International Journal of Entomology Research
www.entomologyjournals.com
ISSN: 2455-4758
Received: 02-12-2025, Accepted: 01-01-2026, Published: 15-01-2026
Volume 11, Issue 1, 2026, Page No. 72-87

Neurotoxins in hemotoxic snake venom and the amplification of their toxicity via endogenous signaling pathways: A detailed review

Anubhav Dubey, Priyanshu Srivastava*
Department of Pharmacology, Maharana Pratap College of Pharmacy Kothi, Mandhana, Kanpur, Uttar Pradesh, India

Abstract
The most important networks of the carcass, particularly the neurological and circulatory systems are the main targets of snake venoms used in hunts. While most rear-fanged snakes and snakes in the snake line create bleeding-causing venoms that primarily target blood coagulation, snakes in the snake family typically produce neurotoxin venoms that contain toxins that target the nervous system. It's not quite evident, though. It has recently been determined that blood-causing stings indeed contain neurotoxic components, and some viperid bites cause neurotoxic symptoms. Viperid phospholipases A2, for instance, may exhibit posterior or pre-synaptic activity and play a role in analgesia and pain. Other neurotoxins come from a variety of families, including big multi-subunit proteins.Baptides like crotamine, these cysteine-filled proteins that secrete, Kunitz-associated inhibitors of protease sarafotoxins, and three-finger toxins are further neurotoxins derived from hemotoxic venoms. A few of these poisons show postsynaptic action.The complex and changeable collection of proteins that make up the active ingredients of snake venoms results in a wide range of medicinal properties and toxicities that are mostly stereotyped. The proportional roles of five major pathologies—neuromuscular dysfunction, inflammatory conditions, coagulopathy, cell/organ damage, and disturbance of homeostatic systems of normal physiology—are determined by the diversity of venom proteins and host susceptibilities. In this study, we explain how signals that dysregulate inflammation, coagulation-dependent neurotransmission, and how well cells survive are amplified in addition to being directly mediated by venom in snakebite. Despite the diversity of venom proteins, a small set of enzyme-type activities and the effects of tiny poisonous peptides are responsible for most significant pathologic events that occur after envenoming.

Keywords: Azemiopsin, cysteine-rich secretory protein, hemotoxic venom, nervous system, nicotinic acetylcholine receptor, metalloprotease, snake venom, intracellular signaling, neuromuscular paralysis, intracellular calcium

Introduction
In the context of Linnean taxonomy, snakes (Serpentes) belong to the class Reptilia and are a subclass of the order Squamata [1]. Snakes come in more than 3,500 kinds as predators without legs, snakes employ a range of hunting techniques. In reality, some snakes use aggressive feeding techniques or constriction to subdue and swallow huge, frequently deadly species of food, protecting them from harm during predatory confrontations. Others immobilise their victim using toxins. Over the course of evolution, saliva gave rise to snake venom. It is created in a unique organ called a venom gland and distributed at the bite on teeth known as "fangs," which include a groove or channel for injecting venom. The most comprehensive list of poisonous snakes, with over 600 species, was available on Wikipedia at the time the assessment was written in early 2023. About 300 species, primarily from the genera Viperidae, Elapidae, and Colubridae, are deemed to be of medicinal significance by the World Health Organisation (WHO). An adaptive competition between venom poisons and prey physiology is thought to be the driving force for the progress of snake venom Venom's composition and activity have changed in tandem with the physiology of prey since venom is a crucial functional characteristic of venomous snakes.Snake venom is a complicated, deadly concoction that targets several systems of the prey organism, including as the neurological and circulatory mechanisms, and is mostly made up of protein and peptides known as "toxins". Neurotoxic and hemotoxic venoms are those that primarily harm the nerve system or blood, respectively. The majority of poisonous snakes are members of the viperid or elapid families. Viperid venoms primarily disrupt blood coagulation and are considered hemotoxic, but elapid venoms typically contain toxins that damage the neurones and are therefore classified as neurotoxic. Neurotoxic venoms are commonly found in the chemicals of kraits, mambas, and most cobras.Snake venoms are a varied and varied blend of enzyme and organic proteins and peptides, according to proteomic science. The complexity of venom poses a number of significant obstacles to our comprehension of venom mechanisms. Determining the distinct impacts of venom component in an implanted animal is the most evident challenge. Table 1 summarises the main known venom dangers and mechanisms, categorised by fundamental effects, molecular type (enzymatic or other than enzymatic), timing of occurrence, and areas of influence. Waheed *et al*. recently released a more comprehensive list of venom components. According to Laustsen, snake venom is the "most complex pharmaceutical target" that has been identified. It is made up of numerous toxin components as well as numerous biochemical interactions [2].

Animal Profile
Some snakes create a specialised chemical called venom, which is primarily employed for defence and hunting. When the snake bites, its hollow or groove fangs release the venom, which is produced in glands behind its eyes. Poison is a complicated blend of proteins as well as enzymes than can damage the prey's blood, muscles, cells, or nervous system, swiftly immobilising or killing it and starting the digestive process. In response to their prey and surroundings, different snake species produce different kinds of venom. Venom is employed to create opiates and treatments for a variety of illnesses, despite the fact that it can be harmful to people.

Aspect	Details	Reference
Definition	Snake venom is a complex biological secretion produced in modified glands (evolved from salivary glands) and injected into prey or threats via hollow or grooved fangs.	[3]
Composition	It contains hundreds to thousands of different proteins, enzymes, peptides, and other molecules that disrupt biological systems.	[4]
Major Toxin Types	Neurotoxins: Affect the nervous system; Hemotoxins: Affect blood and circulation; Cytotoxins: Damage cells/tissues; Myotoxins: Damage muscles.	[5]
Neurotoxic Effect	Interferes with nerve signaling, can cause paralysis by blocking neurotransmission at nerve–muscle junctions.	[6]
Hemotoxic Effect	Disrupts blood clotting, damages blood vessel walls, can lead to internal bleeding or clotting disorders.	[7]
Cytotoxic Effect	Kills or damages cells locally, causing *necrosis*, swelling, and tissue destruction around the bite site.	[8]
Enzymatic Activity	Includes enzymes like phospholipases, metalloproteinases, and serine proteases to break down tissues and spread toxins.	[9]

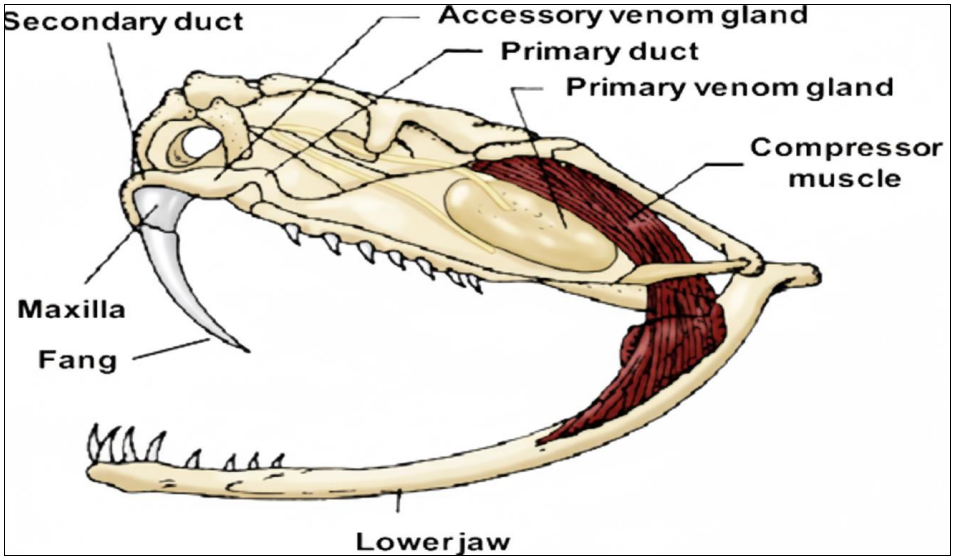

Fig 1: Anatomical view of snake venom [10]

Neurological Signs Produced by Viperid Bites

Most viperids' venom has a haemolytic impact; victims die from many internal organ haemorrhages and blood incoagulability. Neurological symptoms, however, are frequently noted. We were able to locate the earliest known account of neurotoxic symptoms following a snake bite in the 1930s. The Serbian (Valley close to the Sofia Water) vipers, especially berusbosniensis viper. It is commonly recognised that bites from Russell's viper (Daboia russelii) can have neurological impacts. The neuromuscular dysfunction seen in patients was moderate, and these effects were primarily recorded for Sri Lankan Russell's viper. Ptosis, impaired vision, and ophthalmoplegia were its hallmarks, but life-threatening paralysis was uncommon.The longnosed viper, or V. ammodytesammodytes, can cause potentially fatal neurotoxicity when bitten by mong European vipers [11]. The venom produced by this snake contains a number of neurotoxins that are covered below. As previously stated, Serbian V. berus. bosniensis bites cause neurotoxic symptoms. In South-Western Hungary, there have been reports of severe neurotoxic envenomation after a snake bite. There have been reports of neurological issues following Vipera genus snake bites in Switzerland and Italy. Human envenomation following V. asparagus aspis bites in southeast France results in neurological symptoms, primarily cranial nerve abnormalities. Montiviperabornmuelleri venom has been shown to have neurotoxic effects using zebra as a model animal.People and mammals experience neurotoxic symptoms from the venom of snakes belonging to the genus Crotalus. As a result, respiratory paralysis following a Yuma cobra (Crotalus scutulatus) bit may indicate neurotoxic block The first neurotoxic to be isolated from viperid venom was crotoxin, which was obtained from the venom of the rattlesnake C. terrificus by Slotta and Fraenkel-Conrat in 1938 Crotoxin is a member of the secretory phospholipase A2 family.

Secretory Phospholipases A_2

Typically, secretory cleaved A2 (sPLA2) are 12–19 kDa tiny proteins. The primary feature of sPLA2 is the Ca2+-dependent hydrolysis of the phospholipids at the sn2-position, which releases lysophospholipid and unsaturated fatty acid. Nonetheless, sPLA2s have a comparatively high affinity for binding a wide range of other proteins. Asp49 is found in the active centre of an enzyme and can be replaced in homologues that are not enzymatically active. There are now 11 groups of sPLA2s based on their structure and function. Group IA comprises sPLA2s and Elapidae venom, while groups IIA or IIB comprise sPLA2s from Viperidae venom. Six of the seven disulphide bonds found in sPLA2s and spanning groups IA and IIA are preserved in both groups. whereas only group IA has Cys11-Cys77 and group IIA contains Cys51-Cys133. Additionally, group IIA has a seven protein residue C-terminal extension. Group IIB sPLA2s have a terminal expansion of six amino acids residues, only six disulphide linkages, and no Cys61-Cys91 bond [12]. Non-covalent dimers (sometimes trimmers or even pentamers), which are composed of identical subunits are

formed by a number of group IIsPLAs. While one subunit—typically basic—has enzymatic activity (phospholipase), another—typically acidic—is enzymatically inactive and acts as a pharmacological modulator and inhibitor. One species of snake may have many parallel isoforms of sPLA2 in its venom. Thus, crotoxin, the first neurotoxic identified from viperid venom.

Presynaptic Neurotoxicity

Presynaptic neurotoxins,which are also known as β-neurotoxins, are found in snake venom and are embodied by sPLA2s of groups IA and II as well as -bungarotoxins, both of which have a disulphide bond between a sPLA2 amino acid subunit and a Kunitz-type proteins inhibitor subunit. Since β-bungarotoxins are present in the snake venom of kraits belonging to the Elapidae family, they are not taken into consideration here. Nearly all of the β-neurotoxins found in blood-causing viperid venom are group II sPLA2s.A thorough description of the main processes of a presynaptic neurotoxic operation on a spinal terminal may be found in, with updates in [13]. The kinase activity of these toxins, which causes major alterations in the physical and chemical characteristics of the membrane, is essential to presynaptic neurotoxicity. These toxins disrupt the release of a mediator from the presynaptic location. Furthermore, there is no correlation between sPLA2s' levels of enzyme function and presynaptic neurotoxicity. Presynaptic neurotoxins should therefore have several binding sites that direct them to the postsynaptic skin, although a potential receptor is still up for debate. For instance, it might be the N-type sPLA2 receptor, as there is a substantial correlation between the lethality of various sPLA2s and their binding affinities to this receptor. However, presynaptic neurotoxins' phospholipolysis products encourage synaptic vesicle exocytosis, which intensifies the toxic effect. Additionally, certain Ca2+-channels have higher conductivity (perhaps due to presynaptic neurotoxins [14]. which supports kinase activity and encourages the breakdown of SNARE-mediated neurotransmitters. The neurotoxins' quick absorption into nerve cells,It's interesting to note that some enzyme inactive sPLA2 homologues from Bothrops snake venoms (with Lys49 in the active site) exhibit postsynaptic neurotoxic on nerve-muscle preparations since these toxins often destabilise membranes without phospholipolysis [15]. Manganese solution (0.9 mM) reduced the irreversible neuromuscular inhibition of mouse phrenic nerve and diaphragm preparations caused by Lys49 sPLA2-related homologue bothropstoxin-I from a species of jararacussu snake venom. The authors postulated that bothropstoxin-I might work via calcium channels, which manganese shields against the toxin's effects. It should be noted that following bothropic envenomations, no neurotoxic symptoms were seen.Mutagenesis, crystallography, and biophysical techniques have been used to study a number of presynaptic neurotoxins in order to pinpoint specific molecular areas and residues that cause presynaptic neurotoxic and other effects. Ammodytoxin A and C from the venom of V. ammodytesammodytes, also known as (a genuine viper) and β-agkistrodotoxin from the venom of halyspallas are two of the known monomeric synapse sPLA2 of group IIA for which X-ray structures have been found.

Two geographically contiguous sections of the β-agkistrodotoxin molecule, turn 55–61 as well as stretch 85–91, differ significantly from those of harmless sPLA2s and are probably involved in the identification of specific receptors at the presynaptic membrane. Reduced hydrophilic properties and the lack of residues with large hydrophobic side chains (like Trp) which act as membrane anchors are evident in the functional comparison of the putative interface site with non-neurotoxic isoforms. The reduced generalisation the toxic to the non-target layer before it reaches the presynaptic cell membrane and binds the the proposed receptor may be explained by this structural feature of β-agkistrodotoxin

Postsynaptic Neurotoxicity

Postmortem nicotinic acetylcholine (nAChRs) are blocked by elapid α-neurotoxins, which are classified as postsynaptic neurotoxins. Dimeric vipoxin from V. ammo dotes venom was first identified as viperid neurotoxic sPLA2 known as postsynaptic neurotoxin quoted in. nonetheless, information regarding this toxin's postsynaptic action is ambiguous. The sPLA2 with proven postsynaptic activity is bitanarin, which is derived using the puffy adder venom B. arietans. When it comes to binding to human α7 and Zebrafish californica nAChRs, as well as to an acetylcholine-binding proteins from Lymnaeastagnalis, Bitanarin competes with [βI]iodinated α-bungarotoxin (αBgt), a common α-neurotoxin. 40 ± fifteen, 4.3 ± 0.3, and 10 ± 0.6 μM are the IC50 values, respectively. With an IC50 of 11.4 μM, it also reversibly inhibits the acetylcholine-induced activity in single L. stagnalisneurones With a molecular size of 27.4 kDa, the toxin's 28 cysteine residues create 14 disulphide bonds inside a single long chain, and its N-terminal sequence resembles PLA2s derived from snake venoms quite a little. In bitanarin has a strong catalytic efficiency of 1.95 mmol/min/μmol. Among viper sPLA2s, postsynaptic blocking seems to be a pretty prevalent feature. Two monomers of sPLA2s (IIA category) with V. nikolskii venom plus three single-chain sPLA2s in V. ursinii venom likewise demonstrated an antagonistic detrimental impact on individual L. stagnalisneurones.Vurtoxin, Vur-PL, and sPLA2s via V. nikolskii nerve neurones are less than L. stagnalisneurones, which had an IC50 of 2.18 μM. By a radioligand test in competing with labelled αBgt for bound to both human and T. Californian nAChRs, the binding affinity of sPLA2s for human nAChRs and the affinity of AChBPs have been assessed. Both Vurtoxin and Vur-PL exhibit comparable inhibition of α-Bgt bound to α7 nAChR, with IC50 values of Fourteen ± 5 μM and 29 ± 2 μM, etc; however, Vurtoxin is the most potent inhibitor of α-Bgt bound to T. californica nAChR, with an IC50 of 260 ± 20 nM, whilst Vur-PL2 is essentially inactive. The inhibitory potency of agonist-evoked current is greater than that of vurtoxin, which is structurally identical but enzymatically active.It is unclear if sPLA2s have postsynaptic or pre-synaptic neurotoxicity, or both. Three sPLA2s with molecular masses of 13.003, 13.100, and 12.531 kDa, in turn, have been extracted from the venom of the D. russelii snake and demonstrated to have phospholipolytic activity: VRV-PL-IIIc, VRV-PL-VII, and VRV-PL-IX. VRV-PL-V and VRV-PL-VII function as simultaneously pre- and post toxins, whereas VRV-PL-IX functions as a presynaptic toxin, according to electrophysiological research employing cultured hippocampus neurones CB defence against unspecific binding and its directing into particular targets at this membrane has been demonstrated to include the CA subunit. The effects of crotoxin and CB alone on nerve-induced transmitter exocytosis are biphasic, with a brief preliminary enhancement followed by a prolonged decline. Only the heterodimeric compound crotoxin reduces the strength of nerve-evoked muscle twitches, although both compound crotoxin and CB reduced nerve-evoked acetylcholine output by 60% and 69%, respectively.

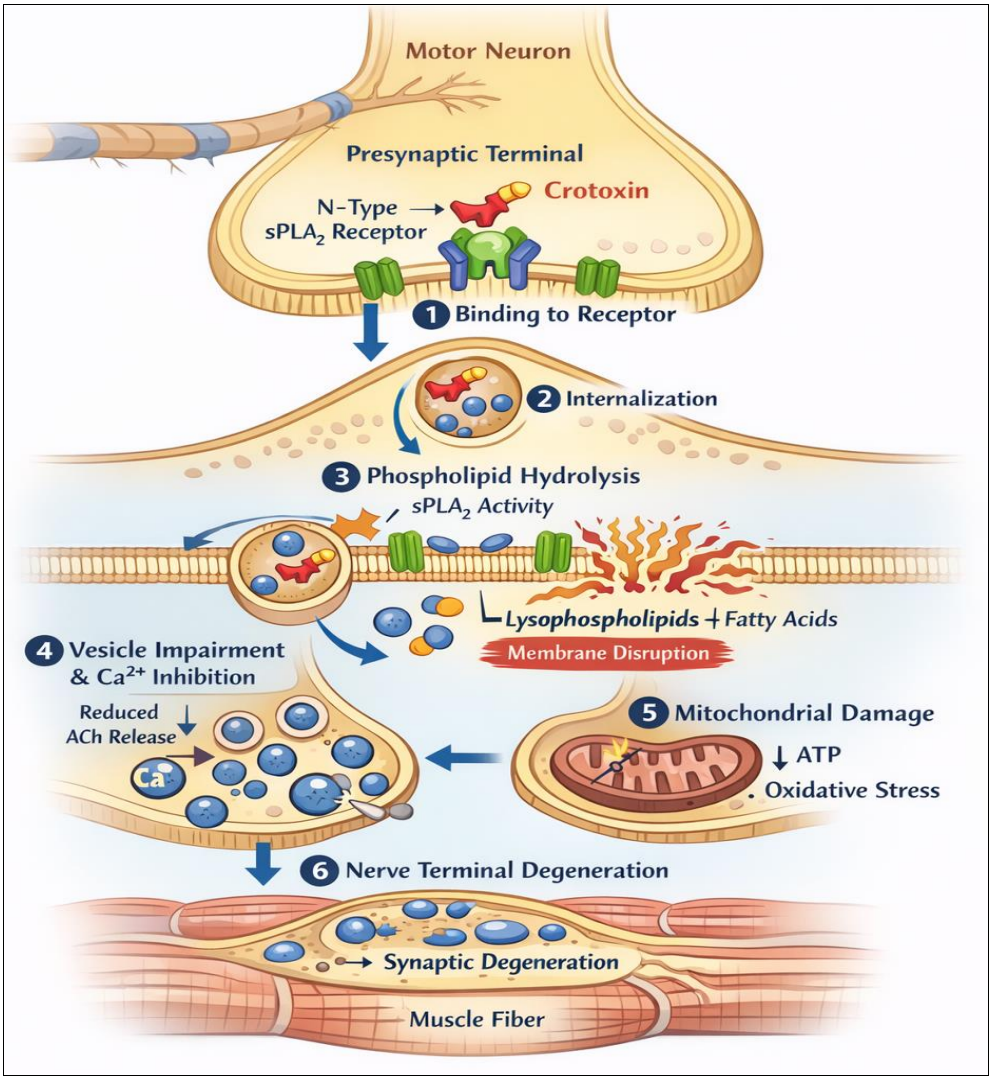

Fig 2: Crotoxin at Neuromuscular Junction [16]

sPLA2s in Pain and Analgesia

Because of their kinase activity, which produces precursors of different mediators, sPLA2s exhibit a variety of biological activities and have been linked in numerous pathophysiological processes, including as inflammation and discomfort. Anti-inflammatory stimuli, such as extracellular PLA2-associated pro-inflammatory substances such prostaglandins, proton pump inhibitors, thromboxanes, leukotrienes, and others, trigger sPLA2-induced hyperalgesia [17]. The anti-nociceptive action of crotoxin, a special snake venom sPLA2, has been thoroughly investigated (see review. It has been determined that the system that manufactures heroin does not appear to be participating in this action; the adrenergic system may be partially implicated, and there is conflicting evidence regarding the involvement of muscarinic receptors. In short, crotoxin can be injected peripherally (intraperitoneally) or centrally (intracerebral ventricular or periaqueductal grey region) in mice and rats.The anti-nociceptive action of crotoxin, a special snake venom sPLA2, has been thoroughly investigated [18]. It has been determined that the opioid receptor system does not appear to be engaged in this action; the adrenergic system may be partially implicated, and there is conflicting evidence regarding the involvement of muscarinic receptors. In short, crotoxin injections at the outer intraperitoneal, or brain (intracerebral ventricular or interior grey region) levels cause antinociception in mice and rats. The antinociceptive action is unaffected by muscarinic or oxytocin receptor activation. When delivered right away (0.01 mM for 10 s) following rat sciatic nerve section, the crotoxin solution inhibits the onset of neuropathic pain. Unlike the previously mentioned effort, A crucial relay for the ascending nociceptive pathways, the thalamic parafascicular nucleus cell's pain-evoked electrical activity is inhibited by an intracranial injection of crotoxin. The result is unaltered by muscle relaxants and morphine receptor antagonists. Functional dependence on blood oxygen level Resonance of Magnets The involvement of certain CNS regions in the repellent effect of crotoxin has been confirmed by imaging analysis. These spots include higher order neurological structures like both secondary and primary sense cortices, which are important for pain perception, as well as brain input structures [19]. Crotoxin causes a sustained decrease in mechanical hypernociception when combined with SBA-15, a drug delivery method. Given the general toxicity of presynaptic neurotoxins, an anti-nociceptive action seen *in vivo* must be considered for consideration. Thus, hot plate latencies are increased by neurotoxic sPLA2 HDP-2 of V. Nikolai venom, although this impact is only seen at the maximum tolerable dose. The observed impact in the hotplate experiment may be the consequence of an overall intoxication rather than an underlying decrease in pain tolerance because the animals exhibit signs of intoxication at this dose, such as depression and a noticeable drop in locomotor activity.It should be mentioned that some viper poisons contain myotoxins, the

majority of which are sPLA2s with no enzymatic activity because Lys, Ser, or Arg have replaced Asp49 in the active region. They cause discomfort and injury to the muscles but are unable to develop the previously stated mediator precursors. The nervous system is undoubtedly impacted by the latter effect, albeit the precise target is still unknown. By acting purinergic receptors or causing the membrane depolarisation of the distal sensory neurone, a myotoxin called non- enzyme Lys49-PLA2 from stinging insect venoms causes muscle cells to produce ATP and K+, which can directly cause pain BomoTx, a like myotoxin monomeric Lys49-sPLA2 derived from the Brazilian spearheaded pit viper.fibres by a procedure that includes the release of ATP and the activation of receptors for purinergic substances P2X2 and P2X3 BomoTx is neither a direct agonists or modulator of purinergic receptors; instead, it causes calcium within the cell release from a particular group of sensory neurones, which opens hemichannel pannexins and releases ATP into the extracellular space. Acute pain behaviours and heat hypersensitivity are caused by the activation of brief responses in certain sensory neurones that encode the receptors for purinergic agents P2X2 or P2X3.

Three-Finger Toxins

Neurotoxic snake venoms are rich in three-finger toxins (TFTs), which are usually the primary constituents of elapid venoms. TFTs get their name from their distinctive spatial structure, which consists of four conserved disulphide bonds stabilising three -sheet loops (fingers) that extend from the central core. This is members of the Ly6 and uPAR family of amino acids, which influence the actions of nAChR in the mammalian central nervous system, among other things. The TFTs have between 57 and 82 amino- acid residues, and some toxin types have an additional fifth disulphide bond in either their N-terminal loop I (also known as "non-traditional" neurotoxins) or central loop II (also known as "long-chain" neurotoxins). This bond's location influences the toxin's biological effect, which varies greatly among TFTs The first proof that viperid venom may include TFTs was published in 1987. The venom produced by the pit viper Overall. halys was shown to include α-Agkistrodotoxin, a potential poison with a molecular diameter roughly 8 kDa [20]. The toxin blocked the binding of the radioactive αBgt to the nAChR in growing myotubes that (IC50 of the toxin = 2 n M) and the carbachol-triggered influx of ions by means of nAChR (IC50 values = 60 nM); it also interfered with antiserum to αBgt [21]. However, its exact sequence of amino acids and potential relationship to TFTs remained unknown.From the poisonous saliva of the 11-year-old viper D. russelli, two nmda neurotoxins with comparable characteristics were extracted. At a dosage of 4 µg/mL, the first one, called DNTx I, inhibited the twitch nearly entirely in frog nerve-muscle preparation With a molecular mass of 6675 Da and a M-terminal amino acid sequence of LECNKLQPIASK, it was 80% similar to a cytotoxin/cardiotoxin from the cobra N. najaatra. The venom sample from Hindustan Park in Calcutta, India, was utilised to separate the toxins In Rana hexadactyla spinal nerve and gastrocnemius musculature preparations, the subsequent one, DNTx-III, showed concentration-varying inhibition of indirectly induced twitches [22]. In 30 minutes, DNTx-III totally blocked the indirectly induced twitch response at a dosage of 10 µg/mL.The existence of transcription factor transcripts in viperids was definitely demonstrated more recently by proteomic and transcriptome studies of poisons and venom glands. Therefore, transcripts encoding transcription factor transcription have been discovered found in the venom glands transcriptomes of a number of Viperidae species, such as C. atrox and Lachesis muta For Sistruruscatenatus, the genetic material encoding TFT has been reported Several viperid venoms, such as the ones from A E. ocellatus, and B. arietanswere found to include TFTs using a proteomic approach. The functional operations of proteins found in this manner is still unknown, though. Two toxic compounds, TFT-AF, TFT-VN, were discovered and produced via heterologous production in Escherichia coli in order to solve the problem of biological function of Viperidae TFTs.Many TFTs have been found in rear-fanged snake venom. With an extra fifth disulphide bond across the first loop, all of these TFTs are referred to as non-conventional toxins. The first established TFT from the venom of the rear-fanged snake the Coelognathus radians (previously the Elaphe radiatus, Colubridae) as a --colubritoxin appeared in 2003, despite the fact that some toxins that could prevent [3H]α-Bgt binding to nAChR were discovered in Duvernoy's secretions of rear-fanged vertebrates beginning in 1999 (in two cat-eyed spp., Colubridae [23].

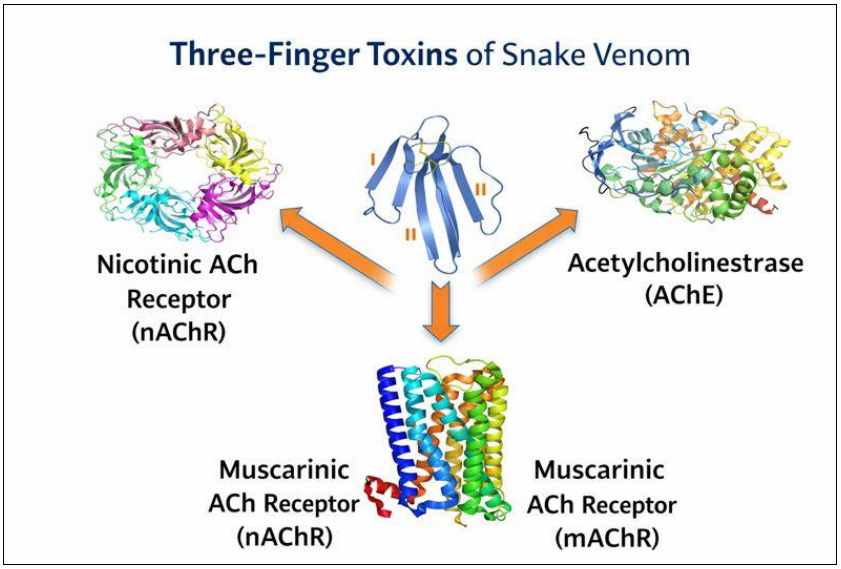

Fig 3: Schematic diagram of Three-Finger Toxins of snake venom [24]

Other Components of Viperid Venoms with Postsynaptic Neurotoxicity

1. Waglerins

Waglerins are brief, proline-rich peptides with one intramolecular disulphide bond that are strongly basic (pIs of 9.6–9.9) and include seven Pro residues for every 22 or 24 total amino acids The venom of the pit snake Tropidolaemuswagleri (previously Trimeresurus wagleri) contained four distinct waglerins that were substantially similar to one another The nucleotide chains encoding the precursor section of the C-class natriuretic peptide were found in the transcriptomic of the T. subannulatus: pit viper saliva gland [25]. The pre-pro portion of this sequence has a significant degree of similarity to waglerins.With an LD50 of 0.22 to 0.58 milligrammes per kilogrammei.p. in adult mice, waglerins are deadly peptides. Waglerin one does not kill newborn mice. The indirect twitch in a mouse phrenic nerve and hemidiaphragm prepared is reversibly blocked by waglerin-1 at 4 μM, however the indirect twitching of the human diaphragm is not blocked at dosages up to 40 μM. Rats are totally resistant to a dose of 10 μg/g, whereas mice are paralysed by a single 0.5 μg/g injection into the vein in as little as 5 minutes.Waglerin's varying affinities for rat and mouse nAChRs account for this discrepancy. Compared to mouse nAChR, interaction with rat nAChR is 100 times weaker [26]. Additionally, waglerin has been shown to differentiate among two antagonist and agonist binding points in nAChRs. Its interaction on mouse nAChR shows two different dissociation constants that diverge by 2100 times, and it binds more tightly to the α-ε site than the α-δ site.For the rat receptor, this difference is 80. Waglerin has a 70-fold reduced reactivity at the – site and a 10-fold reduced retention at the α-δ position at human nAChR. Waglerin-1 specifically inhibits the mouse muscles nAChR protein that contains the ε-subunit, as demonstrated by the utilisation of knockout mice devoid of the ε-subunit gene. There is evidence that waglerins' inhibitory effect at a nerve-muscular junction may be more than just post-synaptic.Therefore, endplate currents (EPCs) generated in response to nerve stimulation are suppressed by sub-micromolar waglerin concentrations. The location of action seems to be post-synaptic because the quantitative substance of EPCs is unchanged. Higher concentrations (1.4–2.9 milligrammes), however, also prevent the transmitter from releasing spontaneously. When waglerin-1 is present, nerve stimulation results in a "rundown" of EPC amplitude, indicating that the toxin works underground to prevent transmitter release [27].

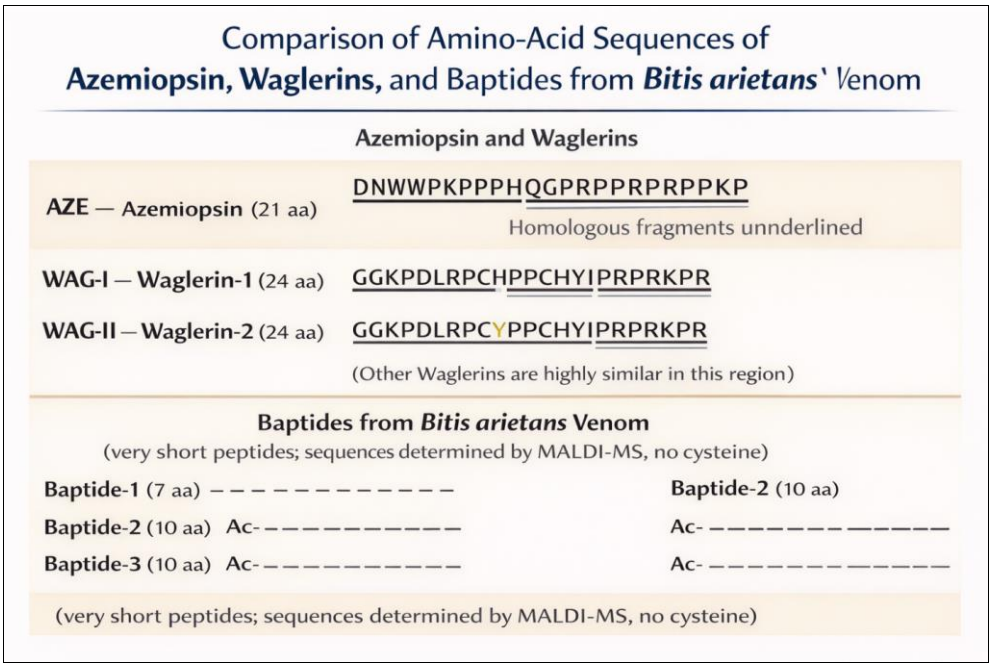

Fig 4: Amino-acid sequences of azemiopsin and waglerins. Homologous fragments are underlined. AZE—azemiopsin, Amino acid sequences of baptides from *B. Arietans* [28]

2. Azemiopsin

In contrast to the great majority the snake toxins, azemiopsin, a basic polypeptide with 21 residues, is derived from the venom of the A. feae viper (sub-family Azemiopinae, which is located within Viperidae) and lacks cysteine residues. However, circular dichroism tests show that this peptide takes on a β-structure. Azemiopsin binds to Torpedo nAChR more effectively than α-Bgt (IC50 0.18 ± 0.0 μM), but less effectively to animal α7 nAChR slightly (IC50 22 − 2 μM) It is more effective against the adult counterpart (α1β1εδ, EC50: 0.44 ± 0.1 μM) versus the foetal form and dose-dependently inhibits acetylcholine-mediated electrical stimulation in Xenopus oocytes that express human muscle-type nAChR.(α1β1γδ EC50 1. 56 ± 0.37 μM). The peptide does not affect 5-HT(3) receptors at concentrations up to 10 μM or the activity of GABAA (1 3 2 or α2β3γ2) agonists at concentrations up to 100 μM Azemiopsin is similar to waglerins in that it shares an homologous C-terminal hexapeptide, inhibits muscle-specific nAChR activity preferring it to mature with similar affinity, and appears to specifically evolve at a similar site as a supposed waglerin from T. subannulatus as a portion of the pre-pro region of a C-linked natriuretic peptide Azemiopsin and waglerins are related, indicating a shared molecular evolutionary history between the two classes of nAChR antagonists Azemiopsin and waglerins are related, indicating a shared molecular evolutionary history between the two classes of nAChR antagonists [Azemiopsin is the

first naturally occurring polypeptide toxin that blocks the nAChRs and lacks disulphide bridges, however unlike waglerins, it can block α7 nAChR but not GABAA receptors. Azemiopsin has an LD50 of 2.57 ± 0.27 milligrammes per kilogrammei.p., 0.51 ± 0.1 grammes per kilogramme via intravenous injection, and 0.732 ± 0.12 mg/kg i.m. in mice. It hardly shows any negative effects at doses of one milligramme per kilogramme and less (once per i.m. shot in mice) and 0.1 milligrammes per kg (i.m. injections daily during the fourteenth day in rats).

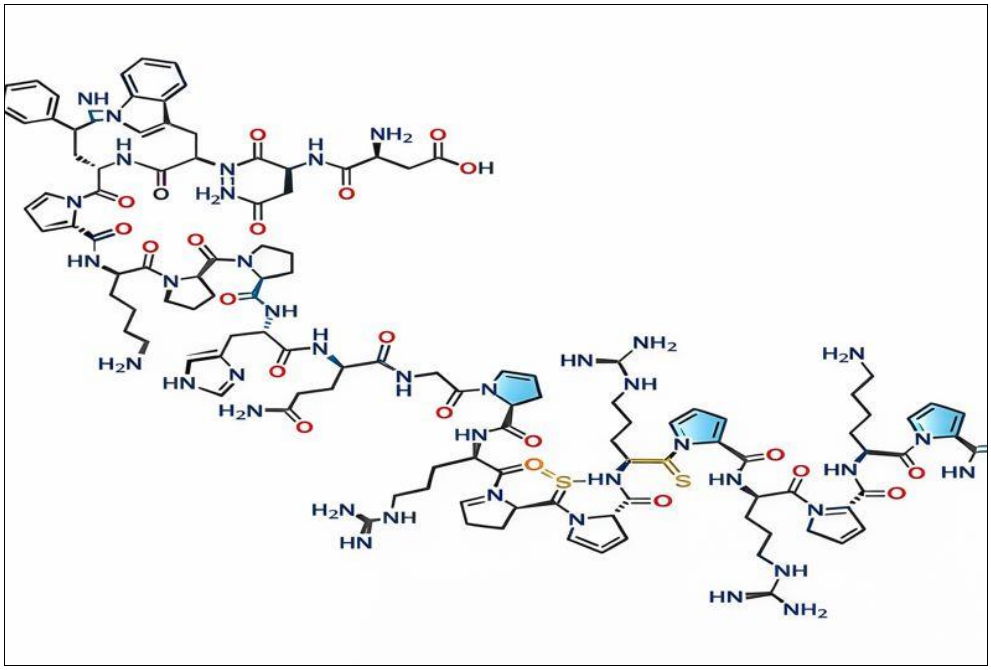

Fig 5: Chemical structure of Azemiopsin [29]

3. Baptides

Three peptides known as baptides 1, 2, and 3 have been extracted from the venom of the puff adder B. arietans. Seven residues of amino acid make up Baptide 1, but the other two, 2 and 3 have ten residues, with the last one becoming modified at the ends of the amino acids Cysteine residues are absent from them. With IC50s of roughly 50 μM and 200 μM, respectively, baptide 3 and 2 inhibit acetylcholine-induced currents in segregated L. stagnates neurones. With an IC50 of roughly 3 μM, Baptide 2 inhibits acetylcholine-induced currents in the muscle nAChR, an enzyme that is heterologously produced in Xenopus oocytes. At concentrations up to 200 μM, the proteins are not fighting with luminescent α-Bgt or interaction to the Torpedo and α7 nAChRs, indicating a non-competitive method of inhibition.

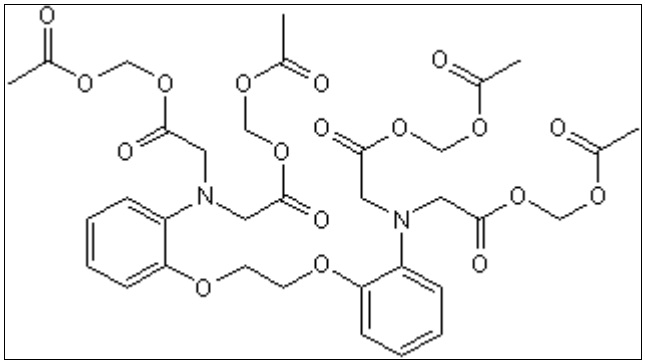

Fig 6: Chemical structure of Baptides [30]

4. C-Type Lectin-like Proteins (CTLPs)

The hemotoxic effects of CTLPs from vampire venom have been found to reduce animals motion and exploration In contrast, CTLPs known as both EM1 и EM2 that originate produced by the saw-billed viper E. multisquamatus prevent fluorescent α-Bgt from binding to human neuronal α7 nAChRs as well as muscle-type nAChRs, from T. californica. Multicolour α-Bgt coupling to muscle-like nAChR is nearly entirely inhibited by EM1 at 23 Angstroms and EM2 at 9μM. There is less interaction that human neuronal α7 nAChR; EM1 at 23μM only inhibits α-Bgt binding by roughly 40%, and EM2 at 9μM by roughly 20% These findings point to afferent activation in CTLPs.

Blockers of Voltage-Dependent Ion Channels

1. Cysteine-Rich Secretory Proteins

The vast family key vertebrate proteins known as cysteine-rich secretory protein (CRiSP) is in charge of a number of biological processes, such as ion channel blocking and reproduction. Venom from snakes The toxin family known as CRiSPs has a significant number of identical sequences. They consist of a single 20–30 kDa polypeptide chain with 16 extremely stable cysteine molecules that generate eight disulphide linkages; ten of these residues are located in the C-terminus's cysteine-rich domain CRiSPs have no haemorrhage, coagulant, proteolytic, or enzymatic activity These proteins are widely dispersed throughout snake venoms and can be found in significant quantities in some venoms. However, their biological importance has not yet been fully determined.The majority of known snake venom CRiSPs exhibit effects on contractions of smooth muscles, typically impacting different ion channels. Thus, at 1 μM, BaltCRP, which is a CRiSP formed from A. alternatus venom with a molecular weight of 24 kDa and an isoelectric point the 7.8, inhibits around 26 percent of Kv1.1, 14% of Kv1.3, 17% of Kv2.1, and 21 percent of Shaker potassium currents while having no effect on Kv1.2, Kv1.4, Kv1.5, and

Kv10. Helicopsin, a CRiSP of about 20 kDa derived from the lateral fang snake Helicops angulatus, shows strong neurotoxic action, with an LD50 of 5.3 mg/kg i.p. and respiratory collapse in mice at 14 µg/mouse Based solely on neurological symptoms common to depolarising neuromuscular blocking neurotoxins, helicopsin is categorised as a neurotoxic.Rat tail arterial smoother muscle contraction caused by high K+-induced depolarisation in the 0.1–1 micromolar zone (about 45–75% from control) is inhibited by ablomin, which comes from the poison of the Japanese Mamushi rat snake (A. blomhoffi), while caffeine-stimulated contraction is not blocked. The L-type potassium channel blocker calciseptine, which comes from mamba venom (Elapidae) has a beneficial concentration for uniform muscle contraction force that is nearly identical to this (Ki of 0.21 µM for ablomin). The IC50 of calciseptine for rat aortic contraction caused by depolarisation is 0.23 µM. Even at 1 µM, the blockage caused by ablomin is incomplete; greater concentrations of the enzyme ablomin (3 µM) decrease the degree of inhibition rather than causing further inhibition. Two more homo-CRiSPs. Similar to ablomin, one of these related protein molecules, triflin from the venom of the pit viper Trimeresurus flavoviridis (previously P. flavoviridis), likewise prevents an arterial contraction brought on by elevated K+ Tigrin from the tiger shark sting of Rhabdophis R. tigrinus (subfamily of Natricinae within Colubridae) is another homologue that does not appear to be neurotoxic. Furthermore, it has been reported that other CRiSPs, such as the piscivorin from A. bacterium piscivorus venom and catrin- 2 and catrin 1- from C. atrocious venom, inhibit the artery smooth muscle contraction induced by high K+ to 79.2 ± 5.8%, 70.7 ± 3.9%, and 90.3% ± 4.1% of that of control, in turn, at a concentration of just 1 millimetre. None of those amino acids prevent caffeine-induced contractions [31].

2. Kunitz-Type Protease Inhibitors

Kunitz-type tyrosine proteinase inhibitors (KSPIs) from snake venom are made up approximately 60 amino acids and share structural similarities with aprotinin (bovine KSPI). They have two antiparallel β-strands connected by a β-hairpin in the middle of the molecule and three conserved disulphide bridges that are responsible for the molecule's stability. Positive Evolutionary selection has separated snake venom chemical substances into two main families based on functional activities: neurotoxic (magnesium and calcium blockers) and non-neurotoxic (trypsin and a substance called inhibitors) lapid snake venoms have been found to include neurotoxic KSPIs that disrupt neuronal transmission. Thus, voltage-dependent potassium channels at the postsynaptic location of the neuromuscular junction are blocked by dendrotoxins that originate from the mamba venom (neurotoxic Elapid). According to reports, KSPIs from viperid mostly target the blood clothing systems [32]. However, at a dose of 5 mg/kg in mice before death, a non-covalent antioxidant complex made up of two of the KSPIs, anticoagulant and rusvikunin-II, from Russell's viper D. russeliirusselii bites has increased respiration rate, dyspnoea, difficulty moving, and hind-limb paresis in addition to an anticoagulant effect. These signs could point to potential neurotoxic activity. KSPI The end-plate potential, the miniature end-plate potential, and an indirectly elicited simple muscular contraction of the mouse diaphragm are all markedly enhanced by VaaChi from the venom of the nostril-horned viper (V. ammodytesammodytes). Although the exact method by which VaaChi facilitates neuromuscular transmission is yet unknown, blocking K+ channels does not appear to be the most likely explanation.

Molecular Effectors in Elapid and Viper Venom

1. Snake Venom Phospholipases (svPLA2)

Almost every type of life, comprising plant life, bacteria, invertebrates, and vertebrates, has phospholipase enzymes. PLA2s play a part in controlling membrane lipid concentrations and phospholipid turnover. The synthesis of the acid arachidonic acid (AA) is their primary physiological function. The synthesis of prostaglandins, leukotrienes, and eicosanoids, among others, begins with AA.

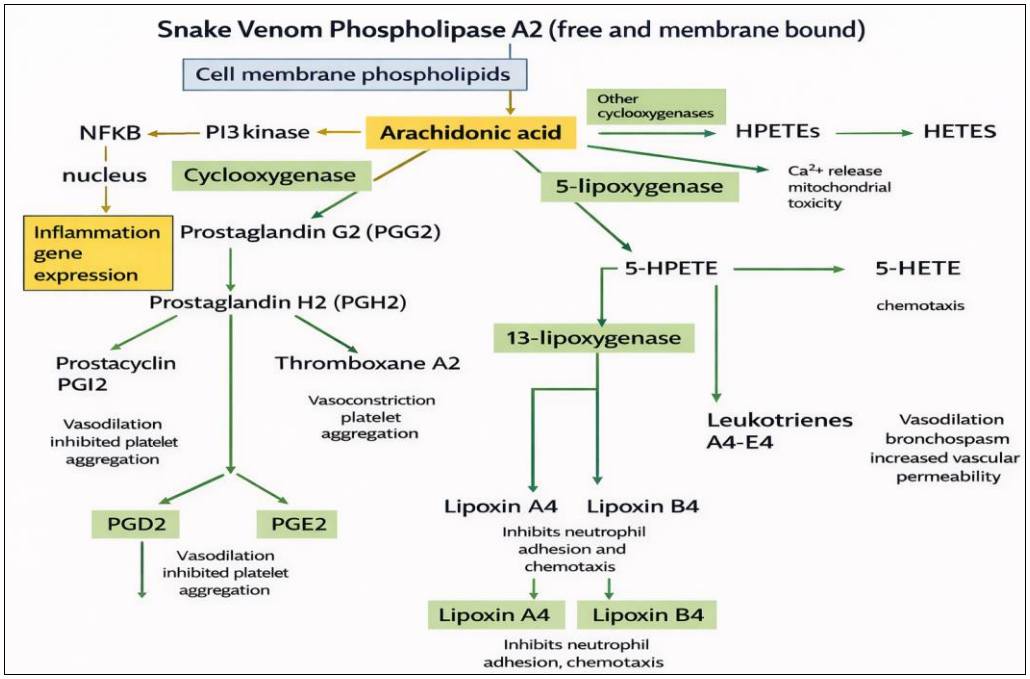

Fig 7: Arachidonic acid metabolism stimulated by snake venom phospholipases [33]

The secreted PLA2s (sPLA2), cytosolic PLA2s (cPLA2), calcium independent plasma PLA2s (iPLA2), platelet stimulating factor (PAF) methyl hydrolase or oxidised lipids lipid associated PLA2s (LpPLA2s), adipose PLA2s (AdPLA2s), and lysosomal PLA2s (LPLA2s) are the main forms. While internal PLA2 is productive in the microscopic level Ca2+ concentration that defines the intracellular environment, extracellular PLA2 requires a concentration equivalent to micromolar [Ca2+] for complete activity.The ester bond at the position known as sn-2 of glycerophospholipids is specifically hydrolysed by svPLA2s, as is the case with all PLA2s. The venom protein's surface contains a groove that serves as the catalytic location for the production of AA. However, it's possible that the PLA2-like proteins present in snake venoms lack catalytic activity. These not-catalytic subunits may have pro-inflammatory, neurotoxic, or myotoxic properties It is unclear how organically active PLA2 toxicity works.

The most chemically potent, multi-effect venom components are likely snake venom PLA2s Almost all snake venoms, as well as the droppings of non-venomous and slightly venomous snakes, include phospholipases to varied degrees, with a noticeable predominance for the venoms of slippery snakes.In order to release free arachidonic acid (AA), the catalytic elements in svPLA2s primarily hydrolyse glycerol into an ester of membrane-bound arachidonic acid. Highly reactive, arachidonic acid activates crucial pathways that control a wide range of biological functions. Members of the cyclooxygenase pathway, which involves prostaglandins and thromboxane; members of the lipoxygenase route, which forms leukotrienes; and the Cytochrome P450 group of enzymes, which includes lipoxygenases. resulting in hydroperoxy-eicosatetraenoic acid derivatives (HPETEs). and hydro-eicosatetraenoic acids (HETEs), are all stimulated by arachidonic acid. An overview of these signalling molecules' functions after snake envenomation, together with notes on how they affect venom pathophysiology. Arachidonic acid must be released from cell membranes by intracellular PLA2 activity, which has potent effects. Crucially, this would include the stimulating of ryanodine receptors and the release of calcium from inside the cell of sequestration, which is caused by arachidonic acid [34]. Since membrane-bound PLA2 produces intracellular arachidonic acid, transport of sPLA2 into the internal compartment is not necessary for PLA2's intracellular activity.The ability of svPLA2s to trigger PLA2 homologs in prey tissues through a process known as homologous protein activation is one of their most intriguing and significant characteristics. As a result, the effects that svPLA2 are amplified beyond those of the venomous alone. Additionally, this pathway allows indigenous catalytic PLA2 proteins to receive toxicity from non-catalytic svPLA2s. In 1979, Shier reported research demonstrating the production of local PLA2 by some amounts of cobra venom, which was the first description of a mobile relay of protein phospholipase activity Cobra's "Lytic factor" mediates this action.sPLA2 is an attractive option for blocking by small molecule drugs due to its near ubiquitous nature in snake venoms alongside clinically significant Recent work has shown that varespladib can inhibit PLA2 activity of a variety of venoms Recent research has demonstrated that varespladib binds to both enzymatic and non-catalytic PLA2s, lowering myotoxicity caused only by a non-catalytic PLA2.

2. Snake Venom Metalloprotease (svMP)

High molecular mass proteins (>50 kDa) are known as metalloproteases. The family of proteases known as metalloproteases was first classified according to their need for divalent cation pairs (zinc and cobalt) in order to function fully. Important variety and groups founded on structure, substrate, and regulatory control were found in later research [35]. Due to the size of their structure, these enzymes mostly function in the cardiac compartment, where they aid in the dispersion of venom components with smaller molecular weights, such as phospholipases, as well as in signalling and enhancing the toxicological effects of other venom parts. Although there is a significant relationship between metalloproteases and matrix metalloproteases (MMPs) through inflammation and increased gene regulation by the digestive enzymes produced by both classes of proteases, it is crucial to remember that metalloproteases are different from MMPs0020It is widely acknowledged that metalloproteases included in snake venoms are essential for haemorrhage because they weaken the connective tissue elements that maintain the structural integrity of blood vessels These metalloprotease enzymes are currently predominantly assumed to be responsible for the breakdown of capillary basement membranes in tissue exposed to hemorrhagic poisonous factors, as reported in the groundbreaking histologic studies of Mclaren and Owenby Protein gel electrophoresis and immunoblot methods have shown that svMPs can break down several kinds of proteins that make up the extracellular matrix *in vitro*, making digestion fragments visible. Membrane nidogen, and enzyme enactin, type IV fibres, fibronectin, and proteoglycans are all hydrolysed by svMPsAn even wider variety of protein targets was identified by a recent proteomic investigation proportionate contribution made by svMP to haemorrhage *in vivo* was difficult to determine for a number of reasons, despite the fact that metalloproteases have many effects *in vitro* which demonstrate a causal involvement in bleeding. First, coagulation proteins are inhibited or changed by other elements of snake stings, such as serine proteases and phospholipases Second, it has only recently become possible to separate the effects of SVMP from matrix metalloproteases using methods such selective small molecule inhibitors. Metalloprotease inhibitors, such as marimastat and prinomastat, were designed to prevent the spread of cancer Hemorrhagic SVMPs work by cleaving structurally significant components of the basement membrane. This involves type IV collagen, which is followed by haemodynamic biophysical forces that mechanically break vessels (a "two-step" process, see It is unclear which parts of svMPs' molecular structure control their capacity to attach to the proteolytic sites for basement membrane proteins. Extracellular network protein fragments and other proteins generated in cellular tissues as a result of svMP action may typically be engaged in the biological processes of tissue regeneration and repair, according to studies through Gutierrez as well as In relation to these protein fragments, svMPs have an additive relationship with PLA2 activity. Numerous findings indicate that endogenous proteases play a significant role in the structural damage that snake venom structural protein proteases induce During the inflammation that accompanies venom-induced tissue injury, both resident and invading cells produce and secrete matrix metalloproteases. The fact that metalloproteases cause and sustain persistent inflammation is another

significant consequence. Studies where reasonably pure venom iron oxide preparations were administered into animals and immunological responses were measured provide evidence for this action. Numerous investigations have documented elevated levels of interleukins, PGE2, and TNF-α, along with alterations in leukocyte subpopulation and movement due to the function of svMPsFor a current analysis of immunological modulation and svMPs

3. Snake Venon Hyaluronidases

Hyuronidases appear to work to increase the cytotoxicity of other venom ingredients by accelerating the rate and distribution of the injected toxins, despite not being present in significant quantities in the venom of various snakes]. Hyaluronidase-produced proteoglycan hydrolysis products have biological action as well. By upregulating matrix metalloproteases, hyaluronan fragments contribute to the acute pharmacological consequences of envenoming, mainly the inflammation response [36]. Several recent research have examined the use of natural or synthetic substances to inhibit venom hyaluronidase activity.

4. Other Directly Cytotoxic Proteins

In cell culture, some snake venom protein have been shown to be directly cytotoxic. Certain venom proteins open cation channels in the cell membranes, overwhelming cells with calcium and sodium and causing cell death by ionic imbalance, calcium intoxication, and excessive water movement, swelling, and rupture. for a review. Non-catalytic elements of PLA2 heteromers are among these toxicities.

5. Non-Enzymatic 3-Finger Toxins (3FTx, - Neurotoxins)

The majority of 3FTx proteins are present in elapid venoms. Around 70 percent of the proteins in the venom of Eastern green mambas (Dendroaspisangusticeps), respectively, and king serpents (Ophiophagus hannah) are 3FTx proteinsAccording to reports, the percentage can reach 95% in dry coral snakes (Micrurus tschudii One of the few categories of venom proteins with a well-defined mechanism of action is this group of snake venom toxins, which are typically powerfully competitors of nicotinic acetylcholine receptors. A recent review examined the genomes of these proteins and the variety of 3FTs [37]. In receptor biology, α-bungarotoxin's high affinity binding to nAChRs is frequently used to identify and investigate nAChRs.

6. Prey Response to Venoms: How Venoms Co-Opt Signaling Pathways to Produce Toxicity

In addition to being directly caused by venom proteins, snakebite is also caused by the envenomed creature's response to the venom. Developing effective treatments to counteract the severe delayed effects of poisoning in first snake bite survivors requires an understanding of further sources of venom toxicity.

Inflammation and Cytotoxicity Mediated via Inflammation

General Processes Involved in Activating Inflammation: Importance of PLA_2

It may come as no surprise that snake venoms can activate every immune response pathway given the variety of venom proteins. The idea that these sort of II immune responses originated in mammals to protect from venom is a unique theory about immunological responses to snakebite. Galli and associates proposed this theory An allergic reaction to food and other frequent antigens are examples of type II immune responses, which typically entail acquiring immunity mediated by antibodies that produce IgE and mast cells. Even in the absence of prior particular immunisation or sensitisation, the mast cell can degranulate after envenomation. Venom exposures that would otherwise be lethal are prevented by the ensuing strong humoral immune response [38]. Following cobra envenoming, a very wide-ranging and intricate venom-induced inflammatory response with both pro- and beneficial aspects is observed The venom of Naja annulifera causes acute generalised inflammation, which includes elevated plasma levels of MCP-1 and IL-6 as well as PLA2-dependent neutrophilia. Neutrophilia and monocytosis were both induced in mice by a 2LD50 dosage of Naja venom. Silva- de Franco *et al*. discovered that the N. annular venom caused oedema and other histopathologic alterations in the mice's hind paws in an in live experimental paradigm. Furthermore, myonecrosis linked to inflammation was noted, a phenomenon frequently observed in elapid envenoming experimental models.This was ascribed to a PLA2 component's cytotoxic activity.

The body experiences pathological inflammation as a result of almost all snake venoms Injury to tissues and organ system failure are both immediate and long-term consequences caused by this pathological inflammation. findings that cobra sting lytic force induced a mast cell breakdown, histamine release, and cytokine production appears to represent the earliest evidence of an inflammatory response to snake venom [According to Brain and Whittle's 1977 study, Russell's viper PLA2's inflammatory properties cause a dose-sensitive release of histamine. Additionally, Brain and Whittle thought that the venom either increased or released endogenous PLA2This results in a reaction that is out of proportion to the venom proteins' immediate direct immunogenicity. High amounts of arachidonic acid and associated inflammatory cytokines are produced in serum and within cells by PLA2 action in venom. A self-amplifying cascade increased pro-inflammatory cytokines, such as IL-6, TNF- and IL-1, chemical messengers, and lipid-mediated mediators, are produced when venoms activate innate immune cells. This results in a beneficial chain reaction of circulating leukocytes and activation. Eicosanoids from the metabolism of arachidonic acid, such as prostaglandins, also called leukotrienes, as well as and thromboxanes, are examples of lipid mediators. These mediators cause a number of clinical and pathologic aspects of inflammation, such as oedema, tenderness, chemotaxis, cytokine production and leukocyte activation, when combined with cytokines and chemokines. Furthermore, certain elements of inflammation are promoted by hyaluronidase, glycosylated proteins, and svMPs.

Inflammation Underlies Increased Vascular Permeability and Tissue Edema

Each organ in the human organism may be impacted by inflammation brought on by envenomation. When inflammation-induced loss of fluid into tissue is severe, it can result in circulatory shock, systemic hypovolemia, and tissue oedema. Organ failure and cell death are two long-term consequences of inflammation. One frequent

pulmonary consequence of snakebite is inflammation-induced pulmonary oedema. Pulmonary haemorrhage [39] and, of course, electrical paralysis and breathing difficulties [are further effects on the respiratory system. Although cardiogenic pulmonary oedema can also happen pulmonary oedema after envenomation is most likely associated with capillary rupture mediated by inflammation-related factors Venom-induced lung damage in humans may be linked to circulating cytokines like TNF-α and systemic inflammation after envenoming. Increases in IL-6 or MCP-1 are shown in the plasma, lungs, and liver in various hemorrhagic shock models along with irritation and lung damage, which may lead to the syndrome of acute respiratory distress. It is crucial to stress that some other venom proteins, like as hyaluronidases and metalloproteases, which target basement membranes, might cause pulmonary haemorrhage in addition to cytokines.

Coagulation Disorders

Many forms of envenoming exhibit bleeding and disrupted coagulation, indicating significant evolution for venom proteins the reason coagulopathy. svPLA2s, svMPs, amino acid serine proteases, or other factors contribute to the complicated coagulopathy that occurs after envenomation [40]. It is not unusual that phospholipases are thought to play a significant role in controlling or interfering with coagulation as phospholipids are powerful co-factors for many enzymatic transformations in the internal and external clotting cascades. By appropriating a small number of crucial coagulation-regulating pathways, venoms' PLA2 activity produces strong, multi-site anticoagulation. Venom PLA2 is therefore an outstanding candidate for therapeutic action in snakebite coagulopathy

Specific Role of svPLA2 in Disordered Coagulation

One important aspect of the pathogenesis of snake-venom-induced coagulation dysfunction is dysregulated platelet adhesion, which is mediated by svPLA2. It appears that Boffa and Boffa first proposed this in the 1970s, then Kini and Evans published it in model form Inhibition of platelet adhesion and the release of thromboxane, serotonin, and adenosine diphosphate are examples of PLA2-dependent actions. Disordered coagulation has a significant impact by each of these platelet-specific factors. The PLA2-dependent synthesis of arachidonic acid that arises from phospholipids either in the outer membrane of platelets and from circulating lipoprotein molecules is the first step in the creation of all these mediators. The neutralisation of the coagulation-destroying effects caused by Naja venom with the particular PLA2 inhibitor varespladib effectively illustrated the significance of PLA2 in coagulopathy [102]. Similar impairment of PLA2-dependent coagulation was reported [41].

Role of svMPs in Hemorrhage

Venom enzymes such as metal and venom-activated prey metalloproteases in the matrix play a crucial role in bleeding. It's unclear if svMP activity is totally direct or if it additionally initiates an amplification cascade of other signalling molecules including bioactive protein digestion outcomes, tissues and coagulation expression, and endogenous enzyme expression. The available data indicates that endogenous complex metalloproteases (or MMPs) and svMPs have a highly intricate connection. According to Gutierrez and colleagues the activity of endogenous metalloproteases of the matrix (MMPs) in prey is necessary for the breakdown of specific forms of fibrillar collagen following envenomation.When endogenous PLA2 is activated and svPLA2 induces inflammation, endogenous MMPs are quickly produced in prey. Proteins in the matrix of cells are hydrolysed by svMPs to produce physiologically active proteins. For instance, endostatin, an inhibitor of angiogenesis, is produced when kinds 15 and XVIII collagen are hydrolysed. Another antiangiogenic chemical, tumustatin, is released when matrix MPs cleave the three-member molecule of type IV collagen. The first effects of the svMP are amplified and expanded by this elaborate mixture of physiologically active extracellular matrix breakdown fragments.Therefore, the pathogenic impacts of bee venom containing svMPs depend critically on how inflammation including protease action interact with the matrix of cells and blood vessel integrity. Due to the potential for angiogenesis inhibition in cancer treatment, these subjects have been thoroughly studied Research on the impacts of substances other than those mediating structural collapse of basement membranes, particularly blood vessel membranes, has only recently expanded. It is acknowledged that the primary cause of bleeding brought on by viperid venoms is disruption of microvessel function Many cytokines (including interleukin-1, IL-1), growth factors, and hormones—some of which are cell type-specific—regulate the expression of matrix Commons and tissues that inhibit the production of MPs by cells.

Paralysis

One of the more severe and lasting consequences of envenomation is paralysis. Nevertheless, one of the least known is the competitive antagonistic effects of 3FTxs (such as α-bungarotoxin) on nicotinic acetylcholine receptors. The hallmark of elapid venoms is paralysis of muscular tissues, particularly breathing muscles, which is also a clinical characteristic of many viper envenomation types. PLA2 activity in the venom (i.e., neurotoxins); this is the primary source of paralysis induced by bites species some from the world's most medically significant snakes, according to a substantial body of evidence. The reduction of prior to synaptic neurotransmitter vesicles, deactivation of nicotinic acetylcholine receptors, and eventual anatomical degeneration of the neuromuscular endplat are some of the clinically significant effects of β-neurotoxinsRecently, Ranawaka and associates examined some of the debates surrounding PLA2 paralysis from the standpoint of krait β-neurotoxin's effects depicts an integrated two-part model of how we think PLA2 conducts a multiple-target attack on neuromuscular signaling [42].

Clinical Features of Paralysis from β-Neurotoxins

Any mechanistic explanation must take into consideration a number of characteristics of the paralysis caused by PLA2 venoms. First, myokymia, or fasciculations, often precede or coincide with the development of clinical weakness. On the other hand, fasciculations are never observed in neuromuscular block caused by rival antagonists of nicotinic such as the non-depolarizing drugs that resemble curare and are used to induce muscle relaxation during surgery or urgent care Additionally, fasciculations are never observed during block recovery with non-depolarizing drugs or even during subclinical block. However, medications that cause

depolarising block, like succinylcholine, or decamethonium or presynaptic toxins, such botulinum or nerve agents, are clearly characterised by fasciculations.These substances depolarise the post-junctional membrane and deplete pre-junctional neurotransmitter due to enhanced acetylcholine release, at least temporarily. Fasciculations are a clinical indicator indicating either activation of extra-junctional receptors, restricted acetylcholine disposal in the neuromuscular junction, or abnormal release and buildup of acetylcholine. Both the elapids and vultures respectively, have been shown to exhibit fasciculations in bites employing PLA2 venoms. Desensitisation of post-junctional nerve receptors for nicotinic acetyl is a second significant (albeit transient) process at the junction of neuromuscular tissue that is preceded by fasciculations.In his groundbreaking research on neuromuscular junction function, Sir Bernard Katz revealed one of the earliest autoregulatory features of nicotinic input at the neuromuscular junction Pre-synaptic cholinergic and muscular autoreceptors mediate the action of calcium-mediated adversarial regulation of neurotransmission in the frog spinal nerve junction Depletion of synaptic vesicles occurs concurrently with desensitisation of post-junctional nicotinic receptors, preventing nerve depolarisation from achieving neurotransmission. The antecedent increased vesicle fusion and elimination, Ca2+ entrance, mixed water promotion of phosphate activation of the particle release protein system form the fundamental component of this pre-synaptic action. In essence, the system that generates neurotransmitters is exhausted and not restored.The afterwards part of the NMJ exhibits the third effect. Nicotinic receptors undergo inactivation and calcium-dependent phosphatases are activated when desensitisation is followed by post-synaptic elevations in [Ca2+]. As this continues, a mechanism known as cytoskeleton-mediated internalisation removes receptors from the synapse. This impact lasts for a long time. Albuquerque's article [goes into detail into the pharmacology of receptors. desensitisation and inactivation.Although this process is based on numerous investigations of nicotinic receptor modulation in different preparations, the activity of β-neurotoxins is more conjectural It is noteworthy that there is evidence that PLA2s, like the more well-defined α-neurotoxins, can function as affordable nAChR antagonist It is unclear how significant this α-effect is statistically [44].

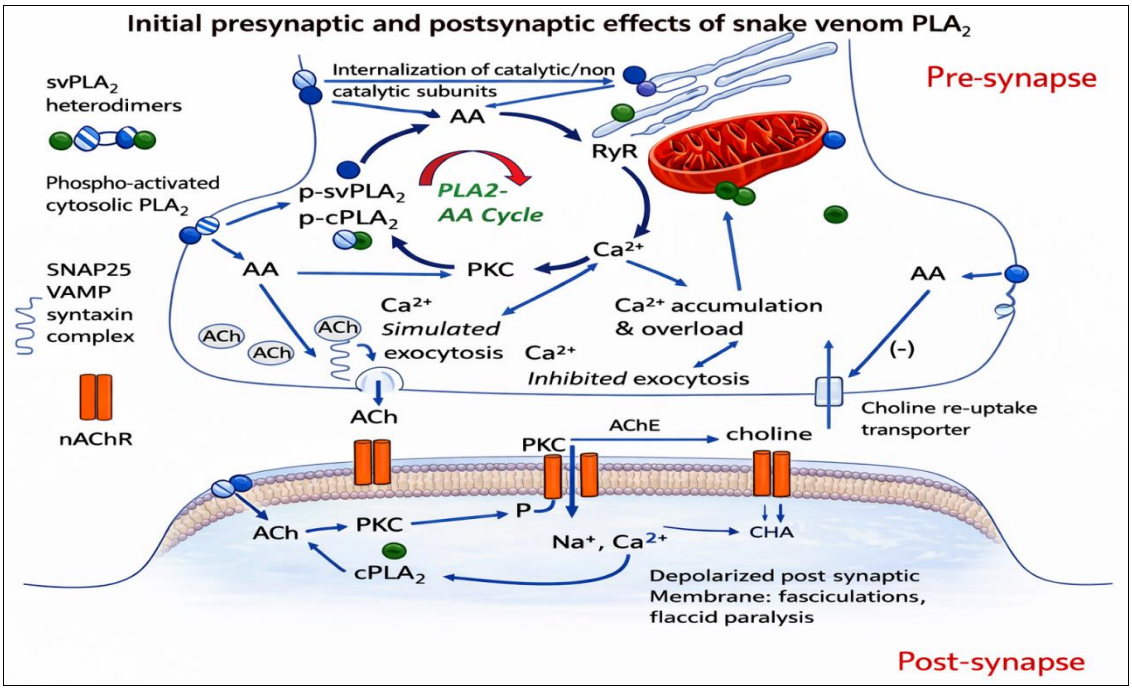

Fig 8: Multi-site failure of synaptic transmission mediated by svPLA2s. Upper panel shows cycle of amplification of arachidonic acid and calcium signaling causing rapid depletion of pre-synaptic acetylcholine vesicle [43]

Is PLA2 and Arachidonic Acid Sufficient to Cause Synaptic Failure

We think that arachidonic acid produced by svPLA2 is powerful enough to explain all of the clinical et pathologic characteristics mentioned above, without ruling out other possibilities. One important mechanism is that AA produced by endogenous PLA2s or catalytic svPLA2s strongly promotes the escape of calcium from its endoplasmic reticulum [45]. which explains the first spike in acetylcholine release resulting fasciculations Other mechanisms, including as Ca2+ entry through channels mediated by voltage, also amplify elevated Ca2+ levels in pre- and post-junctional compartments. These responses are compatible with the electrochemical effects of crotoxin that have been observed. For instance, the basic PLA2 subunit monomer and the crotoxin dimer, which consists of one catalytically active and one catalytically inactive PLA2 subunit, both show a biphasic and calcium-dependent effect on nerve-evoked transmitter exocytosis. AA depletes neural terminals from releasable acetylcholine by inhibiting the choline absorption transporter, which exacerbates pre-junctional failure Blockade of choline reuptake, when combined with other presynaptic effects of arachidonic acid, is a major cause of paralysis. According to electrophysiology conducted in the groundbreaking work of the authors, these actions include pre-synaptic emphasis of PLA2 toxin effects. Technically speaking, though, Cheng's work did not rule out any

blockade at the post-synapse—just not an obstruction of the continuous itself, such as toxicity to myofibrils or protracted limb depolarisation.Additionally, arachidonic acid contributes to the dual effects of -neurotoxins on nerve impulses by binding to SNARE proteins that control neurotransmitter release. This results in a long-lasting decrease of neuromuscular function after an initial stimulation. As previously mentioned, this impact most likely includes simultaneous vesicle exhaustion and receptor deactivation, i.e., simultaneous pre- and post-synaptic suppression of NMJ According to our approach, svPLA2 first causes an excessive and uncontrollable increase in transmitter release, which is followed by the inactivation of post-junctional receptors. Ca2+ is released from cells such the endoplasmic reticulum by arachidonic acid; these changes can be cytotoxic, especially when there are other concurrent cellular stresses.

Post-Junctional Effects of PLA_2 Venoms

AA activates PKC (protein kinase C) in the post-synapse Nicotinic receptors are phosphorylated by activated PKC, which increases their activity but quickly contributes to desensitisation, a conformational phase of a receptor protein that makes it less able to be activated by acetylcholine. Receptor removal by calcium-sensitive phosphatases is a crucial second stage of receptor inactivation that causes these now-inactivated receptors fornication to internalise for a longer period of time. Before being reinserted into the membrane that follows synaptic discharge as functioning receptors, inactivated receptors can stay intact in the cell's intracellular compartment for at least five hoursSubstantial synaptic deactivation occurs during this time Internalisation of nicotinic receptors results in cytoskeletal-dependent structural modifications in the synaptic structure in addition to functional modifications to the synapse. As a result, PLA2 co-opts machinery essential to the pre- but post-synapse function in the junction between neurones through AA, resulting in a multifaceted, deep, and long-lasting suppression of neuromuscular function. Like a-toxins, PLA2 or closely related proteins have been suggested to directly antagoniseFor a number of reasons, we don't think this is a comprehensive explanation. First, neither the starting facilitation of the release of neurotransmitters observed in electrophysiological experiments nor the initial clinical manifestation of PLA2-induced paralysis met the description of an antagonist that competes.

Role of Calcium in PLA_2 Mediated Pre- and Post-Junctional Block of Neurotransmission

Whether venoms permanently harm neuromuscular connections or produce potentially reversible physical alterations in the junction's structure and function is a crucial question. According to current doctrine, the pre-synapse is rapidly The axial degeneration of motor neurones is preceded by physical alterations in the structure of muscular nerve terminals caused by neurotoxins such bungarotoxin In fact, within three to six hours, β-bungarotoxin-paralyzed rat muscles exhibit loss of synaptic vessels, altered mitochondria, bouton loss, and other ultrastructural alterations. Nonetheless, the theory that the morphological alterations seen in three to six hours indicate degeneration (and thus lack of rescue potential)The neuromuscular junction's structure and function are closely linked. For the neuromuscular junction to remain healthy and permanent, it needs continuous input from trophic factors and neurotransmission. The junction between neurones and muscles is extremely adaptable, altering morphological form with function. Because nicotinic receptors are linked to the cytoskeleton, the activation status of these receptors plays a crucial role in this regulation. The skeletal complex, which controls the structure of the NMJ, changes concurrently with the internalisation of inactivated receptors. Both the shape and function of neuromuscular junctions can alter within minutes Mammals, insects, and molluscs all have similar processes for these highly conserved cytoskeletal characteristics Consequently, neuromuscular block causes reversible alterations in synapse structure, regardless of the method. Without real cell degeneration, some of the alterations in synaptic morphology observed in ER studies may be structural modifications brought on by receptor internalisation. In line with varespladib's late rescue of neuronal dysfunction, this potential expands the treatment window for correcting neuromuscular block caused by venoms [46].

Interaction and Amplification of Venom MPs and PLA_2s in Inflammation and Coagulation

We have explained how the physiologically active products of svMPs, svPLA2s, and likely other venom components work in concert. A recent analysis of the confluence and interaction of coagulation problems and inflammation in snake envenomation by Teixeira and colleagues is outstanding [47]. To identify these significant interacting mechanisms and develop therapeutic approaches based on them, more research is required. A combined analysis of known and hypothetical route convergen

Areas Where New Knowledge Concerning the Cellular Effects of Venom Is Needed

It is evident that attempts to develop molecular understandings of venomous activity have been thwarted by the complexity of snake venoms. We are hopeful, nonetheless, that we can move closer to this understanding. Evidence that small molecule medications, such the PLA2 inhibitor varespladib, can reverse late toxicity by acting at certain enzyme sites lends credence to this hope. venom-induced endogenous reactions and previously unidentified or underestimated aspects of venom toxicity may be revealed by other exceptionally specific small molecule inhibitors.New therapeutic approaches for the treatment of snakebite will benefit from a thorough understanding of the mechanisms involved the co-optation of indigenous systems and activities. components. In addition to revealing host-based pathogenic reactions to venom, addressing the ideas in the figure will highlight the benefits and drawbacks of various treatment modalities. In the end, systems must be comprehended in their functional completeness, regardless of whether the dissecting technique is genomic, bio proteomic, or chemistry pathway specific. Some of the more modern methods have received attention due to the World Health Organization's current focus on priority measures on snakebite treatments [49].

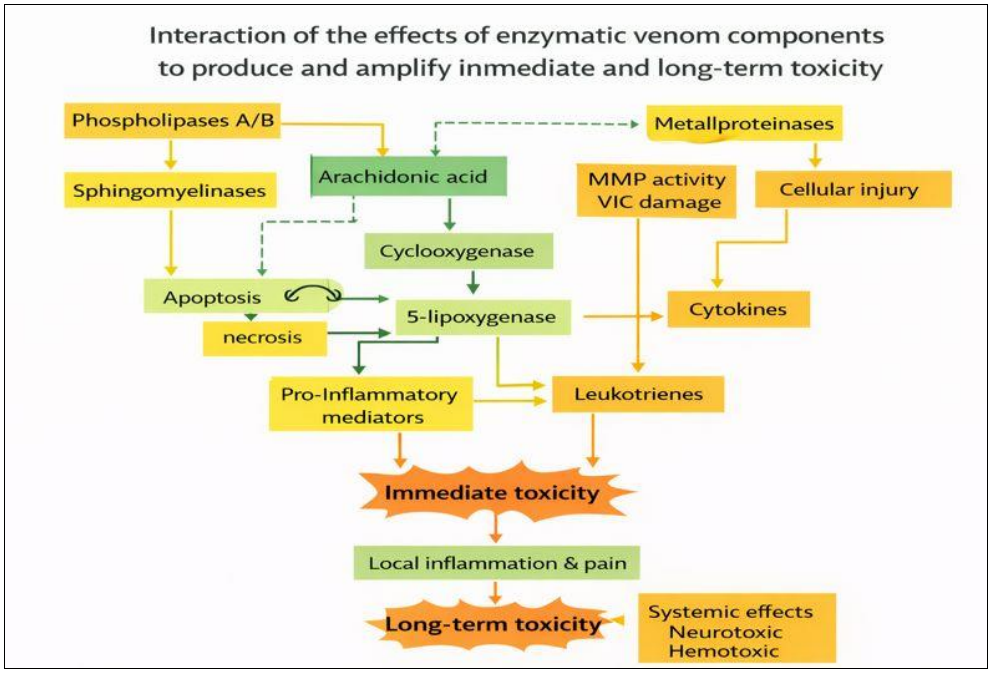

Fig 9: Interaction of the effects of enzymatic venom components to produce and amplify immediate and long-term toxicity [48]

Conclusion

Venoms that harm the blood or nervous system are classified as hemotoxic or neurotoxic, respectively. This is a very traditional division. The Elapidae or Vipers families contain the majority of poisonous snakes. The elapid venoms are often regarded as neurotoxic because they include poisons that impact the nervous system. Venoms from viperids and the majority of rear-fanged snakes are thought to be hemotoxic since they primarily affect blood coagulation. Nonetheless, certain viperid bites cause neurotoxic symptoms [96]. Indeed, hemotoxic venoms were found to include several neurotoxins. We have attempted to organise information on these neurotoxins in this review, taking into account both their functional and structural details. They're called phospholipases A2, which exhibit neurotoxicity either before or after synapses.Baptides and azemiopsinIonic channel activities are disrupted by particular CriSPs that are present in almost all snake venoms, including those of viperids and colubrids. Transcripts encoding putative TFTs, which have been detected in the transcriptomes of venom glands, and typical TFTs have been found in colubrid and viperid venoms. Crotamine and C-type lectin-like proteins are among the additional toxins found in viperid venoms that exhibit neurotoxicity. This shows how neurotoxins are widely distributed in venoms that were previously thought to be hemotoxic. These toxins come from a variety of families, including small peptide neurotoxins and massive plural-subunit proteins, the latter of which may not be neutralised by antivenom. The neurotoxicity of snake venoms from the genera the genera Agkistrodon, Python, Crotalus, the genus Daboia, Vipera, and a few others is covered in this review. Viperid snakes from different genera may exhibit or develop neurotoxicity; this cannot be ruled out. Therefore, when treating bites from venomous snakes belonging to the Viperidae family, the neurotoxic effect for the venoms should be taken into account.

Certain toxins have very positive effects, like analgesic ones, as was previously mentioned. Clinical and scientific studies can be based on these poisons. Crotoxin should be mentioned first because of its well-known painkilling effects It's interesting to note that patients with solid tumours participated in a phase I research study of the crotoxin, and the appropriate dosage before phase II was established This trial demonstrates that crotoxin can be used to treat human patients and may eventually be used as an analgesic.The resulting conjugate resulted in a sustained decrease in mechanical hypernociception. Crotamine is another viperid neurotoxin that interferes with pain. It has an analgesic effect that is 500 times more effective than morphine in terms of molar ratio According to recent research, oral administration of crotamine causes antinociception in mice This outcome creates opportunities for the continued use of crotamine to serve as an analgesic medication by resolving the toxicity issue. Small proteinaceous toxins like ctotoxin and crotamine have the inherent drawbacks of proteins, such as production complexity, immunogenicity, bloodstream instability, toxicities, etc., which must be addressed before they are used.While numerous neurones have been found already in hemotoxic snake venom, not all of these venoms have been thoroughly investigated, and it is reasonable to anticipate the finding of additional toxins with peculiar characteristics. Therefore, even while dna or gene sequences for these toxins are present in viperid venoms, TFTs are typically either lacking or present in extremely modest amounts. Only a limited portion of the venoms of colubrid TFTs, such as those of cat-eyed snakes and certain others, have been described.Making neurotoxins utilising viperid venom and comparing them to conventional three-finger neurotoxins would be fascinating. Small quantities of acetylcholinesterase (AChE) have been detected in the venoms of many snakes, including viperids Acetylcholine hydrolysis within a neuronal cleft is the physiological function of endogenous AChE.In order to create complex signals that appropriate universal vertebrate signalling pathways that control coagulation, inflammation, muscular activity, and cell survival, nake venoms rely on proteases and tiny poisonous peptides. Venoms function inside cells, within cell membranes, in the internal compartment, and in the bloodstream. It is anticipated that inhibitors with small

molecules of PLA2s and MPs will offer synergistic therapeutic advantage because venom can disrupt regulators in the PLA2 and MP metabolic pathways due to a few different types of protease activity. Furthermore, unlike existing serotheran, the distribution of these tiny compounds is unrestricted. We are entering uncharted terrain in a number of significant ways thanks to recent developments in the testing and development of tiny-molecule inhibitors of snake poisons and their effects. Firstly, they offer rescue therapy that is not possible with antivenoms. Second, unlike antivenoms, they shed light on the physiology and pathophysiology of snakebite. We can start to understand how snake venoms not only induce direct toxicity but also co-opt reactive inflammation throughout the prey/victim to produce organ poisoning, paralysis, and other short- and long-term effects due to the remarkable selectivity of novel medicines against venom protease activity [50].

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