor antagonists were used. These mice showed the lowest incidence of S-IRA following tonic seizures: Mice were tested at 8-h intervals after receiving FFA (5-20 mg/kg, i.p.) for 24 h to determine the selective S-IRA blocking effect. The mice that did not show a return of S-IRA susceptibility were tested again at 24-h intervals.

**A Specific Serotonin Receptor Is Critical in the Ability of Fenfluramine to Prevent Seizure-Induced Respiratory Arrest (S-IRA) in the DBA/1 Mouse Model of SUDEP**

**SUMMARY & CONCLUSIONS**

1. A significant reversal (p<0.05) of the FFA-mediated reduction in S-IRA incidence was elicited by the 5-HT4 receptor antagonist (GR125487).

2. The effect of FFA to reduce seizure severity (incidence of tonic seizures) was blocked by the 5-HT4 receptor antagonist (ritanserin).

3. 5-HT receptors, which are involved in mediating the protective effect of fluoxetine in DBA/1 mice, are not involved in mediating the effect of FFA.

**SIGNIFICANCE & FUTURE DIRECTIONS**

1. We show for the first time that 5-HT4 receptors mediate the seizure-induced sudden death prevention effect of FFA in DBA/1 mice.

2. Studies involving intracerebrovascular injection of 5-HT receptor antagonists, along with the i.p. injection of FFA, are needed to confirm its mechanism of action.

3. Our findings align with a previous study that found that 5-HT receptor agonist can mitigate fentanyl-induced respiratory depression.14

4. Future studies should investigate the protective effects of FFA against opiate-induced respiratory depression and the potential prophyliactic role of 5-HT receptor agonists against S-IRA in DBA/1 mice.

**REFERENCES**


**SUPPORT**

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