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Differential ability of serotonergic drugs to selectively block seizure-induced sudden death in the DBA/1 mouse model of sudden unexpected death in Epilepsy (SUDEP)

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Rationale: SUDEP has been recognized as a devastating and all too common cause of death in patients with epilepsy, and seizure-related respiratory depression is a major proposed cause for SUDEP (Shorvon and Tomson. Lancet 378:2028-38, 2011). Prevention of SUDEP has become a high research priority in neurology, and animal models of SUDEP that model respiratory-based sudden death in DBA mice have recently been developed (Faingold et al., Epilepsy Behav. 17:436-440, 2010). Serotonin (5-hydroxytryptamine, 5-HT) is known to enhance respiration by acting on the brain-stem respiratory network. Our previous studies have shown that enhancing the action of 5-HT with a selective serotonin re-uptake inhibitor (SSRI) can block seizure-induced respiratory arrest (SI-RA) in two DBA mouse models of SUDEP at dose that do not prevent the audiogenic seizures (AGS) in these mice. A number of SSRIs are used clinically to treat depression in patients, and there are also a number of new 5-HT agonists that selectively activate one of the many subtypes of 5-HT receptors that occur in the CNS. Therefore, the present study evaluated three different SSRIs and two relatively selective 5-HT receptor agonists to determine if these agents are effective in blocking SI-RA in DBA/1 mouse model of SUDEP.

Methods: DBA/1 mice were evaluated for susceptibility to SI-RA, inducing AGS with an electrical bell (122 dB SPL, re: 0.0002 dyne/cm^2) in a cylindrical chamber. AGS behaviors were recorded on video, and seizure parameters were quantified visually off-line. Mice that exhibited SI-RA were resuscitated using a rodent respirator. At least 24 hr later a serotonergic agent was systemically (i.p.) administered to DBA/1 mice that had exhibited SI-RA and susceptibility to SI-RA was evaluated 30 min after drug.

Results: Fluoxetine, sertraline and fluvoxamine are SSRIs and were all effective in blocking SI-RA in DBA/1 mice, in doses that did not block seizures. However, only fluoxetine was able to block SI-RA in doses that did not significantly reduce seizure severity, while the other agents were not as selective in blocking SI-RA selectively. A relatively selective 5-HT2B/2C agonist (m-chlorophenylpiperazine) was not able to block SI-RA and in highest doses was actually toxic to the animals. A 5-HT$_7$ agonist (AS-19) showed only limited effectiveness (only one dose) in blocking SI-RA in DBA/1 mice.

Conclusion: Each of the SSRIs showed differential effectiveness in selectively blocking SI-RA in DBA/1 mice, suggesting that there may be additional differential mechanisms involved in the SI-RA protective effect of these agents. The inability of the 5-HT$_{2B/2C}$ agonist to block SI-RA and the limited effectiveness of the 5-HT$_7$ agonist to block SI-RA, suggest that these receptors may not play a critical role in the suppression of SI-RA by SSRIs. These data may have clinical relevance for the prevention of human SUDEP, since the peri-seizure respiratory depression seen in most epileptic patients exhibited a reduced intensity in a retrospective study of one group of patients who had been taking SSRIs for co-morbid depression.

Biography

Carl Faingold is Distinguished Professor of Pharmacology at Southern Illinois University. He has published over 150 scientific publications on epilepsy. He researches the role of neuronal networks in this brain disorder and the network effects of anticonvulsants. He established the role of GABA defects in the genetically epilepsy-prone rat and in alcohol withdrawal seizures. His current research is on sudden unexpected death in epilepsy (SUDEP), and he developed a new SUDEP model in mice that demonstrates that drugs, which enhance the action of serotonin, will block SUDEP in this model.

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