50. PHARMACOLOGY OF VENOMS — INTRODUCTORY REMARKS

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The present Introductory Remarks on the Pharmacology of Venoms should cover a large area treated in this Symposium, since most of the subjects which are going to be discussed here have a bearing on the Pharmacology of Venoms. Especially all papers on the biochemical aspects of the action of venoms are of the utmost importance to understand their pharmacological actions.

Obviously, I have to limit my talk to a few personal recollections about our past and present work involving animal venoms.

In the beginning, I was mainly interested in the mechanism of anaphylaxis and related phenomena, from the point of view of a release of histamine. Consequently, I became chiefly interested in the work by Feldberg and Kellaway (1937-38), in Australia, about the release of histamine by the Australian and Indian cobra, the Denisonia superba and the Naja naja. Both venoms, when perfused through the guinea-pig lung, produced a sharp release of histamine, leading almost to exhaustion of the stock of this amine in that organ of the guinea-pig. However, other experiments by the Australian workers, on the circulatory effects of the venoms, as well as on the effects upon the isolated smooth muscle of the guinea-pig ileum, were consistent with the idea that besides histamine, other endogenously released principles might participate in such envenomations. An important outcome of these experiments was the conclusion that, under certain conditions, a slow-reacting substance (SRS) was released and could explain some of the features of the shocks by animal venoms.

These experiments showing the release of histamine and of a slow-reacting substance, by snake venoms, established an obvious parallelism between the symptoms of envenomation and those of anaphylaxis, as had been described in the dog, by Richet and Portier (1902), in the guinea-pig, by Theobald Smith (1906) and in the rabbit, by Arthus and Breton (1903-5).

This analogy was the most striking having in view the way by which anaphylaxis was discovered by Richet and Portier, in 1902. It is well known that the French physiologists were studying the venom of the sea anemona, of the genus Physalia and Actinia, using glycerinated extracts of their tentacles. When injected with a lethal dose of these extracts the animals showed a picture similar to that they could have under the anaphylactic crisis: diarrhea, abdominal cramps, fall in blood pressure, coma and death.

By section, the animals showed profuse hemorrhages and stagnation of blood in the portal region.
The new phenomenon, observed by Richet and Portier and to which they gave the name of Anaphylaxis, was that a similar picture could be obtained with a small fraction of the lethal dose, if such a small amount of the extract was given 15 to 20 days after the animal had been submitted to a previous injection of a non-lethal dose of the extracts. Therefore, they have concluded that instead of becoming protected (immunized) by a previous administration of the toxin, the animals presented an increased sensitivity to it. To denote this absence of protection or phylaxis, Richet and Portier coined the name which became famous of Anaphylaxis.

This story is well known to all those who have worked in anaphylaxis, but the point I wish to raise, is the implication contained in that name of Anaphylaxis, that the primary agent should be the toxic material and that the symptoms arising at the second injection were only exacerbation of the primary toxic effects of the utilized material. What Richet and Portier tried to imply with the name of anaphylaxis was the reduction of protection to the toxic effects of the glycerinated extracts of Physalies or Actinia tentacles. Later on, the name was widely utilized to indicate the development of toxic effects by materials, such as serum, ovalbumin and so forth, which are primarily non-toxic and become so after the repetition of the treatment.

In 1904, Arthus discovered serum-anaphylaxis, i.e., the development of toxic effects in the rabbit by repeated injections of horse serum, and in 1906, the immunologists with Theobald Smith, described in guinea-pigs the anaphylactic reaction to the re-injection of sera to which the animal is normally insensitive. We know what great success had this name of Anaphylaxis to indicate a great deal of pathological phenomena in animals and in humans, where von Pirquet and Schick described serum disease and allergy.

But, why should Richet be fooled in his experiments to the point to think that what he was observing at the second injection was in reality the absence of protection towards the primary toxic effects of his material extracted from the tentacles of the Actinia? It is easy now to answer such a question. In fact, the symptomatology produced by many venoms from animal origin, resembles or mimics the effects that we know to be typical of Anaphylaxis. In other words, what he took as an intensification of the primary effects of his toxin, that he used to call actinocongestin, were actually the similar symptoms produced by Anaphylaxis, which occur as a consequence of an endogenous intoxication, by release of active substances, among which histamine is certainly one of the most important, at least in dogs and guinea-pigs. But, of course, the actinocongestin when acting as a toxic material releases histamine and/or other mediators directly from their endogenous stores, though when acting in the sensitized animal to produce anaphylaxis, the symptomatology develops through an entirely different mechanism, namely by combination with antibodies formed after the first injection. It is this profound analogy between envenomation by animal poisons and the symptomatology of Anaphylaxis that was so nicely explored by Arthus in his book “De l’Anaphylaxie à l’Immunité”, published in 1921 in Paris.

But, in the meantime, the important contribution by Sir Henry Dale, in England, studying the effects of histamine and postulating its participation in the mechanism of Anaphylaxis, should be considered.

In 1919, Dale proposed the name of Autopharmacology to denote this class of phenomena developing in the animal body by the release of endogenous active materials, especially histamine.
And then, the excellent work which followed, by Feldberg and Kellaway (1937-38) and others to show the importance of the release of histamine and slow-reacting substances (SRS) in the mechanism of production of shocks by snake venoms.

Another kind of shock in which histamine appears to participate to a very important extent is the shock produced by *Ascaris*, in guinea-pigs and dogs. This kind of shock was studied by myself, with Graña, Porto and Andrade (in 1915-16), from the point of view of a release of histamine. It is enough to take a portion of a single worm, to macerate it in saline and inject into a 10 kg dog to produce an extremely severe shock, resembling in all details anaphylaxis in this species. For that reason we have called this shock an *Anaphylaxis-like* reaction, instead of using the common expression of *Anaphylactoid*. By that time, I thought that the phenomenon could be explained as true anaphylaxis, assuming that the dogs were probably sensitized to the *Ascaris* material. In agreement with this point of view, Beraldo and his colleagues, in 1961, have presented evidences that the effect of *Ascaris* in the guinea-pig appears to depend upon a real state of sensitization, probably as a consequence of infestation by *Nematoda* parasites, which are common in such animals.

I cannot dwell any longer upon this interesting aspect of the phenomenon, that once more established so close connections between Anaphylaxis and the envenomation by animal venoms.

In the preceding discussion we have mentioned mainly histamine as the principle released by snake venoms and *Ascaris* extracts.

It was, indeed, with this idea in mind that, in 1948, we started doing experiments to decide whether the venom of *Bothrops jararaca* produces its symptomatology in dogs, by releasing histamine from the liver. We were doing, with Beraldo, liver perfusions and have assayed the venom, brought to us by Rosenfeld, to see whether it releases histamine from dog’s liver. Since we had shown, in our previous experiments with *Ascaris* extracts, that the blood was important for the release of histamine, we perfused the liver with defibrinated blood to which the venom was added at the moment of the perfusion. The output was not histamine, but bradykinin and it became clear that the venom released this material from the globulin fraction and that besides the venom, also trypsin would release bradykinin. But, what was most important, the liver itself had nothing to do with the release of the new substance, and if we added the venom directly to the defibrinated blood or to the pseudo-globulin prepared from it, the same activity or even more, was released and could be demonstrated upon the isolated guinea-pig ileum, made insensitive to the venom by repeated previous additions of the same.

But here, again, we had a strong analogy between the action of trypsin, which was found to produce very strong anaphylactoid symptoms when given to dogs and rabbits, and the envenomation by snake venoms. Those who are present to this section of Pharmacology know very well, and some better than I, the conditions in which bradykinin is released by venoms and toxins. I will use the few minutes still left to discuss some of the pharmacological actions of bradykinin: as a vaso-dilator agent not only upon the systemic but also upon the coronary circulation, as a powerful stimulating substance upon the smooth muscle of the intestinal tract in certain animal species and the isolated uterus of many species tested, as the most powerful agent to produce increased capil-
lary (vascular) permeability and as a mediator of pain. Recently, I have assembled a "Bibliography on Bradykinin" which, though incomplete, covers around 900 items.

REFERENCES


2. ROCHA E SILVA, M., Symposium on Vaso-Active Polypeptides, Ribeirão Prêto, Aug. 2-4, 1966, A Bibliography on Bradykinin.