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CORAL SNAKE VENOMS: MODE OF ACTION AND PATHOPHYSIOLOGY OF EXPERIMENTAL ENVENOMATION (1)

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SUMMARY

Coral snakes, the New World Elapidae, are included in the genera **Micruroides** and **Micrurus**. The genus **Micrurus** comprises nearly all coral snake species and those which are responsible for human snake-bite accidents. The following generalizations concerning the effects induced by their venoms, and their venom-properties can be made. Coral snake venoms are neurotoxic, producing loss of muscle strenght and death by respiratory paralysis. Local edema and necrosis are not induced nor blood coagulation or hemorrhages. Proteolysis activity is absent or of very low grade. They display phospholipase A_2 activity. Nephrotoxic effects are not evoked.

The main toxins from elapid venoms are postsynaptic and presynaptic neurotoxins and cardiotoxins. Phospholipases A_2 endowed with myonecrotic or cardiotoxin-like properties are important toxic components from some elapid venoms.

The mode of action of **Micrurus frontalis, M. lemniscatus, M. corallinus** and **M. fulvius** venoms has been investigated in isolated muscle preparations and is here discussed. It is shown that while **M. frontalis** and **M. lemniscatus** venoms must contain only neurotoxins that act at the cholinergic end-plate receptor (postsynaptic neurotoxins), **M. corallinus** venom also inhibits evoked acetylcholine release by the motor nerve endings (presynaptic neurotoxin-like effect) and **M. fulvius** induces muscle fiber membrane depolarization (cardiotoxin-like effect). The effects produced by **M. corallinus** and **M. fulvius** venoms **in vivo** in dogs and **M. frontalis** venom in dogs and monkeys are also reported.

KEY WORDS: Coral snake venoms; Neuromuscular junction; Postsynaptic action; Presynaptic action; Cardiotoxin-like action; Neostigmine antagonistic effect.

INTRODUCTION

Coral snakes are the Elapidae of the New World. Contrary to the main representatives of this family in Asia, Africa and Australia, they are burroing, timid, low agressive snakes. This explains why accidents caused by them are so infrequent. Actually they generally occur when an incautious person handles one of these beautiful snakes thinking they are nonvenomous and inoffensive, a confusion with some coral snake-like serpents (false coral snakes belonging to the family Colubridae). Coral snakes are included in two genera, **Micruroides** and **Micrurus**. **Micruroides** is known from southwestern United States and western Mexico. There is only one species of **Micruroides, Micruroides euryxanthus**, of which three subspecies are recognized. The

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species and subspecies of **Micrurus**, on the contrary, are very numerous, about 120 according to Roze [11]. They are distributed throughout the tropical and warm-temperate parts of North, Central and South America. However, the mode of action of the venom of only a few species has been submitted to investigation. They are the venom of **M. fulvius, M. frontalis, M. corallinus** and **M. lemniscatus**, the first from United States and Mexico, the others from South America. Nevertheless, the following generalizations concerning the effects induced by their venoms, and venom-properties can be made (BRAZIL [2]; ROSENFELD [10]; SHAW [12]). Coral snake venoms are neurotoxic, producing loss of muscle strenght and death by respiratory paralysis. Eyelid ptosis, ophthalmoplegia, paralysis of jaw muscle, larynx and pharynx, besides sialorrhea and paralysis of neck and limb muscles are observed in the poisoning produced by coral snake venoms. Local edema and necrosis are not induced. They do not cause also blood coagulation or hemorragies. Proteolysis activity in substracts such as gelatin, casein or fibrin is absent or of low grade. Coral snake venoms have phospholipase A_2 activity, producing **in vitro** indirect hemolysis. However, **in vivo** they do not cause intravascular hemolysis, and hemoglobinuria does not occur in coral snake venom-induced poisoning. Nephrotoxic effects are not evoked in animal or human envenomation.

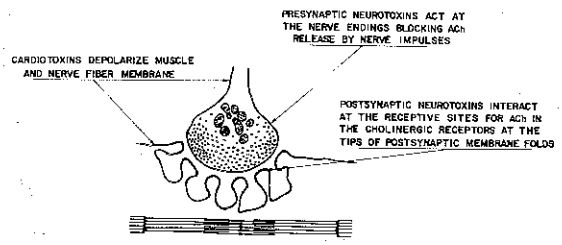

Fig. 1 — Local of action of the elapid neurotoxins and cardiotoxins. Diagram of a neuromuscular junction. In the axoplasm of the nerve terminal, synaptic vesicles (which contain acetylcholine), and mitochondria are represented. At the crests of the folds of the muscle fiber membrane, the acetylcholine receptors are represented by very small black circles.

The main toxins from elapid venoms are postsynaptic neurotoxins, presynaptic neurotoxins and cardiotoxins (LEE [7]). Phospholipase A_2 endowed with myonecrotic (FOHMAN & EAKER [4]) or cardiotoxin-like (LEE et al [8]) properties are other important toxic components from some elapid venoms. Postsynaptic neurotoxins consist of a peptide chain containing 60 to 62 aminoacids and four disulfide bridges (short neurotoxins) or 71 to 74 aminoacids and five dissulfide bridges (KARLSSON [6]). They are low molecular weight basic proteins with isoeletric points in the vecinity of pH9-10. Postsynaptic neurotoxins interact with the end-plate cholinergic receptors, causing a slowly reversible or an irreversible neuromuscular blockade (Fig. 1). As curare they are acetylcholine antagonists at the end-plate nicotinic receptor. Postsynaptic neurotoxins has been found to occur in all Elapidae and Hydrophiinae venoms so far investigated. Presynaptic neurotoxins are proteins larger than the postsynaptic neurotoxins. Some are complex of two or three subunits not covalently linked. All display a week phospholipase A_2 activity which seems to be indispensable for their action. Their primary action is on the motor nerve endings (Fig. 1), inhibiting acetylcholine release produced by nerve impulses and increasing spontaneous acetylcholine release. They may exert also a myotoxic action and, at least in one case (crotoxin), transform the receptor protein from the state of low affinity for agonists to one of high affinity, that is, to induce receptor desensitization (BON et al [1]). Presynaptic neurotoxins are the most toxic components of snake venoms. They occur in some elapine venoms and also in those of a few crotaline (HAWGOOD [5]). Cardiotoxins, also called direct lytic factor, cobramines, cytotoxins or membrane toxins, are as the postsynaptic neurotoxins, basic polypeptide toxins of low molecular weight (about 6000 to 7000 daltons). They cause depolarization and disruption of the membrane of excitable and non excitable cells. Arrhytmias and cardiovascular depression are also evoked by them. Their potency is much lower than that of postsynaptic neurotoxins. They ocur in cobra venoms.

The studies so far carried out show that coral snake venoms interact with end-plate receptor like the postsynaptic neurotoxins. They show also that they may contain components acting like the presynaptic neurotoxins or the cardiotoxins.

CORAL SNAKE VENOMS EXERTING ONLY POSTSYNAPTIC NEUROTOXIN-LIKE ACTION: MICRURUS FRONTALIS AND M. LEMNISCATUS VENOM.

M. frontalis is distributed over centraleastern (Minas Gerais, São Paulo), centralwestern (Southeastern Mato Grosso) and southern Brazil. It is also found in Uruguay, northeastern and northwestern Argentine, Paraguay and Santa Cruz in Boolivia. It comprises seven subspecies (ROZE [11]).

M. frontalis venom from snakes captured in the State of São Paulo induces a reversible neuromuscular blockade in the isolated rat phrenic nerve-diaphragm preparation while the blockade elicited by the venom of snakes from southeastern Mato Grosso is irreversible in that preparation (VITAL BRAZIL et al. [17]). Evoked acetylcholine release at the phrenic nerve-diaphragm preparation is rather increased by the venom, an effect also produced by alpha-bungarotoxin (MILEDI et al. [9]) and whose mechanism is not well understood. In the chronically denervated rat hemidiaphragm, **M. frontalis** venom causes an irreversible inhibition of the contracture induced by acetylcholine. D-tubocurarine protects the denervated hemidiaphragm from the venom action (Fig. 2). D-tubocurarine and **M. frontalis** venom act therefore at the same site in the cholinergic receptor. In the toad sartorius, the resting membrane potential and the miniature end-plate potential (m.e.p.p.) frequency are not altered by the venom. M.e.p.ps. are rapidly depressed. All these results show that **M. frontalis** venom must contain postsynaptic neurotoxin(s), being devoid of

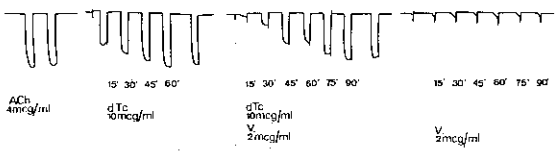

Fig. 2 — Protection by d-tubocurarine (dTc) of the cholinergic receptors from the action of **Micrurus frontalis** venom (V) in the isolated and chronically denervated rat hemidiaphragm. Contractures of the denervated muscle were produced by acetylcholine bromide (ACh) 2 ug/ml. 1. Two responses to ACh before dTc addition to the bath. 2. Addition of dTc 10 ug/ml to the bath; after 30 min the response to ACh was blocked; upon washing of the preparation the ACh-induced contractures gradually returned and after 60 min they were completely recovered. 3. Addition of dTc 10 ug/ml and after 30 min, V 2 ug/ml to the bath; 30 min after V addition and 60 min after dTc addition, washing of the preparation was started; complete recovery of ACh responses occured 90 min after the washing start. 4. Addition of V 2 ug/ml to the bath; washing of the preparation for 90 min had no effect on the depression produced by V of the ACh-induced responses. (From ref. 17).

presynaptic neurotoxins and of depolarizing components.

M. frontalis venom when injected i.v. in anesthetized dogs produces an abrupt fall of blood pressure which can be lethal to the animals (VITAL BRAZIL et al. [17]). However, when injected intramusculary, the effect on blood pressure is always mild and the dogs die from respiratory paralysis. After cessation of spontaneous respiration, the animals can be mantained alive under artificial respiration. The respiratory paralysis is peripheral in origin. This was proven by recording discharges of action potentials in the phrenic nerve after cessation of spontaneous respiration in dogs supported by artificial respiration (Fig. 3). In the dog sciatic nerve-tibialis anterior muscle preparation **in situ**, the neuromuscular blockade produced by the venom is antagonized by neostigmine (VITAL BRAZIL et al.[17]). The same occurs in the rat sciatic nerve-gastrocnemius muscle preparation **in situ** (VITAL BRAZIL & BARRIO [15]). Neostigmine also antagonizes the respiratory paralysis induced by the venom. This was documented by recording the electromyogram of diaphragms of dogs injected with **M. frontalis** venom (Fig. 4). The effectiveness of neostigmine in counteracting the paralysis and preventing death produced by **M. frontalis** venom was also proven in unanesthetized monkeys (Fig. 5) and dogs (Table I).

M. lemniscatus distribution is very large. It is found in the Guyanas, Trinidad, Venezuela, Colombia, Equador, Bolivia and in northern, northeastern and central Brazil until Paraná and Mato Grosso. It comprises four subspecies (ROZE [11]).

M. lemniscatus venom elicits a reversible neuromuscular blockade in the rat phrenic nerve-diaphragm preparation (VITAL BRAZIL [14]). In the chronically denervated rat hemidiaphragm, it inhibits the contracture induced by acetylcholine (Fig. 6) and other cholinergic agonists. It does not depress the contracture produced in that preparation by potassium ions. The amplitude of the responses induced by direct muscle stimulation is not reduced in the innervated diaphragm by the venom. Its effects on acetylcholine release was not investigated .However, since the action of all presynaptic neurotoxins

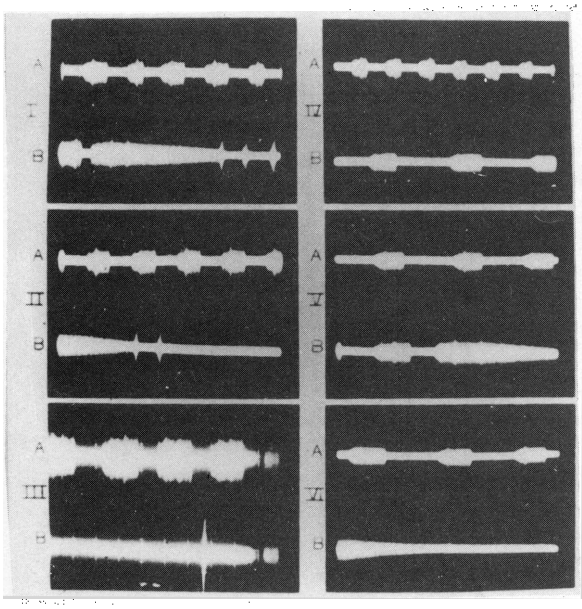

Fig. 3 — Peripheral origin of the respiratory paralysis induced by **Micrurus frontalis** venom. Discharges of action potentials recorded in central slip of a phrenic nerve root of a dog injected with **M. frontalis** venom (0.7 mg/kg i.m.) about 3 h 20 min before the experiment. The dog spontaneous respiration stoped 1 hour before. I A, II A, III A, IV A and B, V A and VI A, discharges of action potentials recorded during artificial respiration. I B, II B, III B, V B and VI B records of the bioelectrical activity in the phrenic nerve after stopping artificial respiration respectively for 0.5, 1.0, 2.0, 1.0 and 2.0 min. IV B, V and VI discharges of action potentials were recorded after section of both vagi (observe in IV B, V A and VI A that the discharges did not accompany any more the rhythm of the artificial respiration). (From ref. 17).

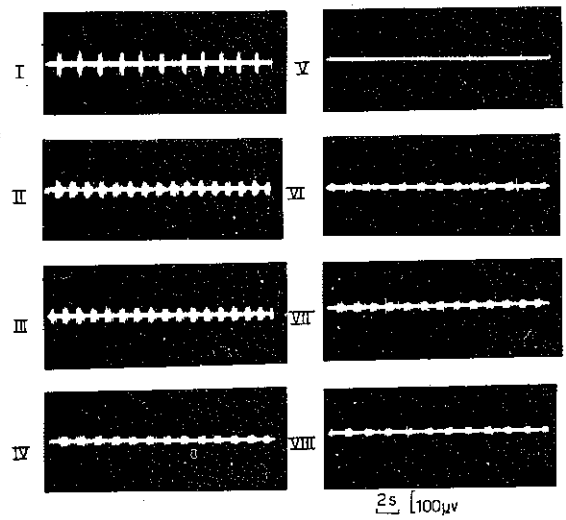

Fig. 4 — Antagonistic effect of neostigmine on the respiratory paralysis induced by **Micrurus frontalis** venom. Electromyogram of the diaphragm of a dog injected i.m. with 0.85 mg/kg of venom. I. Electromyogram before venom injection. II. III, IV and V, electromyograms 110, 135, 200 and 240 min after venom injection. VI, VII and VIII, electromyograms after injection i.v. of 0.1 mg/kg of methylsulfate of neostigmine. Neostigmine was injected 4 min after spontaneous respiration arrest (V). (From ref. 17).

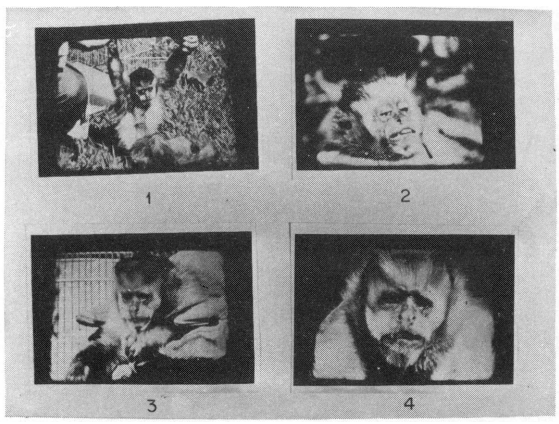

Fig. 5 — Antagonistic effect of neostigmine on the paralysis induced by **Micrurus frontalis** venom in unanesthetized monkeys (Cebus sp). 1 and 2: Photographs of a monkey about 3 h after the injection i.m. of 0.5 mg/kg and 2 h after a second injection 0.4 mg/kg. The photographs show that the monkey has completely lost its muscle strenght and presents eye-lid and mandibular ptosis. 3 and 4: Photographs 5 and 10 min after the injection i.v. of 0.05 mg/kg of methylsulfate of neostigmine. The photographs show that all motor signs of **M. frontalis** venom poisoning have disappeared. The injection of neostigmine was made immediately after the photographs I and II were taken (from the film). The antagonistic effect produced by neostigmine upon the paralysis caused by **Micrurus frontalis** venom, directed by Vital Brazil, O. & Pellegrini Filho, A. See Rosenberg, P. (Ed.) Toxins Animal, Plant and Microbial, Oxford, Pergamon Press, 1978, pp. 437-438).

is irreversible, it seems that **M. lemniscatus** venom induces neuromuscular blockade by interacting only with the end plate cholinergic receptors.

CORAL SNAKE VENOMS EXERTING POSTSYNAPTIC NEUROTOXIN-LIKE AND PRESYNAPTIC NEUROTOXIN-LIKE ACTIONS: MICRURUS CORALLINS VENOM.

M. corallinus is distributed over central and southern Brazil, south of Amazon Basin and northern Argentine; it occurs probably also in Uruguay according to ROZE [11]. Its venom induces an irreversible neuromuscular blockade in the rat phrenic nerve-diaphragm preparation (VITAL BRAZIL & FONTANA [16]). Spontaneous acetylcholine release is increased by **M. corallinus** venom while the evoked one is inhibited (Table II). The venom increases m.e.p.p. frequency before depressing the amplitude of these

TABLE I

Treatment with neostigmine (neostigmine methylsulfate) of experimental poisoning induced by **Micrurus frontalis** venom in dogs

Exp. n.º	Dog (weight)	Venom (0.95 mg, i.m.) injection (hour)	Respiratory depression (hour)	Neostigmine (0.05 mg/kg i.v.) injection (hour)	Result
1	4.9 kg	9 h 55 min a.m.	11 h a.m.	11 h 55 min a.m.*	Survived
	4.0 kg	9 h 50 min a.m.	11 h a.m.	——	Dead at 11 h 50 min a.m.
2	6.3 kg	11 h 50 min a.m.	1 h 20 min p.m.	1 h 30 min a.m.	Survived
	5.8 kg	11 h 30 min a.m.	12 h 50 min noon	——	Dead at 1 h 20 min p.m.
3	7.7 kg	9 h 40 min a.m.	10 h 30 min a.m.	10 h 40 min a.m.	Survived
	6.4 kg	9 h 25 min a.m.	11 h a.m.	——	Dead at 11 h 20 min a.m.
4	5.8 kg	12 h 5 min noon	2 h p.m.	14 h 5 min p.m.**	Survived
	5.3 kg	12 h 10 min noon	2 h p.m.	——	Dead at 2 h 30 min p.m.
5	5.4 kg	10 h a.m.	11 h 55 min a.m.	12 h 15 min noon	Survived
	4.8 kg	10 h 5 min a.m.	12 h 10 min noon	——	Dead at 1 h p.m.

* A second injection of neostigmine was made after 45 min
** A second injection of neostigmine was made after 20 min

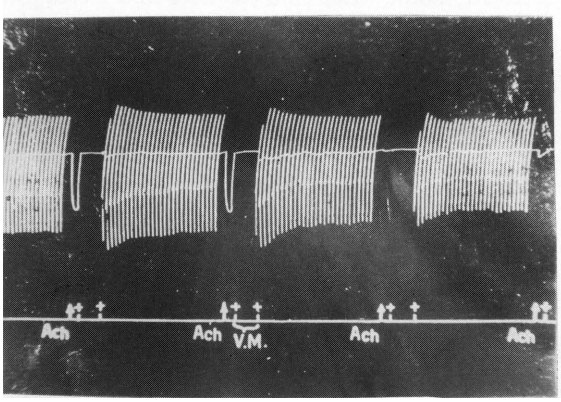

Fig. 6 — Antagonistic effect of **Micrurus lemniscatus** on the acethylcholine-induced contracture in the isolated and chronically denervated rat hemidiaphragm. The denervated hemidiaphragm was stimulated by electrical pulses (0.1 Hz, 40 V, 2 ms) and acethylcholine iodide (4 ug/ml). The venom was added to the bath 30 min before the start of electrical stimulation and 35 min before ACh addition to the bath. (From ref. 14).

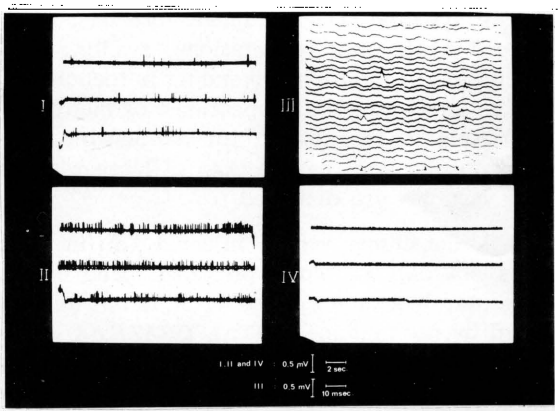

Fig. 7 — Effects of **Micrurus corallinus** venom on miniature endplate potentials (m.e.p.ps.). I M.e.p.ps. before venom addition to the bath. II, III and IV M.e.p.ps. 20, 40 and 60 min after the addition of 5 ug/ml of venom to the bath (From ref. 16).

potentials (Fig. 7). The resting membrane potential and excitability of the rat diaphragm are not altered by **M. corallinus** venom. In the isolated and chronically denervated rat hemidiaphragm, the venom reversibly blocks acetylcholine-induced contracture (Fig. 8). These results show that **M. corallinus** venom must contain postsynaptic and presynaptic neuroto-

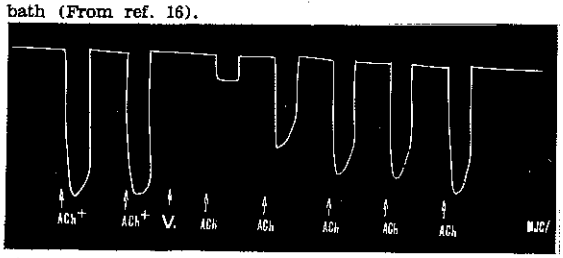

Fig. 8 — Antagonistic effect of **Micrurus corallinus** venom on the acetylcholine induced contracture in the isolated and chronically denervated rat hemidiaphragm. Acetylcholine iodide (ACh), 4 ug/ml; venom, 2 ug/ml. The responses to ACh gradually returned on washing the preparation. (From ref. 16).

TABLE II

Effect of Micrurus corallinus venom on acetylcholine (ACh) release (in nanograms). Rat phrenic nerve-diaphragm preparations

Exps.	ACh release before venom addition to the bath		ACh release after neuromuscular blockade induced by 10 ug/ml of venom	
	Spontaneous release	Release by nerve impulses	Spontaneous release	Release by nerve impulses
1	6.4	55.6	9.1	21.1
2	8.4	64.8	14.0	28.0
3	8.5	49.0	15.0	30.0
Mean ± S.E.M.	7.7 ± 0.9	56.4 ± 0.9	12.7 ± 2.5	26.4 ± 3.8

xins and that it is devoid of myotoxic components.

The ultrastructure changes caused by **M. corallinus** venom were investigated in the mouse phrenic nerve-diaphragm preparation (CRUZ HÖFLING et al. [3]). They were found to be similar to those produced by the presynaptic neurotoxin beta-bungarotoxin: reduction in number of synaptic vesicles, appearance of omega-shaped axolemmal indentations, swelling and disruption of motor nerve ending mitochondria. At the latest stages disappearance of many nerve terminals, increase in the axoplasmic electron opacity and the presence of large vesicles and vacuoles are observed.

M. corallinus venom injected i.m. in dogs does not depress blood pressure. The neuromuscular blockade elicited by it is not antagonized by neostigmine (VITAL BRAZIL & FONTANA [16]). This suggests that in the dog the main cause of the neuromuscular blockade is presynaptic in origin.

CORAL SNAKE VENOMS EXERTING POSTSYNAPTIC NEUROTOXIN-LIKE ACTION AND INDUCING DEPOLARIZATION OF MUSCLE FIBER MEMBRANE: **MICRURUS FULVIUS** VENOM.

M. fulvius is distributed over southeastern North Caroline to the tip of Florida, the Gulf coastal plain to the Mississippi River and, west of it, Louisiana. Arkansas and Texas in United States, and northeastern Mexico. It comprises five subspecies (ROZE [11]).

M. fulvius venom was investigated by WEISS & McISAAC [18] in anesthetized cats, isolated rat muscle preparations and frog **rectus abdominis** muscle. The venom slowly infused i.v. in cats evokes a rapid and temporary fall of blood pressure. Neuromuscular and respiratory depression are manifest after one hour. After complete neuromuscular blockade, the muscle (**tibialis anterior**) responds to direct stimulation for about one hour. Artificial respiration after cessation of spontaneous respiration maintains the cats alive for some time (bteween 2.5 and 9.5 hours after the start of venom injection) but they finally die presumably from hypotension. In isolated rat muscle preparations the venom produces neuromuscular blockade and also depression of the responses to direct muscle stimulation. The neuromuscular blockade was not antagonized by neostigmine or edrophonium, and prolonged washing of the preparation causes only less than a 10 per cent recovery. **M. fulvius** venom induces depolarization of the muscle fiber membrane and cause muscle fiber swelling and hyaline degeneration. A small reduction, not dose-dependent, is produced by the venom in the responses of the frog **rectus abdominis** to acetylcholine. WEISS & McISAAK [18] conclude from the results of their research that **M. fulvius** venom acts in a fashion analogous in some respects to the cardiotoxin from cobra venom and that it possibly contains a fraction which blocks the acetylcholine receptors. On the other hand, SNYDER and co-workers [13] isolated from **M. fulvius** venom a neurotoxic fraction which produces neuromuscular blockade in chick biventer cervicis nerve-muscle preparation and inhibits the acetylcholine-induced contracture in this preparation in a dose-dependent manner. It does not show the depolarizing activity of the crude venom. The action of the fraction is irreversible.

VITAL BRAZIL, O. — Coral snake venoms: mode of action and pathophysiology of experimental envenomation. **Rev. Inst. Med. trop. São Paulo, 29:119-126, 1987.**

RESUMO

Peçonhas de cobras corais: modo de ação e fisiopatologia do envenenamento experimental.

As cobras corais são os representantes da família Elapidae nas Américas. Classificam-se em dois gêneros **Micruroides** e **Micrurus**. O gênero **Micrurus** compreende a quase totalidade das espécies de cobra coral e todas as que causam acidentes no homem. Podem-se fazer as seguintes generalizações quanto aos efeitos produzidos por suas peçonhas e a algumas propriedades destas. As peçonhas das cobras corais são neurotóxicas, causando perda da força muscular e morte por paralisia respiratória. Não provocam edema local e necrose assim como não produzem coagulação sanguínea ou hemorragias. A atividade proteolítica das peçonhas de cobras corais é pequena ou nula. Exercem atividade fosfolipase A_2. Não induzem efeitos nefrotóxicos.

Os componentes tóxicos da peçonha das Elapidae são as neurotoxinas pré-sinápticas, as neurotoxinas pós-sinápticas, as cardiotoxinas e fosfolipases A_2 com atividade mionecrótica ou semelhante à das cardiotoxinas.

O modo de ação das peçonhas de **Micrurus frontalis, M. lemniscatus, M. corallinus** e **M. fulvius** foi investigado em preparações neuromusculares isoladas e é aqui exposto. Mostra-se que enquanto as peçonhas de **M. frontalis** e **M. lemniscatus** devem conter apenas toxinas que atuam através de ligação com os receptores colinérgicos da placa terminal (neurotoxinas pós-sinápticas), a de **M. corallinus** atua também na junção neuromuscular inibindo a liberação de acetilcolina pelos impulsos nervosos e a de **M. fulvius** induz despolarização da membrana das fibras musculares. Relatam-se também os efeitos produzidos pelas peçonhas de **M. corallinus** e **M. fulvius in vivo** em cães e os provocados pela peçonha de **M. frontalis** em cães e macacos.

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