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Current review on inducible nitric oxide synthase and Src tyrosine kinase inhibitors as disease-modifiers in preclinical models of epilepsy

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Summary. Acute exposure to seizurogenic chemicals, such as organophosphates (OPs) or domoic acid (kainate analogue), can trigger status epilepticus (SE), marked by central (seizures) and, with OPs, peripheral effects due to irreversible inhibition of acetylcholinesterase (AChE). The initial seizurogenic activity in the brain initiates a cascade of molecular and cellular changes, known as epileptogenesis, the process by which epilepsy develops. Among the several signaling pathways involved in epileptogenesis, this review discusses the roles of the Src family of tyrosine kinases (SFK), especially Fyn kinase, and inducible nitric oxide synthase (iNOS) mediated mechanisms. Both signaling molecules are upregulated following initial seizures and persist for a long time, contributing to neuroinflammation, elevated levels of reactive oxygen and nitrogen species (ROS/RNS), and proinflammatory cytokines, as well as neuro-degeneration and spontaneously recurring seizures. Epilepsy is a progressive disease associated with unprovoked seizures and cognitive decline. While the current standard of care can alleviate symptoms and reduce mortality, they do not address long-term neurological consequences. In this review, we discuss preclinical testing of two CNS-targeted drugs, iNOS and SFK inhibitors 1400W and Saracatinib (SAR; AZD0530), respectively, as potential disease-modifiers.

Key words: Status epilepticus, Acetylcholinesterase, Organophosphate, Src family of tyrosine kinases, Inducible nitric oxide synthase

Epilepsy overview

Epilepsy is the fourth most common brain disorder in all age groups and is prevalent worldwide (Milligan, 2021). As per the International League Against Epilepsy, an individual is considered a patient with epilepsy if the individual has at least two unprovoked (or reflex) seizures over a day apart or had an unprovoked seizure with a high likelihood (i.e., >60%) of experiencing further seizures over the next 10 years, similar to the general recurrence risk after two unprovoked seizures or an individual has been diagnosed with an epilepsy syndrome (Fisher et al., 2014). It is a chronic and progressive neurological condition caused by abnormal and uncontrolled excessive electrical disturbances in the brain, which manifest as seizures (Huff and Murr, 2025). Epilepsy is marked by spontaneous recurrent seizures (SRS) that can be provoked or unprovoked, which are required for diagnosis and treatment.

Burden of epilepsy

Epilepsy impacts over 70 million globally, including more than 2.9 million in the United States, representing a substantial public health burden (Thijs et al., 2019; CDC, 2024). Epilepsy can affect individuals of all ages, but it is most commonly seen in infants under one year and adults over the age of 50, with a higher incidence in people over the age of 70 (Thijs et al., 2019). Worldwide, the prevalence of epilepsy is estimated to be between 4 and 10 cases per 1,000 individuals, while the annual cumulative incidence is approximately 67.77 cases per 100,000 people (Fiest et al., 2017; Chen et al., 2023). About 10% of people will experience at least one seizure (provoked or unprovoked) during their lifetime (InformedHealth.org, 2023). If the first seizure is unprovoked, the risk of recurrence is 30% and 50%. This risk increases significantly to 70-80% following a second unprovoked seizure (Pohlmann-Eden et al., 2006). The incidence of sudden unexpected death in epilepsy (SUDEP) is estimated as 0.2 per 1,000 person-years in children and 1.2 per 1,000 person-years in adults (Harden et al., 2017).

As of 2021-2022, approximately 1.1% of the U.S. population is living with active epilepsy, while an

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additional 0.6% (around 1.6 million people) have inactive epilepsy, with about 1/3rd being resistant to antiepileptic drugs. Among them, about 456,000 children aged 17 and under are affected by epilepsy (Kwan and Brodie, 2000; Kobauet al., 2023; CDC, 2024). Approximately 150,000 new cases of epilepsy are diagnosed every year (National Institute of Neurological Disorders and Stroke (US), 2025). The incidence of SUDEP is 1 per 4500 in children and 1000 adults (CDC, 2025).

Epilepsy is unevenly distributed worldwide, with approximately 80% of cases occurring in low- and middle-income countries (Espinosa-Jovel et al., 2018). It results in a significant economic burden on both caregivers and society, with annual costs ranging from $204 to $11,432, depending on the income level of the country (Begley et al., 2022). In the United States, from 2010 to 2018, the average annual healthcare cost per person with epilepsy was $6,853, contributing to a total of $24.5 billion in expenses directly linked to seizures and epilepsy (Moura et al., 2022).

Causes and consequences of epilepsy

A seizure occurs due to an imbalance in the brain's electrical activity (hyperexcitability and hypersynchrony) caused by excessive neuronal excitation or insufficient inhibition (Bozzi et al., 2018). Hyperexcitability occurs due to increased sensitivity of neurons to stimuli, which leads to excessive neuronal firing. This often results in hypersynchrony, where groups of nearby neurons fire simultaneously in a disordered manner. Although there are many factors for the seizure onset, the underlying mechanism is not fully known in all types of epilepsy. However, any form of brain insult, depending on its severity, may develop epilepsy. The etiology of epilepsy can be broadly grouped into structural, genetic, immune, metabolic, infectious, and unknown causes. Structural causes can be genetic or acquired (Scheffer et al., 2017). The acquired epilepsy may occur due to a tumor, traumatic brain injury, stroke, prolonged seizures (status epilepticus, SE) resulting from brain infections (intracranial abscesses, encephalitis, or meningitis), hypoxia, febrile seizures, drug toxicity, metabolic irregularities, autoimmune disorders and exposure to harmful seizurogenic chemicals (Scheffer et al., 2017; Wylie et al., 2025).

The development of acquired epilepsy occurs in three continuous phases, starting with an initial brain insult such as SE, followed by the epileptogenic phase (latent period), and the SRS (chronic/established) phase. The epileptogenic phase extends to the SRS phase and is not just limited to the latent period (Dudek and Staley, 2011). Acquired epilepsy accounts for roughly 50% of all epilepsies (DeLorenzo et al., 2005). There are numerous cases of SE-induced epilepsy. As per the revised guidelines of the Neurocritical Care Society 2012, SE is characterized by either continuous electrographic and/or clinical seizure activity lasting 5 minutes or more, or recurrent seizures without a return to baseline consciousness between episodes (Brophy et al., et al., 2012; Trinka et al., 2015). The incidence of SE is 41 per 100,000 per year, with a mortality of 20% (Trinka et al., 2012). SE caused by an initial brain insult leads to progressive structural (cellular and molecular) and functional alterations in the brain known as epileptogenesis, which may contribute to the development of SRS. Another important contributing factor to SE is exposure to toxic chemical agents that cause hyperexcitability. A large class of chemicals that induce seizures is organophosphates (OPs).

Experimental models of epilepsy

Animal models of epilepsy are critical to understand the mechanism of epileptogenesis, to investigate the causes of drug resistance, and to develop new therapeutic agents targeting specific molecular mechanisms. Various animal models of seizures and epilepsy have been characterized to study disease progression and to test the efficacy of therapeutic agents. There is no clear distinction between the seizure model and the epilepsy model. For example, the genetic model of epilepsy is used as a seizure model. Epilepsy models are divided into acute (provoked) or chronic models (unprovoked), where the seizures/epilepsy are induced by chemical or electrical stimulation. The acute seizure models include the maximal electroshock seizure (MES) and the pentylenetetrazole (PTZ) model. In the MES model, animals are induced with a seizure using electrical stimulation of sufficient intensity (50-150mA) depending on the animal model (Castel-Branco et al., 2009). PTZ is a chemical agent that induces neurological effects that mimic seizures. PTZ is a non-competitive antagonist of γ-aminobutyric acid type A ($GABA_A$) receptors and activates N-methyl-D-aspartate (NMDA) receptors, in turn causing Na^+ and Ca^{2+} influx (Monteiro et al., 2024). Both MES and PTZ models induce a single acute seizure. The MES model is used to assess a drug's ability to prevent seizure propagation, while the PTZ model helps identify compounds that elevate the seizure threshold (Mandhane et al., 2007). These models are used to test the efficacy of anticonvulsant, antiepileptic, or anti-seizure medication (Löscher, 2002). The chronic model of epilepsy includes animals that have been epileptic either by genetic or acquired means through chemical or electric stimulation. These models are used to test antiepileptogenic and disease-modifying agents. Chemical-induced or chemoconvulsant chronic model can be a single exposure that induces SE lasting more than 20 minutes or by kindling, a repeated exposure that increases behavioral and electrographic seizure resulting in SRS (Gage et al., 2021; Rao et al., 2022). Various chemicals are used to induce kindling in rodents, such as PTZ, bicuculline, picrotoxin, and NMDA (Schmidt, 1987; Uemura and Kimura, 1988; Yeh et al., 1989; Shimada and Yamagata, 2018). Kindling causes an increase in seizure susceptibility and seizure severity, exhibiting stage 5

seizure (Racine scale 0-5), leading to the development of SRS (Racine, 1972). Other common models of chronic epilepsy using chemoconvulsants are the pilocarpine and kainic acid (KA) models. Pilocarpine (M1 receptor agonist) and KA (L-glutamate analogue; ionotropic kainate receptor agonist) injections have been shown to induce SE and epilepsy resembling human temporal lobe epilepsy (Lévesque and Avoli, 2013; Lee et al., 2018). Pilocarpine produces more rapid SE than kainic acid (Curia et al., 2008). In rats, the dose of pilocarpine tested was 100-400 mg/kg. However, pretreatment with lithium 24 hours prior to pilocarpine administration significantly reduces the dose of pilocarpine to 30 mg/kg. Despite a reduction in the dose, the SE severity remains unchanged compared to without lithium pre-treatment (Turski et al., 1983; Clifford et al., 1987; Curia et al., 2008). The duration of latency (SE to first SRS) ranged from 14 to 52 days, depending on the duration of SE (Lemos and Cavalheiro, 1995). The KA model has also been shown to recapitulate features of human temporal lobe epilepsy. The most vulnerable region of the brain for KA-induced neurotoxicity is the hippocampus due to its higher density of kainate receptors (Darstein et al., 2003). Intraperitoneal or intrahippocampal administration of KA induces SE, which subsequently leads to the development of SRS within days to a month following SE (Lévesque and Avoli, 2013; Puttachary et al., 2016; Sharma et al., 2018; Rao et al., 2023; Putra et al., 2024a). A repeated low dose of KA, 5 mg/kg intraperitoneal at 30-40 minute intervals, with a total dose maxed at 25-30 mg/kg per animal, produces SE in rodents with reduced mortality and variation in SE severity between animals (Puttachary et al., 2015b; Rao et al., 2023; Putra et al., 2024a).

Organophosphate (OP)

OPs include a diverse group of chemical compounds, such as chemical nerve agents (CNAs) and harmful pesticides/herbicides. OPs are a group of chemicals that are formed by the esterification of alcohols with phosphoric acid (Adeyinka et al., 2023). Several OPs have been synthesized, and around 200 compounds are currently available. A Swedish pharmacologist discovered the first OP cholinesterase inhibitor, tetraethyl pyrophosphate (TEPP), in 1854 (Costa, 2018). In 1930, diisopropylfluorophosphate (DFP) was synthesized and patented as an insecticide and a mold control agent. Although it was also classified as a potential chemical warfare agent (CWA), it was never used for that purpose (Sogorb et al., 2015). OP CWAs are broadly divided into volatile G agents and the non-volatile V agents. CWAs were developed during and after the Second World War in Germany, the UK, the USA, Russia, and a few other countries. A German scientist developed the first nerve agent known as Tabun (GA) in 1936, which led to the development of the G series nerve agents such as sarin (GB) in 1939, soman (GD) in 1944, and cyclosarin (GF) in 1949 (Abdollahi and Mostafalou, 2014). The V series nerve agent was discovered as a pesticide in the UK in 1952, known as VG (Amiton). Later, it was classified as a Schedule 2 chemical under the Chemical Weapons Convention (CWC) (Michael Blake for Technology Concepts and Design, 2025). V series nerve agents include VX, VE, VM, VG, and VM. These V series agents are 20 times more potent than the G series. Certain V-series CWAs, such as VX, are designed as binary agents, wherein the individual precursor components are non-toxic on their own but become highly toxic upon chemical combination (Schaffer et al., 2025). The VR/RVX or Russian VX nerve agents were developed in the Soviet Union, which led to the development of a new generation of CWA NOVICHOK agents (A-230, A-232, and A-234) between 1970-1990, which are 5-8 times more toxic than VX (Chai et al., 2018; Nepovimova and Kuca, 2018; Jeong and Choi, 2019).

Incidence and prevalence of OP poisoning

Most cases of OP toxicity occur due to unintentional or deliberate exposure to insecticides or pesticides. Suicidal cases with self OP poisoning account for 300,000 deaths each year globally (Ahmed et al., 2014). The cases are more commonly seen in Asia-Pacific and African countries (Sinha et al., 2022). Each year, approximately 25 million agricultural workers are globally exposed to pesticide poisoning. In the United States, about 16% of farmers report having suffered at least one such incident in their lifetime (Alavanja, 2009). The most alarming aspect of OPs is their use as a nerve agent in military operations and acts of terrorism that pose significant risks to both public and military health. The first use of the OP nerve agent occurred during the Iran-Iraq War (1980-1988), when Iraq deployed Tabun (GA) against Iranian forces in 1984 (>300 died within 30 minutes of exposure, and thousands were poisoned), followed by GB, GA, and VX towards the end of the war (Ali, 2001; Balali-Mood and Balali-Mood, 2008). It was estimated that around 100,000 individuals were poisoned during the war (Balali-Mood and Saber, 2012). During the First Gulf War in 1991, U.S. soldiers were potentially exposed to a range of hazards, including chemical and biological agents, which led to Gulf War Illness (GWI). It is estimated that over 100,000 soldiers were exposed to low-level nerve agents, and 30% of them had various neurological symptoms (Ribeiro and Deshpande, 2021). The first terrorist attack involving a nerve agent occurred in 1994 with sarin, followed six months later by a major incident in the Tokyo subway system, approximately 6,100 people were poisoned and 18 deaths occurred (Okumura et al., 1996; Moshiri et al., 2012). Since 2011 and 2017, the Syrian Civil War has resulted in 1,206 deaths due to a series of OP CWAs such as sarin (Rodriguez-Llanes et al., 2018). OP nerve agents have also been used in targeted attacks and assassinations, including the use of VX in 2017 and Novichok in 2018 (Chai et al., 2017; Stone, 2018; Clarke and Weir, 2020). Although current medication for OP

poisoning saves lives if treated immediately, there is no effective treatment for the long-term effects of poisoning. Furthermore, the mechanism of disease development post-exposure is largely unknown. Therefore, experimental models of OP intoxication are useful to investigate these unmet clinical needs.

Experimental models of OP intoxication

The animal model of acute OP exposure has been shown to induce SE and initiate the development of SRS. Acute exposure to OP pesticides or nerve agents has been studied in various animal models such as rats, mice, guinea pigs, rabbits, pigs, and nonhuman primates. The LD_{50} of OPNA is approximately the same among various animal models, with an increasing LD_{50} from VX to soman to sarin (Fawcett et al., 2009; Pereira et al., 2014). An animal model to study nerve agent exposure was developed to mimic both the military and civilian populations' exposure. To mimic real-world military exposure scenarios, animal models of military exposure include treatment with pyridostigmine bromide (PB) prior to OP exposure; however, pretreatment is impractical in the civilian population. Therefore, direct exposure to OPNAs without pretreatment mimics a real-world civilian exposure scenario. Atropine, oximes, and midazolam are administered in both models as part of the standard-of-care (SOC) protocol typically implemented following nerve agent exposure. Acute exposure to DFP (surrogate for soman/sarin used in academic laboratories) has been well characterized in the rat model (Shih and McDonough, 1999; Putra et al., 2020c; Gage et al., 2021; Rao et al., 2022). Acute soman (GD,132 μg/kg, s.c.) and DFP (4 mg/kg, s.c.) exposure causes electrographic and behavioral convulsive seizures. Female rats exhibited significantly higher seizure severity than males following soman exposure; however, no such sex difference was observed with DFP exposure (Gage et al., 2021; Vasanthi et al., 2025; Massey et al., 2025b). The mortality was around 2-5% in soman and DFP-exposed rats during the first week of exposure (Gage et al., 2021; Rao et al., 2022). In the long-term, convulsive SRS was observed in 85% of animals, correlating with significant brain pathology following nerve agent exposure (Gage et al., 2021).

The other model of OP has also been developed to mimic GWI to study disease pathology. These animal models can be used to test the efficacy of therapeutic agents that would benefit veterans with GWI. It is challenging to develop ideal GWI models as there are various factors that need to be considered, such as the time chosen for experimental animals that mimic GWI suffering veterans; conditions and chemicals used, which recapitulate the surrounding environment. There are various protocols used to create the GWI model, using oral and dermal drug administration. The rat GWI model includes oral administration of PB followed by dermal exposure to N, N-diethyl-m-toluamide (DEET) and permethrin (PM), followed by the induction of stress using a restrainer for 5 minutes; repeating the protocol for 4 weeks (Wu et al., 2021; Reddy et al., 2023). Chronic exposure to GWI chemicals with stress induces cognitive and psychiatric deficits, demonstrating the mechanism of GWI symptoms and comorbidities. The mouse model of GWI includes chronic (14 days) administration of PB/ DEET, subchronic (7-14 days) administration of the steroidal anti-inflammatory agent corticosterone (CORT), followed by acute DFP exposure on day 15 (O'Callaghan et al., 2015). Other models of GWI include low-grade repeated exposure to nerve agents such as DFP, which mimic exposure to sarin in GW (Haley and Tuite, 2012; Ribeiro and Deshpande, 2021). Various combinations of chemicals (PB, DEET, PM, DFP, and chlorpyrifos) and stress are used in rodents to replicate GWI (Nutter et al., 2013, 2015; Ribeiro and Deshpande, 2021). All these models are useful to investigate mechanisms of disease onset, progression, and possible treatment strategies.

Mechanism of OP-induced SE

AChE-mediated mechanism

Acute exposure to OPs irreversibly inhibits acetylcholinesterase (AChE) in both the central and peripheral nervous systems (CNS, PNS), resulting in excessive accumulation of the neurotransmitter acetylcholine (ACh) at synaptic junctions. Irreversible binding of OP to AChE is through phosphorylation of a nucleophilic serine residue of the enzyme's catalytic site (Sirin and Zhang, 2014). Progressive inhibition of AChE leads to a dealkylation reaction, leading to a non-reactivatable state of the enzyme after a certain period known as aging (Curtil and Masson, 1993). Aging is an irreversible process. The duration varies between OP agents. Soman exhibits the fastest aging with a t1⁄2 of only 2 minutes, Sarin 3-4 hours, Tabun 13-14 hours, and VX 22 days (Newmark, 2009). Toxic effects of OP are observed at 50-80% of AChE inhibition (Lotti, 2010). This leads to neuronal excitotoxicity due to increased stimulation of muscarinic (mAChR) and nicotinic (nAChR) receptors, triggering a cholinergic crisis (Kaur et al., 2014). The seizurogenic activity of OP can originate in various brain regions and spread progressively to other regions such as the cortex, hippocampus, thalamus, and amygdala (Vasanthi et al., 2023b, 2025; Neff and Reddy, 2024). Acute clinical signs that occur within 12 hours include muscarinic (83%), nicotinic (17%), and CNS involvement (78%) (Lee and Tai, 2001; Kovarik et al., 2024). They can be classified into peripheral and central effects. The central effects (seizures) can be detected by an electro-encephalogram (EEG) (Fig. 1).

PNS effects

The most common clinical signs of OP poisoning originate from the PNS. These include salivation,

lacrimation, urination, defecation, gastric secretions, and Emesis (SLUDGE) syndrome due to peripheral parasympathetic muscarinic activity (Peter et al., 2014; Gage et al., 2021). Another important clinical sign is miosis (100%) and respiratory failure (77.7%) (Baser et al., 2021). ACh plays a critical role in controlling respiration. Respiratory failure in OP poisoning could result from a central or peripheral response, such as neuromuscular junction disruption or involvement of respiratory centers, respectively (Sungur and Güven, 2001; Eddleston et al., 2008). Peripheral respiratory symptoms, such as bronchorrhea and increased pulmonary secretions, occur due to increased muscarinic activity of the parasympathetic system (Rusyniak and Nañagas, 2004; Eddleston et al., 2008). In contrast, increased nicotinic activity of the sympathetic system causes hypertension, tachycardia, and sweating. At the neuromuscular junction, excessive activation of nicotinic receptors causes muscle weakness, fasciculations, and paralysis (Eddleston et al., 2008). All these collectively can lead to high mortality and morbidity if not treated immediately (Shorvon, 2013).

CNS effects

The CNS effects are attributed to hyperstimulation of muscarinic and nicotinic receptors in the brain. OP toxicity initially causes increased respiration due to increased nicotinic activity, followed by receptor desensitization, causing CNS-mediated respiratory depression, followed by central apnea due to muscarinic receptor hyperstimulation (Aroniadou-Anderjaska et al., 2023; Nomura et al., 2023). The most common symptoms following acute OP exposure include seizures (13% of patients), coma, and decreased mental status (Rusyniak and Nañagas, 2004). Neuronal hyper-excitability is caused predominantly by increased stimulation of muscarinic receptors. Of the several receptors, M1 receptor density is high in the hippocampus and cortex, M2 in the thalamus and cerebellum, M3 throughout the brain, M4 in the striatum, and M5 in the brain stem and hippocampus.

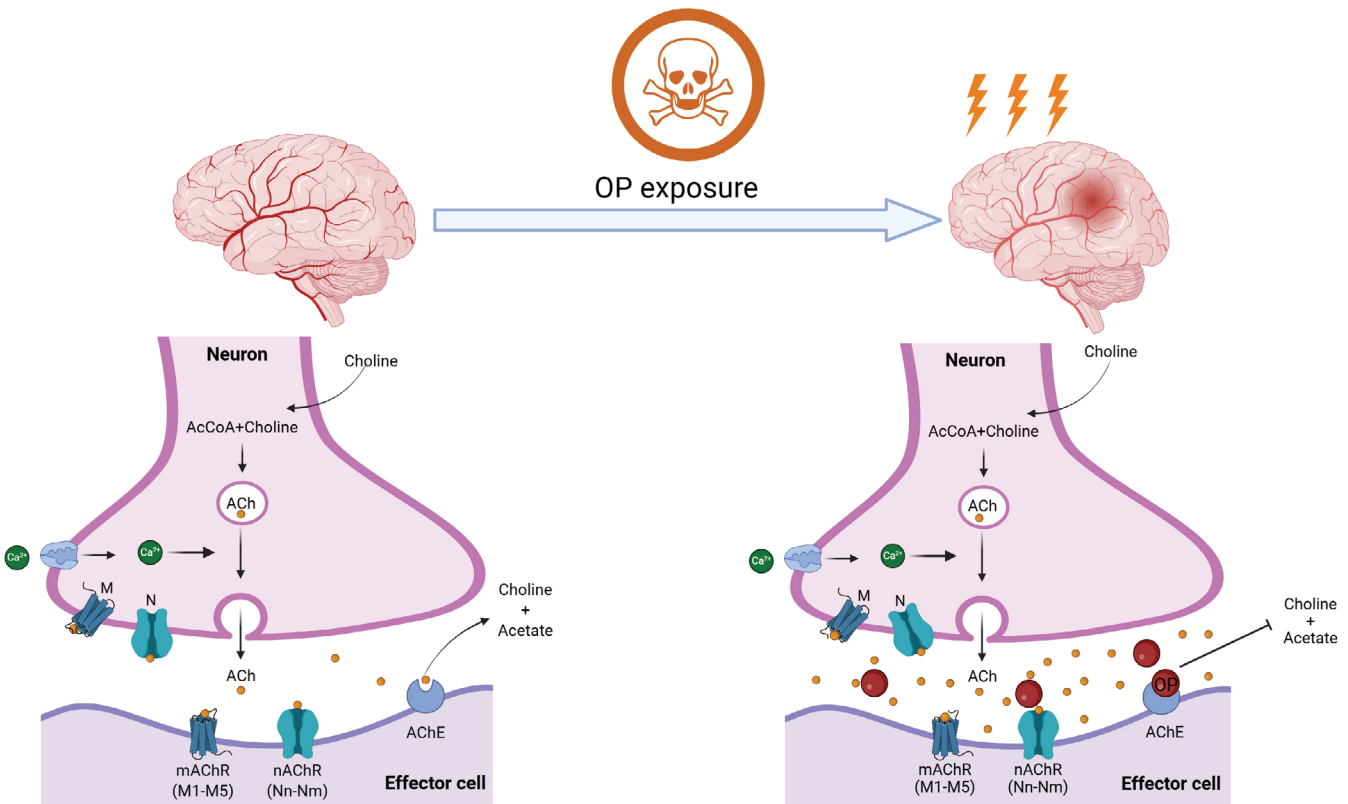

Fig. 1. Schematic diagram of OP induced SE. In cholinergic neurons, acetylcholine (ACh) is synthesized from acetyl coenzyme A (AcCoA) and choline, catalyzed by the enzyme choline acetyltransferase (ChAT). ACh is packed into storage vesicles along with other co-transmitters. Depolarization opens calcium channels and increases intracellular Ca^{2+}, which triggers the release of ACh, which is facilitated by vesicle-associated membrane proteins (VAMPs) and synaptosome-associated proteins (SNAPs). Released ACh in the synaptic cleft acts on muscarinic and nicotinic receptors (mAChR and nAChR) to cause a response. The excess ACh in the synapse is metabolized by acetylcholinesterase (AChE) in the synaptic membrane to choline and acetate. Acute exposure to OPs causes increased ACh due to the irreversible inhibition of AChE, causing a cholinergic crisis (Sirin and Zhang, 2014; Brunton and Knollman, 2023).

The nicotinic receptors have a minor role in causing neuronal excitability, and their distribution also varies from region to region. For example, the α4 and β2 subunits are found in the brainstem, thalamus, and midbrain, while the α7 subunit is present throughout the brain (Schliebs and Roßner, 1994; Rong et al., 2014, Jett et al., 2018; Wang et al., 2021).

In vivo and *in vitro* studies have demonstrated that M1 receptors play a predominant role in the initiation of seizures following OP exposure, with the basolateral amygdala (BLA) identified as a key region involved in seizure generation (Prager et al., 2013; Miller et al., 2017). OPs such as soman, VX, and paraoxon will also induce presynaptic long-term depression. This effect appears to involve cannabinoid type 1 receptors (CB1R), as well as M1 and M3 receptors, functioning as a compensatory mechanism that operates independently of NMDA receptor activity (Hoffman et al., 2019; Thompson and Tobin, 2020). Increased SE due to ACh also causes increased glutamate receptor interaction (NMDA, AMPA, and metabotropic) (Solberg and Belkin, 1997; Phillips and Deshpande, 2020). M1 activation evokes upregulation of NMDA receptors directly via Src non-receptor tyrosine kinases through a protein kinase C (PKC) signaling cascade (Felsch et al., 1998; Lu et al., 1999a). Glutamate also stimulates an increase in ACh release, which will prolong the seizure (Anderson et al., 1994). Increased NMDA receptor stimulation causes increased influx of intracellular calcium (Ca^{2+}), leading to alteration of calcium-dependent enzymes such as phosphatases, kinases, proteases, and lipases, which affect cell proliferation and information processing in the neurons (Berridge, 2005; Bengtson and Bading, 2012). There are non-cholinesterase targets of OPs, such as carboxylesterase, neuropathy target esterase, transferrin, kinesin, ATP Synthase, and tubulin (Huff et al., 1994; Chanda et al., 1997; Grigoryan et al., 2008, 2009a,b; Terry, 2012). Although these receptors' activation is transient, the aftereffects on the brain if not treated early can be devastating. The cellular and molecular mechanisms in the brain that led to the reorganization of the neural circuits are not fully known.

Damage-associated molecular patterns (DAMPs) such as HMGB1 (High mobility group) are emerging as one of the several other molecular targets for epileptogenesis. Seizures increased the expression and translocation of HMGB1 from the nucleus to the cytoplasm in neuronal and glial cells (Massey et al., 2019; Pauletti et al., 2019; Ahmad et al., 2025). HMGB1 activates pattern recognition receptors (PRRs), including TLR4 and the receptor for advanced glycation end products (RAGE), causing the TLR4/ NF-κB signaling pathway, promoting increased cytokine signaling (IL-1β/TLR signaling in neurons) and neuroinflammation (Maroso et al., 2010; Choi et al., 2011; Paudel et al., 2018; Dai et al., 2021; Zaben et al., 2021). Under physiological conditions, NF-κB remains in an inactive state through its association with inhibitory kappa B (IκB), which binds to its active subunits, p50 and p65 (Baldwin, 1996). Upon activation, NF-κB dissociates from p50 and translocate to the nucleus to initiate transcription of various cytokines, chemokines, immunoreceptors, as well as multidrug resistance proteins such as P-gp (Baldwin, 1996; Liu et al., 2000; Yu et al., 2011; Chen et al., 2015). P-gp, a regulator of blood-brain barrier (BBB) permeability of antiepileptic drugs, has a significant role in refractory epilepsy (Garg et al., 2020).

Reactive oxygen and nitrogen species (ROS/RNS)

During the epileptogenic phase after acute exposure to OPs, the initial seizures cause persistent mitochondrial dysfunction and upregulation of free radicals, pro-inflammatory cytokines, and chemokines. Normal levels of free radicals are required for physiological functions (Salim, 2017). Increased ROS and peroxynitrite, derived from nitric oxide (NO), contribute to the formation of reactive nitrogen species (RNS), which are highly toxic to cellular macromolecules such as proteins, lipids, and DNA (Sinha et al., 2022; Walker, 2023). Reactive species (RS) include superoxide ($O_2^{\cdot-}$), hydroxyl radicals ($OH^{\cdot}$), and hydrogen peroxide (H_2O_2), which are produced by NADPH oxidases (NOX), nitric oxide synthases (NOS), and halo-peroxidases (Pearson-Smith and Patel, 2020). The physiological level of oxidative stress is regulated by a complex endogenous antioxidant enzyme system mediated by the transcription factor Nuclear factor erythroid 2-related factor 2 (Nrf2) and antioxidant response elements (ARE) (Schreibelt et al., 2007). Endogenous antioxidants may be enzymatic or non-enzymatic. Enzymatic antioxidants are catalase (CAT), superoxide dismutases (SODs), glutathione peroxidases (GPx), glutathione reductase (GR), peroxiredoxins (Prx), and thioredoxin (Trx). The non-enzymatic antioxidants include albumin, transferrin, ferritin, cysteine/glutamate antiporter, vitamins C and E, melatonin, ketogenic diet, polyphenols, and ceruloplasmin (Puttachary et al., 2015a; Mirończuk-Chodakowska et al., 2018).

The brain is highly susceptible to oxidative stress due to the high oxygen consumption of about 20%, despite comprising only 2% of body weight and being predominantly composed of lipids (Sastry, 1985; Carvalho and Moreira, 2018). Various sites of mitochondria in the electron transport chains (ETC) are involved in ROS generation, particularly complexes I and III during ATP synthesis. NOX, Xanthine oxidase, and cytochromes P450 are a few other sources of $O_2^{\cdot-}$ (Mostafalou and Abdollahi, 2018; Kim et al., 2013).

Under physiological conditions, the superoxide produced is converted by superoxide dismutase (SOD1 in the intermembrane space of mitochondria and SOD2 in the mitochondrial matrix) to form hydrogen peroxide (H_2O_2), which in turn is converted to water (H_2O) by CAT, GPx, and Trx. During the process, reduced glutathione (GSH) is converted to oxidized glutathione

(GSSG), which is resynthesized to GSH by glutathione reductase in the presence of NADPH (Puttachary et al., 2015a). Exposure to OPs causes mitochondrial stress, leading to an imbalance between the oxidants and the antioxidant enzyme defenses. This causes the excess superoxide in the presence of Fe^{2+} to react with H_2O_2 to form highly toxic hydroxyl radicals, causing cell damage (Fenton and Haber-Weiss reaction) (McCord and Day, 1978).

Reactive nitrogen species (RNS) and epilepsy

Under physiological conditions, NO is produced when L-arginine is converted to L-citrulline, catalyzed by NADPH-dependent NOS (Turrens, 2003). In pathological conditions, activation of NMDA receptors leads to an increase in intracellular calcium levels, which in turn stimulates Ca^{2+}/calmodulin-dependent NOS to produce elevated amounts of NO (Jacobsson et al., 1999). There are three isoforms of NOS: neuronal (nNOS), inducible (iNOS) in glia, and endothelial (eNOS). There is 51-57% structural similarity between the isoforms of NOS. (Alderton et al., 2001). eNOS and nNOS physiologically produce low levels of NO, which is protective, whereas iNOS is upregulated due to injury and in response to various cytokines in pathological conditions, such as brain insult. NO production mediated by iNOS is toxic (Thippeswamy et al., 2006; Thomas, 2015; Puttachary et al., 2016; Staunton et al., 2018; Putra et al., 2020a,c; Massey et al., 2023). eNOS-derived NO prevents hypertension, atherosclerosis, relaxes the smooth muscle, and promotes angiogenesis (Maccallini et al., 2017; Garcia and Sessa, 2019). Mild activation of NMDAR at the synapse causes nNOS-mediated NO production, which activates soluble guanylate cyclase to increase cGMP signaling, together regulating long-term potentiation, a mechanism of learning and memory (Lu et al., 1999b; Maccallini and Amoroso, 2016). nNOS plays a significant role in KA-induced SE (Beamer et al., 2012). Excessive superoxide and NO generated during oxidative stress combine to produce highly toxic peroxynitrite ($ONOO^-$) and dinitrogen trioxide (N_2O_3), which mediates the pathogenesis of SE-induced SRS, Alzheimer's disease, Huntington's disease, Parkinson's disease, stroke, and amyotrophic lateral sclerosis (Bredt, 1999; Liy et al., 2021). Together, these events contribute to gliosis, neuroinflammation, and neurodegeneration, which lower the seizure threshold for the onset of SRS.

Glial cells and neuroinflammation

The glial cells of the brain include microglia, oligodendrocytes, and astrocytes. Microglia are the resident macrophages (mononuclear) of the brain, representing 5-20% of brain cells depending on the species (Arcuri et al., 2017). Microglia are derived from erythromyeloid precursors in the yolk sac and are not from bone marrow, as seen in other circulating macrophages (Alliot et al., 1999; Ginhoux et al., 2010). The disease progression is different in bone marrow-derived phagocytes and yolk sac-derived microglia (Prinz et al., 2011). During neuroinflammatory diseases such as epilepsy and Alzheimer's disease, there is infiltration of bone marrow-derived macrophages in the brain due to BBB dysfunction (Thériault et al., 2015; Huang et al., 2020; Pang et al., 2025). Homeostatic microglia, M2 type (resting state), are seen in healthy individuals, which are required for physiological functions such as myelin synthesis, synaptogenesis, synaptic pruning, apoptosis, oligodendrocyte differentiation, astrocyte growth, and activation (Wright-Jin and Gutmann, 2019; Saucier et al., 2023). Diseases such as traumatic brain injury (TBI), stroke, and epilepsy caused by OP exposure polarize microglia (ramified to reactive amoeboid-like morphology), also known as disease-associated microglia (DAM) (Ransohoff, 2016; Paolicelli et al., 2022). Reactive microglia migrate to the injured site to clear toxic cellular debris by phagocytosis and release immune factors such as cytokines and chemokines. Microglia can be visualized under a microscope by immunostaining brain sections with IBA1 (ionized calcium-binding adaptor molecule 1) (Ito et al., 1998). IBA1 also stains meningeal macrophages and brain-infiltrated perivascular cells. The other markers of microglia include CD68, CD11b, CD14, CD45, CD80, CD115, CX3CR1 (fractalkine receptor), ferritin F4/80, FCER1G and vimentin (Jurga et al., 2020; Lier et al., 2021). Distinguishing between resident CNS microglia and peripheral macrophages is challenging, as they share most epitopes. However, certain markers, such as CD44, are uniquely expressed in brain-infiltrated macrophages and not by resident microglia (Jurga et al., 2020; Gao et al., 2023). TMEM119 and P2ry12 are the unique biomarkers of homeostatic microglia (Schwabenland et al., 2021; Kenkhuis et al., 2022). The common DAM markers include APOE, TREM2, CD11c, LPL, P2X7R, and CLEC7A (Paolicelli et al., 2022; Alves et al., 2024). OP-exposed brains predominantly contain IBA1+CD68 co-labeled cells, considered reactive microglia, that drive neuroinflammation (Vasanthi et al., 2023b, 2025).

Astrocytes are another major subpopulation of glial cells in the CNS that originate from the neuroectoderm (Hattori, 2025). These represent approximately 19-40%, varying by brain region (Pelvig et al., 2008; von Bartheld et al., 2016; Gradisnik and Velnar, 2023). Astrocytes contribute to the regulation of the extracellular matrix, including ion and fluid homeostasis via aquaporin-4 water channels, and are also involved in the production of neurotrophins and adhesion molecules (Manley et al., 2000; Gradisnik and Velnar, 2023). Astrocytes are essential for maintaining the integrity BBB (Heithoff et al., 2021). Astrocytes are involved in glutamate, glycine and GABA homeostasis. During epileptogenesis, there is an imbalance in excitation and inhibition; either there is increased excitatory neurotransmitters or decreased inhibitory neurotransmitters, leading to epileptiform spiking and the onset of spontaneous seizures. Astrocytes play an important role

in maintaining the levels of these neurotransmitters. During glucose metabolism in astrocytes, α-ketoglutarate produced in the TCA cycle is converted into glutamate. This glutamate is then further metabolized into glutamine, which is transported to either glutamatergic or GABAergic neurons. In these neurons, glutamine serves as a precursor for the synthesis of glutamate or GABA, respectively. Approximately 75-80% of glutamate in astrocytes is converted into glutamine, while the remaining 20-25% undergoes degradation (Hertz and Rothman, 2017). Glutamate acts on both ionotropic and metabotropic glutamate receptors to cause its effects. Excess glutamate is cleared from the synaptic cleft primarily through reuptake mechanisms by astrocytes through the excitatory amino acid transporter (EAAT), which is then converted into glutamine by glutamine synthetase (Rowley et al., 2012). Glutamine can be transported back to glutamatergic neurons, where it is converted back to glutamate. Astrocytes also deliver glutamate to GABAergic neurons, where GABA is synthesized by glutamate decarboxylase (GAD), which uses glutamate as substrate. Inhibition of GAD causes seizures (Zhang et al., 2017). Astrocytes are also involved in the synthesis of the antioxidant, GSH. Cystine plays an important role in GSH synthesis, which is transported via the cystine glutamate antiporter enzyme and exported into the extracellular space through multidrug resistance-associated protein (MRP1 and 2) in the astrocytes (Bannai, 1986; Dringen and Hirrlinger, 2003; Satarker et al., 2022). OP-induced SE causes reduced GSH production (Massey et al., 2023; Vasanthi et al., 2023b). As a compensatory response, the activity of the cystine/glutamate antiporter may increase, resulting in elevated extracellular glutamate levels, in turn causing excitotoxicity (Satarker et al., 2022). Genetic deletion of cystine/glutamate antiporter has been shown to be less susceptible to seizures, but did not alter behavioral effects, indicating that cystine/glutamate antiporter is an important target in epilepsy (De Bundel et al., 2011).

Astrocytes can be classified into two types: A1 (reactive; proinflammatory) and A2 (homeostatic; anti-inflammatory). Neuroinflammatory disease, such as OP exposure, causes the transitioning of A2 astrocytes to A1, with an increased proliferation of astrocytes termed as astrogliosis (Vasanthi et al., 2023b, 2025). Anti-inflammatory type astrocytes secrete neuroprotective molecules to promote the growth and repair of neurons. Glial fibrillary astrocytic protein (GFAP) is used as a marker for astrocytes. Various other markers include structural and membrane proteins (CD109, CD14, CD36, nestin, EMP1, Cx30, Cx43); secreted proteins (C3, CXCL10, PTX3, Serpin G1, TSP-1); intracellular proteins (iNOS, S100β, SOX9, STAT3, SPHK1) (Rothermundt et al., 2003; Jurga et al., 2021). Exposure to DFP causes an increase in GFAP-positive cells (astrogliosis) along with an increase in C3-positive astrocytes (proinflammatory phenotypes) and S100A10 (anti-inflammatory phenotypes) in the piriform cortex across multiple time points, extending up to 28 days (Andrew et al., 2024b; Vasanthi et al., 2025). Activation of pro-inflammatory astrocytes persists beyond the initial response of pro-inflammatory microglia. DFP exposure has been shown to produce a significant positive correlation between C3-positive astrocytes and CD68-positive microglia (Vasanthi et al., 2025). The elevated C3 levels secreted by astrocytes may contribute to the increased microgliosis, as microglia express receptors for C3. This suggests a functional interaction between astrocytes and microglia in the neuro-inflammatory response (Lian et al., 2016; Hong et al., 2016; Wei et al., 2021; Vasanthi et al., 2023b). Genetic knockout of C3 and its acute depletion using cobra venom factor have been shown to reduce astrogliosis and memory impairments following chemoconvulsant-induced SE (Schartz et al., 2023, 2024). In contrast, individuals with drug-resistant epilepsy exhibit an abnormal complement cascade, with significantly decreased Complement Component Subunit 1q (C1q) levels in both sexes and lower C3b/iC3b levels in females compared to males (Pinzon-Hoyos et al., 2025).

Cytokines and chemokines in response to OP exposure

Reactive gliosis post brain injury releases interleukin (IL)-1α, tumor necrosis factor (TNF)-α, and C1q by reactive microglia, which causes the upregulation of A1-type astrocytes (Liddelow et al., 2017; Ding et al., 2021). TNF-α promotes the production of IL-6 by proinflammatory astrocytes, contributing to glial scar formation in a mouse model of spinal cord injury (Sawada et al., 1992; Nakamura et al., 2005; Ishijima and Nakajima, 2021). Inhibition of IL-6R by its antibody has been shown to decrease glial scar formation and improve spinal cord injury (Nakamura et al., 2005). Exposure to OPs, such as soman and DFP, resulted in significantly higher levels of IL-6 production than IL-17A, TNF-α, IL-18, and IL-1α in both serum and cerebral spinal fluid (CSF) (Massey et al., 2025a; Vasanthi et al., 2025). Acute SE induced by soman and other chemoconvulsants has been shown to result in glial scar formation, highlighting IL-6 as a potential target for therapeutic interventions (Rao et al., 2023; Massey et al., 2025b).

Acute OP exposure causes a significant increase in the transcription of various proinflammatory cytokines and chemokines at chronic time points. Rats pretreated with PB and atropine methyl nitrate, followed by soman or DFP exposure, have been shown to upregulate mRNA levels of C-C motif chemokine ligand (CCL)2, CCL3, CCL4, CXCL10, and TNFα at 4 days post-exposure (Rojas et al., 2018, 2021). These studies also showed elevated levels of COX-2. DFP exposure at 1 month has also been shown to increase IL-17, TNF-α, IL-6, IL-18, IL-1α, and monocyte chemoattractant protein (MCP)-1 (Vasanthi et al., 2025). This study also discussed the correlation analysis between different glial cells (reactive astrocytes) and proinflammatory cytokines/

chemokine (Vasanthi et al., 2025). Acute soman exposure also causes a significant increase in the proinflammatory cytokines and chemokine such as IL-17A, TNF-α, IL-6, IL-18, IL-1α, and MCP-1 in the serum and CSF at 18 weeks post-exposure, along with elevated mRNA levels in the rat brain, implying the cytokines originated from the brain but not from the periphery (Massey et al., 2025a).

Elevated gliosis contributes to neuroinflammation through upregulation of cytokines and nitro-oxidative stress, which in turn causes neurodegeneration. Neurological symptoms during OP poisoning often result from the impairment of various subtypes of neurons and altered neurotransmitter release in different brain regions (Reddy et al., 2021; Vasanthi et al., 2023b; Andrew et al., 2024a; Urquizu et al., 2024; Massey et al., 2025b). Neurodegeneration is a continuous process that leads to cognitive impairment following OP intoxication (Deshpande et al., 2014; Aroniadou-Anderjaska et al., 2016; Flannery et al., 2016; Guignet et al., 2020; Vasanthi et al., 2023b). Costaining neurons (stained with NeuN) with Fluoro Jade dyes, a marker for degenerating cells, would confirm neurodegeneration (Schmued et al., 1997; Colombo and Puissant, 2002; Damjanac et al., 2007; Massey et al., 2023). OPs such as soman, DFP, paraoxon, as well as chemoconvulsants like pilocarpine and KA, have been shown to cause significant neurodegeneration/neuronal loss across various brain regions (Deshpande and DeLorenzo, 2020; Zare et al., 2020; Vasanthi et al., 2023b; Rao et al., 2023; Reddy et al., 2024).

A battery of behavioral tests revealed behavioral and cognitive deficits following acute or chronic exposure to OP compounds in various animal models (Mamczarz et al., 2010; Terry et al., 2012; Deshpande et al., 2014; Ribeiro et al., 2022). Novel object recognition is a test to evaluate cognitive function in rodents. Soman exposure causes significant cognitive impairment, indicated by reduced discrimination and recognition indices in the novel object recognition, with increased neuro-degeneration in the hippocampus. Additionally, a positive trend was observed in the correlation of functional MRI of the hippocampus with the novel object recognition task (Vasanthi et al., 2023b; Massey et al., 2025b). The open field test and elevated zero maze test are used to assess exploratory and reduced anxiety-like behavior, respectively. An open field test evaluates emotional and exploratory behavior in animals (Himanshu et al., 2020). Rodents tend to spend more time in the periphery of the open field test arena compared to the center, reflecting fearful and anxious behavior. In contrast, the elevated zero maze evaluates anxiety on an elevated open platform. This test reduces potential confounds from basic locomotion and anxiety deficits that may affect results in the open field test. Rodents typically spend more time in the closed arm than in the open one. OP exposure causes significant alteration in these behaviors, likely driven by gliosis and neurodegeneration within the amygdala, a brain region critically involved in regulating anxiety-related responses, particularly the BLA and central amygdala (CeA). The BLA experiences severe neurodegeneration, particularly in inhibitory neurons, over 7, 14, and 30 days following nerve agent-induced seizures (Prager et al., 2014; Babaev et al., 2018).

There are various subtypes of inhibitory neurons in the brain. Parvalbumin (PV) comprises ≈50%, Somatostatin ≈30% and Calretinin ≈15% (Wonders and Anderson, 2006). In early development, GABAergic neurons have depolarizing (excitatory) properties, whereas in the mature phase, they change to hyperpolarizing (inhibitory) (van van Hugte et al., 2023). Pilocarpine-induced SE shows that there is higher function of Na^+-K^+-$2Cl^-$ cotransporter (NKCC1) and lower function of K^+-Cl^- cotransporter (KCC2), which results in a shift of GABAergic neuron function from hyperpolarization to depolarization (Barmashenko et al., 2011). Loss of the $5HT_{2A}$ receptor causes decreased PV activity in the BLA, which increases fear, leading to anxiety in rodents, indicating an alteration in anxiety (Jiang et al., 2009; Babaev et al., 2018). This shows that PV GABAergic interneurons play a significant role in anxiety and cognition (Leitch, 2024). In a rat epilepsy model, loss of inhibitory neurons revealed anxiety-like behavior, which significantly correlated with seizure frequency (Buckmaster et al., 2017). OP exposure also causes a significant loss of PV and somatostatin-positive cells, leading to behavioral deficits and SRS (Vasanthi et al., 2023b; Massey et al., 2025b).

Therapeutic strategies

Medical countermeasures

There are several therapeutic targets to treat acute OP poisoning. The currently available countermeasures involve treating acute symptoms to counteract cholinergic crises resulting from nicotinic and muscarinic receptor overstimulation. The timeframe for acute exposure to OP, particularly through inhalation of nerve agents like soman vapor, is extremely narrow. The therapeutic strategies for nerve agent exposure are different for military deployment and civilian populations.

Pyridostigmine bromide (PB, FDA approved), a reversible AChE inhibitor, is a prescribed prophylactic treatment for military personnel (US Food and Drug Administration, 2013). PB is a hydrophilic carbamate compound that normally doesn't cross the BBB (Pavlovsky et al., 2003). PB inhibits 20-40% of peripheral AChE reversibly without impairing normal neurotransmission. The recommended dose is a 30 mg tablet every 8 hours. During the Gulf War, approximately 250,000 military soldiers took at least one dose of PB (Institute of Medicine (US) Committee on Health Effects Association with Exposure during the Gulf War, 2000). PB is ineffective if given after nerve agent exposure. The toxic effects of PB were examined

over the years. Repeated administration of 30 mg PB every 8 hours didn't alter pilot performance, even when the blood AChE inhibition reached 29% in normal individuals (Izraeli et al., 1990). The effectiveness of pretreatment with PB in animal studies was beneficial with soman and tabun exposure, whereas no beneficial effects were observed against DFP, VX, and sarin, indicating the difference in the efficacy of PB in different animal models (Dunn et al., 1997; Bruun et al., 2019). However, pretreatment is not practical for civilians.

Oximes and atropine sulphate are current medical countermeasures (MCM) for OP intoxication worldwide. Since the discovery of oximes such as pralidoxime (2-PAM, FDA approved) in the 1950s, various other oximes were discovered, such as trimedoxime (TMB-4), obidoxime, and HI-6 (Wilson and Ginsburg, 1955; Gupta and Parmar, 2025). Oximes speed up the reactivation of OP-induced AChE inhibition and hence prevent excitotoxicity by inhibiting overstimulation of ACh muscarinic and nicotinic receptors. The reactivations depend on concentration, affinity, type of OP compounds, and aging rate. Currently available oximes have limited CNS effects due to poor BBB permeability; for example, 2-PAM has a mean BBB permeability of only 10% (Wei et al., 2016). The recommended dose of 2-PAM in humans for acute OP patients begins with a 2 grams loading dose over 30 minutes, followed by 1 gram/hour for 48 hours, and then 1 gram/hour every 4 hours (Eyer and Buckley, 2006). 2-PAM is effective against VX, sarin, and tabun but has minimal effect against soman; however, HI-6 was 3-5 times more effective than 2-PAM (Koplovitz and Stewart, 1994). HI-6 is the first oxime to have demonstrated efficacy against soman-induced OP toxicity (Wei et al., 2016). A recent study demonstrated that HI-6-lipo bypasses the BBB and directly delivers into the brain, thereby improving the efficacy of free HI-6 in the brain (Fan et al., 2023; Shen et al., 2023).

Atropine (FDA approved) is the first choice of medication in acute OP poisoning, which is a competitive, reversible antimuscarinic agent that reduces the peripheral effects of OP poisoning. Atropine acts by inhibiting postganglionic ACh receptors and has a direct vagolytic action, where there is increased parasympathetic inhibition, leading to increased cardiac output and other associated effects (Patel et al., 2025). It acts on ACh receptors at the neuromuscular junction to dampen muscle fasciculations and tremors. It decreases muscarinic symptoms but has no impact on nicotinic effects. In OP poisoning, atropine is usually combined with oxime for better outcomes. Atropine decreases glandular secretions, nausea, diarrhea, dilates bronchi, and improves cardiorespiratory effects (Jokanović, 2009). The dose of atropine is 0.05 mg/kg in adults and 0.015-0.05 mg/kg in pediatrics, given over 3-30 minutes, respectively. Atropine has been demonstrated to have mild anticonvulsant and neuroprotective effects in animal models (McDonough et al., 1987; Shih and McDonough, 1999).

Atropine and other anticholinergics in combination with oxime have been shown to improve the peripheral effects caused by OPs; however, the central effects caused by SE are harder to treat. Considering the mechanism of OP poisoning, anticholinergic countermeasures and oxime are effective in the acute stages, whereas glutamate receptor antagonists may be effective in both acute and later stages when NMDA, AMPA, or kainate receptors are involved (Miller et al., 2015). Additionally, focusing on the inhibitory system during acute exposure by activating $GABA_A$ has proven effective (Martin and Kapur, 2008; Goodkin and Kapur, 2009; Reddy et al., 2024). The currently available standard of care (SOC) for treating seizures caused by SE is benzodiazepine. It is a positive allosteric modulator of $GABA_A$ receptors, leading to an increase in intracellular chloride, resulting in membrane hyperpolarization and a reduction in neuronal hyperexcitability. Diazepam, lorazepam, and midazolam (all FDA approved) are a few of the benzodiazepines used to treat acute SE, including OP-induced seizure (Reddy and Reddy, 2015). A controlled clinical trial indicated that midazolam was more effective than diazepam for treating SE (McMullan et al., 2010). Diazepam is effective in treating seizures when given within 5 minutes after SE and progressive brain pathology, which is practically impossible in emergencies (Shih et al., 1999). Midazolam is not effective in controlling seizures 40 minutes after seizure onset due to early maladaptive internalization of receptors (Shih et al., 1999; McDonough Jr et al., 1999; Niquet et al., 2017). Midazolam is effective in the early stages of SE; however, it does not prevent SRS or long-term neurodegeneration (Vasanthi et al., 2023b; Massey et al., 2025b). Therefore, the timing of treatment is a critical factor for allosteric modulation of GABAAR by benzodiazepine due to synaptic loss and receptor internalization.

Nitric oxide synthase inhibitors as adjunct therapy

All these MCM effectively address the acute symptoms of OP toxicity; none of them prevent long-term complications such as SRS, cognitive decline, gliosis, and neurodegeneration. Another critical target for preventing the long-term consequences of acute OP exposure is oxidative stress pathways. As mentioned above, NO plays a vital role in oxidative stress and the development of epilepsy. The role of NOS inhibitors is controversial, as studies have reported both anticonvulsant and proconvulsant effects (Kirkby et al., 1996). The efficacy of these pharmacological inhibitors depends on the potency and isoform selectivity of NOS inhibition, as non-selective inhibition can be toxic (Thippeswamy et al., 2006). Under normal conditions, baseline NO promotes the expression of activity-dependent neuroprotective protein (ADNP), while a broad-spectrum NOS inhibitor, L-NAME (L-Nω-

nitroarginine methyl ester), or soluble guanylyl cyclase (sGC) inhibitor ODQ, accelerates the onset of the first seizure in the KA model. Interestingly, while KA increases NO production and, in turn, decreases ADNP levels, pre-treating with NOS or sGC inhibitor reverses the loss of ADNP within 3 days, indicating the critical role of NO-cGMP signaling in epileptogenesis (Cosgrave et al., 2008). Recent studies showed a persistent increase in iNOS in reactive microglial cells and 3-nitrotyrosine in neurons for a long term (3 months post-exposure) after the induction of SE (Putra et al., 2020c) . Blocking NO production has demonstrated disease-modifying effects in epilepsy; however, the effectiveness of this strategy depends on the specific use of NOS inhibitors as well as the timing and dosage of treatment (Puttachary et al., 2016; Putra et al., 2020c; Massey et al., 2023; Vasanthi et al., 2023b).

The mechanisms by which NOS can be inhibited can be categorized into L-arginine uptake inhibitors, agents that prevent the required cofactors for NOS-catalyzed conversion of L-arginine; agents that inhibit the substrate binding to NOS and inhibitors of NO (Hobbs et al., 1999). The first developed NOS inhibitor was N^G-monomethyl-L-arginine (L-NMMA) (Palmer et al., 1988). L-NMMA is a naturally occurring L-Arginine analogue and is a competitive, nonselective NOS inhibitor. Animal studies showed that L-NMMA reversed sepsis-associated hypotension; however, human clinical trials reported various adverse effects following treatment, which is due to inhibition of endothelium-dependent relaxation (Rees et al., 1989; Kilbourn et al., 1990; López et al., 2004; Moncada and Higgs, 2006). L-NMMA didn't show any anticonvulsant action in an animal study (Czuczwar et al., 1999). Another L-Arginine analogue includes L-N^{ω},N^{ω}-Dimethylarginine (ADMA, naturally occurring) and methyl ester prodrug of nitro-L-arginine (L-NNA), L-NAME, a synthetic compound. L-NNA and the prodrug L-NAME have been used in various animal studies (Tabrizi-Fard and Fung, 1996; Bradman et al., 2011). Pretreatment of L-NAME before thalidomide treatment augmented the antiepileptic effect of thalidomide (Payandemehr et al., 2014). L-NAME potentiated the effects of clonazepam and diazepam, whereas it decreased the efficacy of phenobarbital and valproate. However, NNA had no effects on classic antiepileptic drugs (AEDs) such as diazepam, phenobarbital, and valproate (Banach et al., 2011). The anticonvulsant efficacy of L-NAME in the PTZ model was seen at the dose rate of 70 mg/kg, where it decreased the severity of seizures (Jelenković et al., 2002). L-NAME has also been shown to have antimuscarinic effects (Buxton et al., 1993). All these studies indicate that nonspecific NOS inhibition has a broad range of effects in various epilepsy models (Kirkby et al., 1996; Takei et al., 2001; Hagioka et al., 2005; Banach et al., 2011).

The adverse effect of NOS inhibition could be decreased by using a selective NOS inhibitor. As discussed earlier, upregulation of nNOS expression has been seen in the early phase of epileptogenesis (Cosgrave et al., 2008; Kim, 2010; Beamer et al., 2012). nNOS is found in both the cytosolic and postsynaptic membranes of neurons through its interaction with the NMDA receptor-PSD-95 complex (Sattler et al., 1999; Maccallini and Amoroso, 2023). Excessive NMDA receptor activation leads to activation of nNOS in a calcium-dependent manner, resulting in increased NO production in the brain, contributing to nitro-oxidative stress, in turn causing neurodegeneration and SRS. The nNOS-specific inhibitor, Nw-propyl-L-arginine (L-NPA), has 3158 and 149 times greater affinity to iNOS and eNOS, respectively (Zhang et al., 1997). A strong disease-modifying effect of L-NPA was observed in KA-induced SE. Pretreatment with L-NPA significantly reduced SE, in turn reducing biomarkers of epileptogenesis at various timepoints (Beamer et al., 2012). An *in vitro* study also showed a decreased seizure-like event following the nNOS-selective inhibitor 7-nitroindazole (7-NI) (Kovács et al., 2009). However, nNOS inhibitors are ineffective if administration is delayed by 15 minutes (Favié et al., 2018).

The iNOS inhibitor is another potential pharmacological tool to decrease NO production in the brain with minimal effects on other forms of NOS. iNOS inhibitors have shown to have minimal effects on pain and septic shock; however, they have shown promising results in cancer, neurodegenerative disease, experimental models of epilepsy, and pulmonary diseases (Puttachary et al., 2016; Roy et al., 2023; Vasanthi et al., 2023b). iNOS inhibitors are broadly classified into natural and synthetic, based on their source of origin. Synthetic is further classified into arginine and non-arginine analogues. The most selective and potent inhibitor of iNOS is N-(3-(Aminomethyl) benzyl)acetamidine (1400W, molecular weight 250.17) (Garvey et al., 1997). 1400W is an extremely slow or an irreversible inhibitor of iNOS with a Kd value $\leq$7 nM, but a relatively weaker, rapidly reversible inhibitor of nNOS and eNOS. 1400W is 5000-fold more selective for iNOS than eNOS. The selectivity of 1400W towards iNOS is due to its benzyl group connected to an amidino nitrogen (Minhas et al., 2020). 1400W has been shown to have minimal cardiovascular side effects due to its specific activity on iNOS rather than eNOS (Wang et al., 2019, 2020; Roy et al., 2023). An *in vitro* study has shown that 1400W effectively blocked iNOS and NO production in lipopolysaccharide (LPS)-stimulated microglia and preoligodendrocytes (He et al., 2010). 1400W has shown efficacy in various *in vivo* studies (Jafarian-Tehrani et al., 2005; Pérez-Asensio et al., 2005; Putra et al., 2020c; Massey et al., 2023; Vasanthi et al., 2023b). The extent of iNOS inhibition plays a crucial role in preventing harmful inflammatory responses in the brain. For instance, in multiple sclerosis (MS), partial inhibition of NOS using iNOS inhibitors has been shown to prevent disease progression in animal models. In contrast, complete deletion of iNOS (*iNOS*$^{-/-}$) in a knockout mouse model worsens the condition,

suggesting the optimization of the dosage of iNOS inhibitors for effective disease control (Ghasemi and Fatemi, 2014). The dose and duration of treatment determine the effectiveness of 1400W; while short-term administration is beneficial in some models of epilepsy, prolonged inhibition of iNOS may worsen the condition (Sinz et al., 1999; Jafarian-Tehrani et al., 2005). 1400W has been shown to inhibit ischemia-induced ATP depletion and increase in glutamate release (Pérez-Asensio et al., 2005). 1400W is well tolerated at doses up to 25 mg/kg, with no observed adverse effects on hemodynamics (Garvey et al., 1997). Mortality was noted at an i.v. bolus dose of 50 mg/kg in mice and rats, while rats tolerated i.v. infusion at a dose of 120 mg/day for 7 days (Garvey et al., 1997). Our lab has previously tested the efficacy of 1400W in various animal models of epilepsy, such as kainate and OP models. Although the results are promising, the precise mechanism of action remains unclear. Our lab has optimized the dose of 1400W for the epilepsy model at 20 mg/kg via the intramuscular route based on the serum and brain pharmacokinetics (Vasanthi et al., 2023b). Peak serum concentrations were observed at 30 minutes, and traces of 1400W were detected up to 12 hours, providing the basis for twice-daily administration for the first three days post-SE to target high iNOS activity during this period (Putra et al., 2020c). The concentration of 1400W was higher in the piriform cortex than in the hippocampus (Vasanthi et al., 2023b). 1400W (20 mg/kg, i.m.) had no adverse effect on cardiac and lung function as measured by echocardiogram and flexiVent, respectively (Puttachary et al., 2016).

An initial study using mouse brain slice cultures demonstrated a significant reduction in KA-induced epileptiform spiking following treatment with 1400W. An *in vivo* study demonstrated that 1400W significantly reduced neuronal hyperexcitability, glial cell proliferation, and neurodegeneration during both the early epileptogenic and the SRS phase following KA administration (Puttachary et al., 2016). Elevated levels of pro-inflammatory mediators start after the initial brain insult, and their levels persist for several weeks to months (Putra et al., 2020c; Massey et al., 2023; Vasanthi et al., 2023b). As mentioned above, 3-NT serves as a marker of protein nitration and nitro-oxidative stress. The increased iNOS activity, as indicated by excess 3-NT-positive M1-type microglia in the brain, was significantly decreased by 1400W in 7 days post KA (Puttachary et al., 2016). This decrease in iNOS activity in the glial cells by 1400W may be a possible reason for decreased epileptiform spike and neurodegeneration at 1-week post-insult. Kir 4.1 and GLT-1 play key roles in removing excess potassium and glutamate from the extracellular space (Mitani and Tanaka, 2003; Kinboshi et al., 2020). 1400W partially restored Kir 4.1; however, GLT-1 levels were unaffected (Puttachary et al., 2016). This indicates that the neuro-protective mechanism of 1400W could be mediated by inhibiting the glial source of pro-neuroinflammatory mediators. 1400W was also effective against OP induced toxicity. DFP (soman surrogate) exposure has been shown to cause a significant increase in the serum nitrite (a measure of nitro-oxidative stress) levels at 24 hours, 8 days, and 6 weeks post-exposure. The levels of iNOS and 3-NT were higher in the hippocampus and piriform cortex compared to control at 24, 48 hours, and 7 days, and persisted even at 12 weeks. The immunohisto-chemistry data indicate that 3-NT and iNOS are predominantly co-localized with neurons and microglia at 7 days and 12 weeks, respectively. DFP-induced expression of iNOS in glial cells led to gliosis and neurodegeneration during both the epileptogenic (day 7) and the SRS phase (12 weeks). We also observed a significant increase in pro-inflammatory cytokines//chemokines in the hippocampus at 6 weeks post-DFP injection. 1400W significantly attenuated all of these pathological changes, leading to decreased epileptiform spiking and SRS (Putra et al., 2020c; Massey et al., 2023). We further evaluated the efficacy of 1400W in the soman model. Acute exposure to soman (GD, 132 µg/kg, s.c.) induced SE. Although SOC treatment was administered, it failed to prevent the long-term effects associated with acute OP exposure. 1400W was administered at 20 mg/kg, i.m., twice daily for the first three days, followed by a single dose per day for the next 11 days (Vasanthi et al., 2023b). Even with severe SE of >20 minutes, we observed a significant and long-term disease-modifying effect at 3.5 months post-soman exposure. 1400W was able to recover motor and cognitive dysfunction; reduced proinflammatory cytokines in the serum and a few cytokines in the CSF; reduced nitrite, ROS levels, and improved antioxidant GSH: GSSG levels. 1400W also decreased neuro-inflammation as indicated by reduced gliosis and neurodegeneration. 1400W has recovered soman-induced PV-positive neurons in the amygdala. Functional network connectivity of the hippocampus, cortex, and thalamus was reduced following GD exposure, and 1400W was able to mitigate the losses in most brain regions except the thalamus.

Iron-induced ferroptosis in reactive glial cells leads to neurodegeneration (Ji et al., 2022; Benarroch, 2023). Soman exposure causes impairment in iron metabolism, indicated by elevated levels of ferritin (FTH-1), an iron storage protein. 1400W could decrease these effects in a few regions of the hippocampus and piriform cortex (Putra et al., 2024b). Further, we observed that glial cells were responsible for iron deposition. Morphometric analysis showed a significant correlation between FTH-1 levels in microglia and altered microglial phenotypes. We further evaluated the impact of 1400W on nitro-oxidative stress and observed a significant improvement in iNOS, 3NT, and NOX2 (gp91^{phox} subunit); however, the expression of 4-HNE and antioxidant marker Nrf-2 in the hippocampus was lower but not statistically significant compared to the soman group. These findings suggest that a selective iNOS inhibitor, such as 1400W, could be one of the new potential therapeutic agents to

treat acute OP exposure.

Src tyrosine kinase inhibitors as adjunct therapy

We discovered SAR as a novel disease-modifying agent that targets Src family tyrosine kinases (SFKs) expressed in both neurons and microglia. SFKs (molecular weight 60-kD) are a broad group of non-receptor binding proteins comprising nine members: Src, Fyn, Lyn, Yes, Blk, Fgr, Hck, Lck, and Yrk (Brown and Cooper, 1996; Mandal et al., 2011). In the CNS, six members of SFK are found (Src, Fyn, Lyn, Lck, Yes and Yrk) in various cell types such as neurons, glial cells, and oligodendrocytes (Colognato et al., 2004; Nie et al., 2021). Structural details and pathological activation are discussed in a review article (Gage and Thippeswamy, 2021). SFK phosphorylation has been shown to cause neuronal hyperexcitability and neuroinflammation due to reactive gliosis in various diseases (Kaufman et al., 2015; Sharma et al., 2018; Panicker et al., 2019; Gage and Thippeswamy, 2021). Increased SFKs in microglia post-SE mediates neuroinflammation, while in neurons, they interact with tau and post-synaptic molecules such as PSD95 and NR2B to mediate hyperexcitability and neurotoxicity. Therefore, an SFK inhibitor, such as SAR, can target both cell types to modify epileptogenesis (Sharma et al., 2021; Putra et al., 2024a)

Tau is a soluble microtubule-associated protein found predominantly in neurons, which regulates cytoskeletal stability, intracellular transportation, and axonal development in the central nervous system (Weingarten et al., 1975; Dixit et al., 2008; Pooler et al., 2013; Wang and Mandelkow, 2016). Tau undergoes various post-translational modifications under both normal and pathological conditions. These modifications include phosphorylation, ubiquitination, glycosylation, polyamination, glycation, truncation, nitration, and aggregation (Gong and Iqbal, 2008). Tau pathology is found in various diseases such as epilepsy, Alzheimer's disease, Parkinson's disease, and frontal temporal dementia (Gendron and Petrucelli, 2009). We have shown that serum levels of the phosphorylated AT8 tau epitope at Ser202 were significantly higher in epileptic rats, which serve as a peripheral biomarker (Putra et al., 2024a). The activated SH3 domains of Fyn and Src have been shown to interact with the proline-rich sequence of tau, causing hyperphosphorylation. This interaction, along with NR2B-PSD protein 95 (PSD95) interactions promoting hyperexcitability, has been demonstrated in rodent models and human epilepsy (Ittner et al., 2010; Putra et al., 2024a). This indicates that inhibiting the molecular interactions of tau can have a positive impact on seizures and brain pathology (Fig. 2).

We have previously shown the effect of PTZ on the genetic ablation mouse models of Fyn KO (*fyn*$^{-/-}$), tau KO (*tau*$^{-/-}$), and double knockout (DKO) (*fyn*$^{-/-}$/*tau*$^{-/-}$). The results indicate that DKO mice had the least gliosis. The mortality rates were 27.37% and 63.64% in control and Fyn KO mice, respectively; however, none of the tau KO or DKO mice died post-PTZ administration. Most of the Fyn KO that died had hydrocephalus, indicating insufficient neuroprotection (Putra et al., 2020b). Moreover, the gene knockout approach is not clinically feasible. Vector-mediated *fyn*-shRNA transduction into the rat hippocampus (neuronal-specific fyn knockdown model), followed by repeated low-dose KA a week later, caused a significant reduction of hippocampal Fyn, along with a reduction of total tau, pNR2B^{Y1472}, NR2B, and PSD. Surprisingly, there was a compensatory upregulation of SFK (pSFK^{Y416}:Fyn) and tau hyperphosphorylation (AT8:total tau). There was no change in the proximity ligation assay (PLA) of Fyn-tau interactions, indicating tau may be engaging with other SH3 domain-containing proteins (Rao et al., 2025). Fyn-Tau blocking peptide (Tau-PxxP5/6) has been shown to reduce Tau phosphorylation by Fyn, without affecting

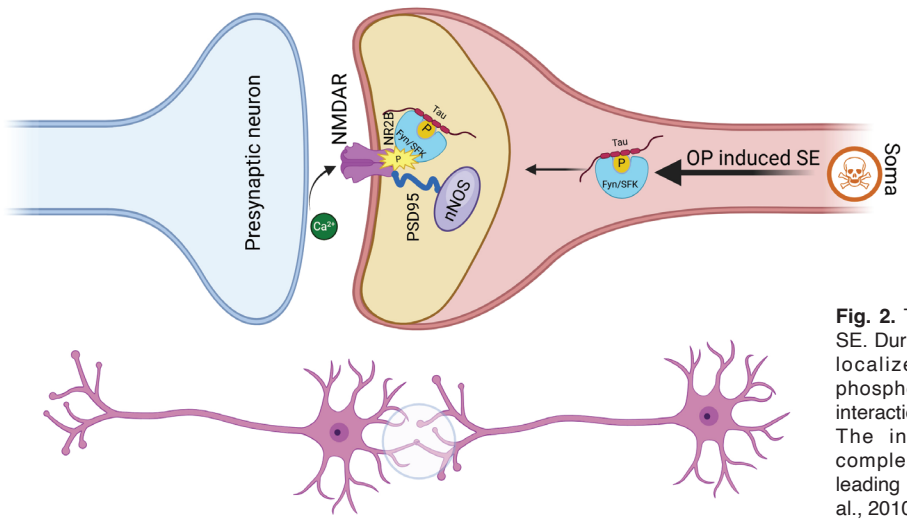

Fig. 2. The Fyn-tau signaling cascade in neurons post-SE. During epileptogenesis, Fyn phosphorylates tau that localizes to the postsynaptic density, where it phosphorylates NR2B at Tyr1472, leading to stable interaction with scaffolding protein, PSD-95, and nNOS. The interaction of Fyn/tau/NR2B/PSD95/nNOS complexes causes excessive Ca^{2+} and Na^{+} influx, leading to persistent neuronal hyperexcitability (Ittner et al., 2010; Putra et al., 2024a).

the activity of Fyn, thereby preventing its migration to PSD, followed by NMDAR activation (Rush et al., 2020; Roth et al., 2023). Reports have also shown that tau phosphorylation at Y18 is mediated not only by Fyn but also by other kinases, including spleen tyrosine kinase (Syk) and Lck; moreover *in vitro* study has also

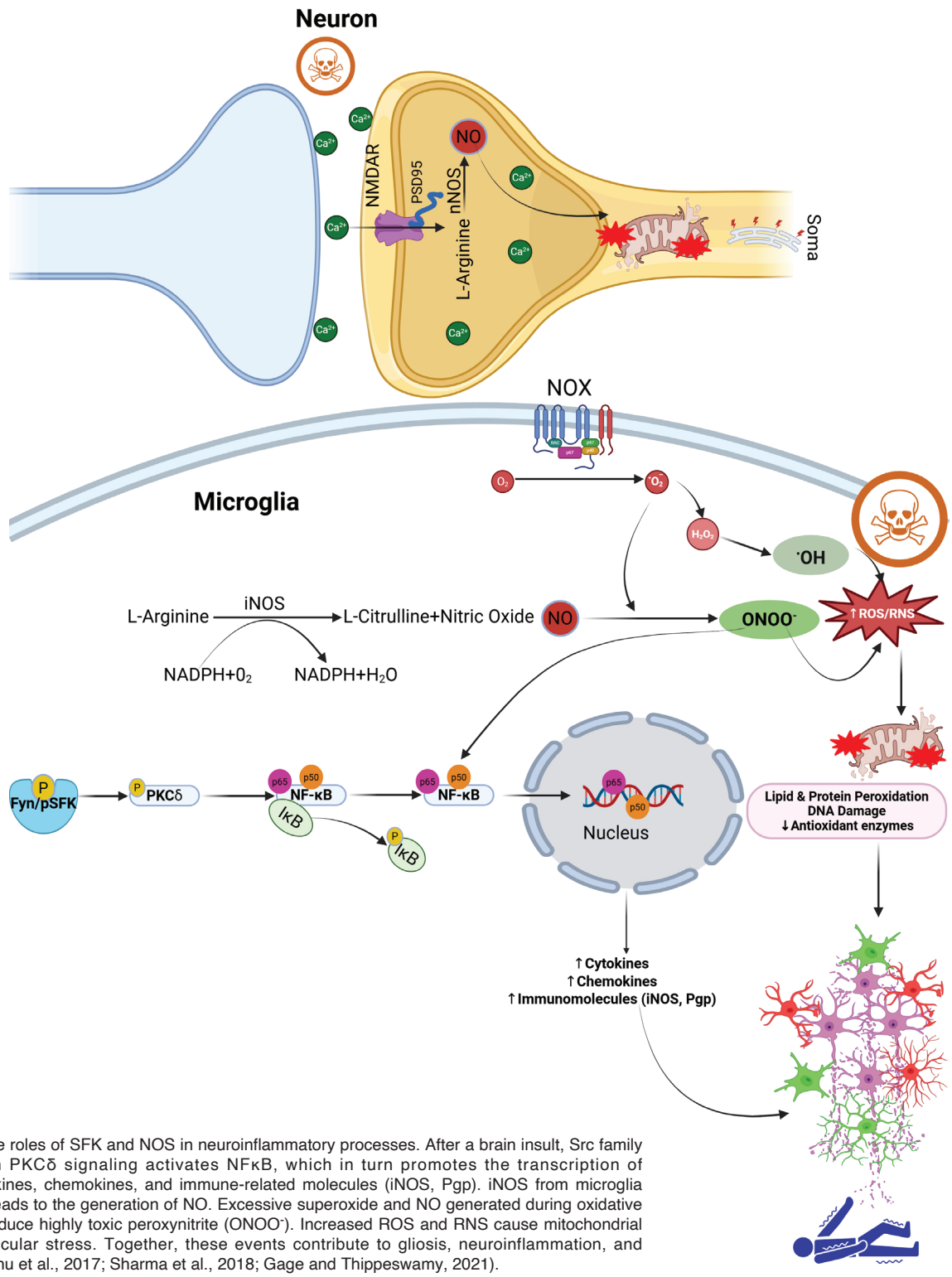

Fig. 3. Overview of the roles of SFK and NOS in neuroinflammatory processes. After a brain insult, Src family kinase (SFK)-driven PKCδ signaling activates NFκB, which in turn promotes the transcription of proinflammatory cytokines, chemokines, and immune-related molecules (iNOS, Pgp). iNOS from microglia and neuronal nNOS leads to the generation of NO. Excessive superoxide and NO generated during oxidative stress combine to produce highly toxic peroxynitrite ($ONOO^-$). Increased ROS and RNS cause mitochondrial and endoplasmic reticular stress. Together, these events contribute to gliosis, neuroinflammation, and neurodegeneration (Zhu et al., 2017; Sharma et al., 2018; Gage and Thippeswamy, 2021).

shown that phosphorylation of Y18 is independent of Fyn-tau interaction, facilitating neurotoxicity (Lebouvier et al., 2009; Scales et al., 2011; Miyamoto et al., 2017). The more effective strategy to prevent interaction or to inhibit Fyn/SFK activation and rescue chronic epilepsy is to use pharmacological inhibitors of Fyn/SFK. Multiple classes of SFK inhibitors have been in clinical trials for various clinical conditions, such as epithelial and non-epithelial cancers (Summy and Gallick, 2003). Dasatinib, bosutinib, ponatinib, and vandetanib have been approved by the FDA for the treatment of chronic myelogenous leukemia and medullary thyroid cancer, respectively (Roskoski, 2015). Saracatinib (SAR; AZD0530) and AZD0424, the two test drugs developed by AstraZeneca, are in clinical trials for solid tumors, such as breast and lung cancers. All these compounds are ATP-binding competitive inhibitors. A few of the compounds, such as dasatinib, have shown limited efficacy in treating diseases like glioblastoma, primarily due to poor BBB permeability and active efflux mechanisms. Specifically, dasatinib, a substrate of P-glycoprotein (Pgp), is actively expelled from tumor cells due to upregulation of Pgp expression within these cells (Agarwal et al., 2012; Lassman et al., 2015). Notably, SAR has demonstrated superior efficacy compared to dasatinib, as it inhibits ABCB1 transporters such as Pgp. This property increases its ability to penetrate the BBB, making it suitable for use either as monotherapy or in combination with other agents to improve the concentration of the drug in the brain (Liu et al., 2013, 2019). SAR is a selective dual inhibitor of Fyn/Src and ABL with IC50 values of 10 and 2.7nM for Fyn and c-Src, respectively (Green et al., 2009; Cirotti et al., 2020). We have tested the efficacy of SAR in various animal models such as KA, DFP, and soman models (Sharma et al., 2021; Gage et al., 2022; Vasanthi et al., 2025; Massey et al., 2025b). We have conducted detailed pharmacokinetics analysis of SAR in naïve rats and in OP models (Vasanthi et al., 2023a, 2025; Massey et al., 2025b). Optimizing the dose of SAR to improve delivery and efficacy by incorporating the drug into the rat diet and testing in OP models yielded promising disease-modifying effects (Vasanthi et al., 2025; Massey et al., 2025b).

Macrophage mobility is mediated by iNOS-induced Src expression. LPS stimulation increases iNOS expression, which promotes NO production, and promotes nitrosylation and subsequently activates SFK, which in turn triggers NF-κB signaling and increases macrophage motility (Maa et al., 2008). iNOS-induced Src expression causes IFN-production in the macrophages during inflammation (Hsieh et al., 2014). Cancer studies indicated that iNOS is a downstream target for phosphorylation (Tyr1055) by activated Src kinase (Tyryshkin et al., 2010). These studies highlight the critical role of SFK in regulating iNOS activity by stabilizing its half-life, which subsequently promotes inflammation and disease progression. Based on this premise, we are testing a combinatorial therapeutic strategy using an iNOS inhibitor (1400W) and a SAR (SFK inhibitor) in a soman rat model (Fig. 3).

Conclusion

This review provides a comprehensive overview of epilepsy, specifically OP-induced SE, covering its epidemiology, causes, and consequences. We have detailed various experimental models, with a particular focus on OP animal models. The core emphasis is on the mechanisms of OP neurotoxicity and the exploration of potential therapeutic strategies. Current medical countermeasures are discussed, highlighting their benefits and limitations. Special attention is given to iNOS and SFK inhibitors. We have discussed in detail the safety, efficacy, and toxicity profiles of various potential CNS drugs, advocating for combination therapies as a more promising approach than monotherapy.

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