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Review Article

Emerging Canine Drug-Resistant Epilepsy: A Review of Current State and Future Solutions

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Abstract

Canine epilepsy is a disease characterized by sudden alterations in neurological behavior and involuntary muscle movements. About three-fourths of the cases are refractory to conventional anti-epileptic drugs. Drug tolerance has led to the emergence of canine drug-resistant epilepsy (CDRE) which primarily affects male dogs aged 6 months to 6 years. This review focuses on thorough knowledge about the causes, diagnosis, and mitigation strategies for CDRE, elucidating the mechanisms of drug resistance for better understanding. The estimation of CSF and plasma biomarker levels such as IL-1β, microRNAs, and high-mobility group box-1 as well as electroencephalography and MRI, could provide the promising diagnostic aid. Challenges like probable sudden unexpected death in dogs with epilepsy (pSUDEP) and sudden unexpected death in dogs with epilepsy (SUDEP) need to be addressed. Add-on doses, neurostimulation, behavioral therapy, and ketogenic diet may improve CDRE. Finally, drug repurposing, nanodrug development, and gut-brain axis modulation are the novel therapeutic approaches which could serve as the cornerstone of future CDRE treatment strategies. In-depth information regarding therapeutic strategies that can lessen the emergence and global spread of CDRE has been thoroughly covered in this article.

Keywords: Anti-epileptic Drugs, Canine Drug Resistant Epilepsy, Drug Tolerance, pSUDEP, Nanodrug, SUDEP.

Introduction

Epilepsy is a brain disorder marked by temporary, sudden changes in neurological behavior, as outlined by the occurrence of more than two reflex seizures with intervals exceeding 24 hours (Fisher *et al*., 2017). Under normal circumstances, neurons in the brain communicate through electrical signals in a highly regulated manner. However, reduced GABAergic inhibition or excessive glutamatergic stimulation can result in increased neuronal excitability and increased likelihood of canine epilepsy (Charalambous *et al*., 2017). Canine epilepsy can be classified into three stages: (1) pre-ictus, (2) ictus, (3) post-ictus. The pre-ictus stage further comprises of the prodrome and aura phases. The prodrome phase often goes unnoticed by the owner without the detection of any changes in behavior of the dogs. It can last from weeks to months. Aura phase is defined by licking, pacing, hiding, hypersalivation, attention seeking, and vomiting for 1-2 minutes. The ictus stage is the true seizure phase, visually perceived by the owner as unconsciousness and involuntary muscle movements ranging from 1-3 minutes. The post-ictus stage is expressed by unusual behavior like disorientation, restlessness, aggression, and even blindness persisting from seconds to days (Hobbs *et al.,* 2020).

Based on the response to treatment, canine epilepsy can be classified into two categories: a) Refractory or drug-resistant epilepsy: Epilepsy that does not respond adequately to anti-epileptic medications and continues despite treatment adjustments. b) Responsive epilepsy: Epilepsy responds well to anti-epileptic medications and is effectively controlled with treatment (Berendt *et al*., 2015). Therefore, it is a challenge to the scientific community to find different approaches and techniques to lessen the global spread of drug-resistant epilepsy in canine populations. Accordingly, the subsequent sections of this article address the mechanisms that contribute to the development of anti-epileptic drug resistance and the emergence of drug-resistant epilepsy. Furthermore, an extensive review of the different innovative approaches that might be employed to mitigate canine drug-resistant epilepsy is also explored.

Emerging Canine Drug-Resistant Epilepsy (CDRE)

Drug resistant epilepsy, also known as refractory epilepsy or uncontrolled epilepsy or intractable epilepsy or pharmaco-resistant epilepsy, is defined as the inability to achieve lasting freedom from seizures despite adequate use of two well-tolerated and properly selected anti-epileptic drugs (AEDs) either individually or in combination. Drug tolerance facilitated by changes in the sensitivity of voltage-gated channels to AEDs or by the over expression of drug transporters is a potential cause for resistance (Stabile *et al.,* 2017). The male dogs of Labrador and German Shepherd breeds and aged between 6 months and 6 years are at a higher risk of developing CDRE (Griffin *et al.*, 2022). Frequent co-occurring conditions such as anxiety, apathy, dementia, aggression, aberrant perception, and attachment disorder are the comorbidities seen in CDRE (Peek *et al.,* 2024).

Mechanisms of AED Resistance and CDRE Emergence

There are several contributing elements, including genetic, environmental, disease- and drug-related factors for the emergence of CDRE (Fig. 1):

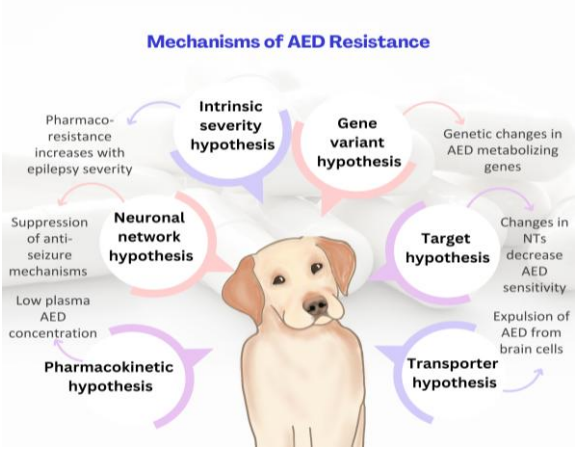

Fig. 1: Underlying mechanisms driving anti-epileptic drug (AED) resistance in dogs

***1. Pharmacokinetic hypothesis*:** Enhanced activity of efflux transporters in the intestine, liver, and kidneys leads to diminished drug absorption and metabolism, ultimately elevating its excretion. As a result, the drug's plasma concentration drops, making it less able to pass through the blood-brain barrier and causing CDRE (Tang *et al.*, 2017).

2. Neuronal network hypothesis: The body's natural anti-seizure defenses are suppressed by seizure-induced neuronal network reconfiguration and degeneration. This process lowers the efficiency of AEDs by preventing target access and triggers CDRE (Löscher, 2022).

3. Intrinsic severity hypothesis*:* Pharmaco resistance is an inherent aspect of the disease's severity, varying from mild to intense, with the most severe cases of CDRE exhibiting maximal resistance (Potschka *et al.,* 2023).

4. Gene variant hypothesis: Genetic variations in the genes responsible for metabolizing AEDs, ion channels, or neurotransmitter receptors targeted by AEDs contribute to the development of CDRE (Rodrigues *et al.,* 2022).

5. Target hypothesis: Alterations in the composition of ion channels or neurotransmitters reduce drug sensitivity, heightening refractoriness and potentially serving as a contributing factor to CDRE (Fonseca-Barriendos *et al.,* 2022).

6. Transporter hypothesis: The ATP-driven membrane pumps actively expel AEDs from cells, restricting their entry into brain cells, ultimately leading to CDRE (Czornyj *et al.,* 2022).

Approaches to Diagnosis of CDRE

The diagnostic characteristic of CDRE is the absence of a response to appropriately chosen and dosed traditional AEDs, however, the following criteria could provide additional diagnostic aid:

1. ***History:*** The dog experiences episodes characterized by mild tetraparesis, potentially suggestive of seizures. The timing of these episodes and their relation to exercise, feeding, or other triggers should be noted for a comprehensive assessment (Folkard *et al.,* 2023).

2. ***Neurological examination:*** Mild tetraparesis suggests neurological dysfunction, which could be related to the observed seizures or underlying neurological condition. Absence of postural reaction and menace reflex further indicates neurological impairment (Fischer and Volk, 2023).

3. ***Laboratory tests:*** Neutrophilia and thrombocytopenia in the complete blood count (CBC) indicate an inflammatory response or infection. In serum biochemistry, elevated creatinine levels and decreased copper, copper: zinc ratio, and selenium levels point to possible liver malfunction and metabolic disorders (Rosendahl *et al.,* 2023).

4. ***Novel biomarkers****:* Decreased concentration of GABA transaminase (GABA-T) in blood platelets suggests impaired GABAergic neurotransmission. Increased interleukin-1 beta (IL-1β) cerebrospinal fluid (CSF) concentration indicates neuroinflammation (Kostic *et al.,* 2019). Other markers include plasma-derived exosomal microRNAs (miR-132, miR-16, miR-93-5p, miR-574, miR-27, and miR-142) (García-Gracia *et al.,* 2024), high-mobility group box-1 (HMGB-1) (Paudel *et al.,* 2018) and urinary neurotrophins (NT) (Schimdt *et al.,* 2022).

5. ***Electroencephalographic (EEG) findings***: Generalized spike-wave discharges (GSWDs) that are interictal symmetric, bisynchronous, and regular, as well as generalized polyspike-wave discharges (GPSWDs), are consistent with epilepsy (Reddy and Shreenu, 2022).

6. ***MRI findings****:* Hyperintense gray matter on MRI may indicate areas of increased neuronal activity or inflammation. This could be associated with the observed neurological signs and seizure activity (Spinillo *et al.,* 2020).

Ancillary Therapeutic Strategies for CDRE Management

The following classes of drugs are included in traditional AEDs (Cui *et al.,* 2018; Ochoa-Morales *et al.,* 2023), as listed below:

(i) GABA potentiators e.g. diazepam: 0.5-2 mg/kg, i.v.; phenobarbitone: 1-2.5 mg/kg, p.o.

(ii) Sodium channel blockers e.g. phenytoin: 25-30 mg/kg, p.o.; valproic acid: 75-200 mg/kg, p.o.

(*iii) Synaptic vesicle protein 2A modulators* e.g. levetiracetam: 20 mg/kg, p.o.

(iv) Chloride ion competitors e.g. potassium bromide: 20-30 mg/kg, p.o.

(v) Monoamine oxidase inhibitors e.g. zonisamide: 3-5 mg/kg, p.o.

(vi) Calcium channel blockers e.g. ethosuximide: 20 mg/kg, p.o.

However, to address CDRE effectively, various supplementary treatment approaches have been employed alongside traditional AEDs.

1. Add-on therapy: Drugs such as topiramate (5-10 mg/kg p.o.), felbamate (15 mg/kg p.o.), pregabalin (4 mg/kg p.o.), levetiracetam (24 mg/kg p.o.), and firocoxib (5 mg/kg p.o.) are given to enhance the effects of pre-existing anti-epileptic treatment (Fischer and Volk, 2023).

2. Neurostimulation: Modulating nerve function by invasive (microelectrodes) or non-invasive (transcranial magnetic stimulation) means: **a) Transcranial magnetic stimulation (TMS):** In TMS, electrodes are applied to the skull, emitting magnetic pulses that influence neural activity. This non-invasive procedure aids potential therapies (Nieminen *et al.,* 2022). **b) Transcutaneous vagus nerve stimulation (tVNS):** In tVNS, electrodes are usually placed near the ear to deliver low-frequency electrical impulses. This noninvasive therapy aims to modulate the vagus nerve (Nowakowska *et al*., 2022).

3. Behavior modulation: This involves implementing strategies to improve a dog's behavior while living with epilepsy that does not respond well to medication. This may include-

a) Behavioral training: Implementing positive reinforcement-based training to address specific behaviors or reactions associated with seizures.

b) Monitoring and record-keeping: Keeping a detailed record of seizure episodes, triggers and behavioral changes to assist in understanding patterns and adjusting strategies accordingly.

c) Environmental enrichment: Offering mental stimulation through toys, puzzles, and activities to keep the dog engaged (Packer *et al*., 2019).

4. Dietary modifications: This includes offering a ketogenic diet. Generally, begin with a 2:1 ratio of fat to protein/carbohydrates, and then progressive transition to a 3:1 or 4:1 ratio within a span of 1-2 weeks is done (Verdoodt *et al.,* 2022). A diet rich in medium-chain triglycerides (MCT) and devoid of gluten is to be provided (Berk *et al*., 2022).

5. Surgical procedures: The common approaches are anterior temporal lobectomy, anterior temporal resection, extratemporal resection, and laser interstitial thermal therapy (LiTT) (Salem *et al*., 2023).

Innovative Approaches to Fight CDRE

Drug Repurposing

It refers to identifying new uses for existing drugs that were originally developed for different therapeutic indications. Few drugs might be repurposed to fight CDRE, such as atorvastatin (Forsgard *et al*., 2019), telmisartan (Hanael *et al*., 2022), fenfluramine (Tabaee Damavandi *et al.,* 2023), everolimus (Talevi, 2021) and megestrol (Wang *et al*., 2019).

Modulation of Gut-Brain Axis

Gut bacteria that produce lipopolysaccharides (LPS) influence the endocannabinoid system, which plays a role in endogenous seizure control (Chatzikonstantinou *et al*., 2021).

Current Challenges Associated with CDRE

The management of dogs with CDRE becomes more challenging due to the occurrence of probable sudden unexpected death in dogs with epilepsy (pSUDEP) and sudden unexpected death in dogs with epilepsy (SUDEP) (Heunerfauth *et al*., 2021). New-onset refractory status epilepticus (NORSE) defines the epilepsy associated with autoimmune encephalitis (Fischer and Volk, 2023). Pseudo resistance in CDRE is a situation where it appears that the epilepsy is not responding to treatment, but in reality, factors such as incorrect classification, incorrect diagnosis, inadequate dosing, suboptimal drug concentration, or poor owner compliance contribute to the drug resistance (Kajin *et al*., 2023).

Current Research Gaps and Future Opportunities in CDRE Treatment

(a) Use of biodegradable nanodrugs with a specific focus, like polymeric nanoparticles containing diazepam (Bonilla *et al*., 2022).

(b) Oral administration of tetrahydrocannabinol at a dose of 9 mg/kg body weight per day has demonstrated an effectiveness of approximately 24% against CDRE (Rozental *et al.*, 2023).

(c) Developing innovative polypharmacological therapeutics: Padsevonil and cenobamate are in phase II of drug development (Löscher, 2021).

(d) Responsive neurostimulation (RNS) involves the implantation of electrodes connected to areas identified as seizure foci. These electrodes detect seizure waves and allow for simultaneous intracranial EEG recording and transmission. The RNS system can then deliver personalized stimulation to manage seizures in dogs with CDRE (Gouveia *et al*., 2024).

Conclusion

Canine drug resistant epilepsy manifests when two adequately dosed AEDs prove ineffective in dogs. It primarily affects male dogs aged 6 months to 6 years, with drug tolerance emerging as the predominant cause. Exploring innovative biomarkers and repurposing drugs, coupled with advances in polypharmacological and nanodrug research, and supplementary therapies like neurostimulation and dietary modifications, offers potential solutions in the battle against CDRE.

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Contribution by Authors

All the authors contributed equally to writing the manuscript. The final manuscript was read by all authors and consented to publication.

Conflict of Interests

There is no conflict of interest.

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