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Jan M Keppel Hesselink*

Institute for Neuropathic Pain, Bosch en Duin, Netherlands

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***Corresponding author:** Jan M Keppel Hesselink, Institute for Neuropathic Pain, Bosch en Duin, The Netherlands, Email: jan@neuropathie.nu

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Mini Review

Kambo: A ritualistic healing substance from an Amazonian frog and a source of new treatments

Abstract

Kambo is the name of a complex mixture of a number of bioactive peptides, secreted via the skin of a tropical frog, Phyllomedusa bicolor. Since centuries this secretion is harvested from the living animal by members of tribes living in the Amazonian forest, and applied to little wounds in the arms or legs, in order to enhance hunting skills.

Since some decades the use of this frog secretion has migrated to the West, is used in Kambo rituals and administered by Kambo practitioners to volunteers. The aim of the Kambo application is to heal or integrate, and sometimes to cure or lessen symptoms such as chronic pain, anxiety, depression, or chronic eczema. Apart from this ritualistic use, Kambo is identified as a source for leads for new treatments, from antibiotics up to analgesics.

We will briefly review the Kambo ritual and discuss three important neuropeptides from Kambo with analgesic properties.

Introduction

To find new medicines for chronic pain is not easy. Moreover, many drugs currently used, for instance in neuropathic pain, are just marginally effective, with high numbers needed to treat (NNT). Pregabalin is widely used as a first line treatment in neuropathic pain, but its NNT is 7.7, indicating that only few patients (1 out of 7.7) find sufficient pain relief [1].

There is a general agreement between pain specialist about the fact that there is still poor knowledge of the pathophysiology of neuropathic pain, and the best choice to be made for the treatment.

A related problem was very recently outlined by Professor Nadine Attal at a congress of the European Pain Federation (EFIC) on 'Unmet needs in Neuropathic Pain" (in Bergamo, 5-6 October 2018): as the quality of our clinical studies randomized clinical trials (RCT) increases, the effectiveness of the evaluated analgesics decreases. Therefore, at this EFIC meeting, a call was made to find new and therefore different test paradigms for pain outside of the classical RCT field, as well as to find new leads to treat patients suffering from chronic pain. Such new leads might be found in a special source: in the secretion of the skin of the Amazonian frog, Phyllomedusa bicolor.

This secretion contains a cocktail of compounds and is becoming more popular in certain ritualistic settings in the West, with the intention to heal and/or transform the user.

We will discuss Kambo and outline one family of compound in this secretion, which might have potential as new analgesic drugs, compounds called deltorphine, dermorphine and cerulein or ceruletide.

Kambo: secretion of an Amazonian frog

Kambô is the name for the secretion of the frog's skin, and the secretion is also known under different names, such as 'Campu', 'Acaté', 'Sapo' and 'Vacino da Floresta.'

Melchiorri and Negri discussed in 2009 some of the newly identified valuable painkilling compounds in the skin of certain Amazonian frogs [2]. They pointed out that Italian pharmacologists discovered these peptides in Amazonian frogs in the 80s of last century, but members of an Upper Amazonian tribe, the Matses, already knew of these pharmacological properties of the skin of this frog for a long time. They stated that for centuries the Matses had already used the dried skin secretions of a certain tree frog, Phyllomedusa bicolor, and they called that secretion Sapo, based on the Spanish word Sapo, meaning toad (but P.bicolor is not a toad, but a frog).

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Traditionally the dried secretion of the skin was and is used by various tribes in countries around the Amazon (especially by the Katukina, Kaxinawá, Matsés, Mayoruna and Yawanawá people). These tribes applied or apply Sapo via the administration of cuts or burns in the skin during shamanistic hunting rituals. The application lead to enhanced hunting skills, partly due to the opioid analgesic activity of the compounds deltorphin, dermorphin and cerulein, probably all acting synergistically with each other, and with other bioactive peptides present in Sapo. These other peptides have broad mechanisms of actions, mainly on the level of the cardiovascular and the gastrointestinal system. Some of these peptides are phyllocaerulein, phyllokinin, sauvagine and adenoregulin.

Kambo rituals have been coming to the West since the beginning of this century, and more and more users report positive health effect after its use [3]. After the collection of the frog slime, it is dried on a so called Kambo stick (Figure 1).

Kambo is removed from the stick, and diluted with some fluid, and subsequently applied to a fresh wound, mostly in the upper arm (male) or under leg (female), the wound is a blister created via a smoldering twig. The bioactive peptides quickly enter the lymphatic system and subsequently the blood. Within seconds to minutes the Kambo-user experiences symptoms, mostly starting with palpitations and feelings of a rush. Further effects vary from nausea, vomiting, diarrhea and dizziness to feeling like a God, mostly after the ritual. Also, symptoms like Quincke's edema around the eyes, lips or entire face may occur following the application of Kambô. Most if not all of the symptoms can be explained by the pharmacological properties of the peptides. The symptom complex quickly resolves, mostly within an hour. Side effects have been discussed in more detail in a different paper [3].

Clearly, many of the bioactive peptides in Kambo are quite promising sources for modern medicine. Interesting painkilling molecules in Kambo are the opioid receptor agonist deltorphin, dermorphin and cerulein. None of these molecules are comparable to the structure of opioids, as they all are peptides (Table 1).

Peptides in Kambo with morphinomimetic properties

In the secretion of the frog at least 3 bioactive peptides have been isolated, with clear painkilling properties. Two of these peptides activate he morphine-related opioid receptor, MOR, and one has high affinity for the delta-opioid receptor, DOR. In animal models, all these 3 molecules have analgesic properties; dermorphin and cerulein have also been tested in humans, both in healthy volunteers, as well as in patients, for instance suffering from cancer pain.

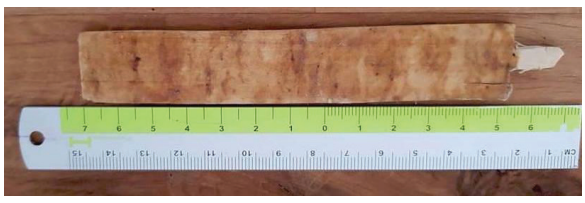

Figure 1: Kambo stick containing dried secretion of the frog.

Table 1: The peptide structures of dermorphin, cerulein and deltorphin, the chemical compositions.

Peptide	Structure	Chemical composition
Dermorphin	H-Tyr-D-Ala-Phe-Gly-Tyr-Pro-Ser-NH_2	$C_{40}H_{50}N_8O_{10}$
Cerulitide / cerulein	Pglu-Gln-Asp-Tyr[SO_3H]-Thr-Gly-Trp-Met-Asp-Phe-NH_2	$C_{58}H_{73}N_{13}O_{21}S_2$
Deltorphine	Tyr-D-Met-Phe-His-Leu-Met-Asp-NH_2	$C_{44}H_{62}N_{10}O_{10}S_2$

Dermorphin and cerulein have a high affinity for the MOR receptor. Both compounds have been evaluated in patients. Dermorphin displayed a very potent analgesic activity in rat models for pain, especially when given by intracerebroventricular injection. The ED 50 of the peptide in the tail-flick test was 23 pmol/rat [4]. Caerulein for a part (7 aminoacids) is identical to the cholecystokinin (CCK) octapeptide, and its affinity to the CCK receptor is in the same magnitude [5].

Caerulein and morphine intramuscularly applied were compared in 36 cancer patients [6]. Pain scores were documented via the 100 mm VAS scale. Patients should not have received any analgesics for at least 6 hours before the study. Pain scores were assessed after 15, 30 and 60 minutes, and 2, 3, 4 and 6 hours after administration. There was no statistical difference between the clinical response on morphine or cerulein. Around 30 minutes after injection pain reduction started, and it lasted between 4-5 hours. More patients treated with morphine complained of side effects, mostly nausea, vomiting, dizziness, sweating, dry mouth and cognitive impairment.

Dermorphin was evaluated in 150 postoperative patients intrathecally administered versus morphine versus a control arm [7]. Pain was scored during 5 days after operation on the 100 mm VAS scale. Dermorphin was significantly superior to morphine, and both where significantly better than the control arm. 88% of the control patients, 58% of the morphine patients and only 22% of the dermorphin patients required additional painkillers. The mean duration of postoperative analgesia was significantly longer in the dermorphin group when compared to both other groups. The mean postoperative hospital stay was significantly shorter in the dermorphin group compared to the control group. Dermorphine therefore displayed a very potent and long lasting analgesic activity and compared favorably to intrathecal morphine. Related to the mu (MOR) and delta (DOR), opioid receptors the following. The DOR is member of the opioid receptor family that has been under investigation with the aim to avoid classical morphine-induced side effects, which are mostly triggered by the MOR receptor. DOR agonists have mentioned to be non-addicting analgesic drugs [8]. Since that first suggestions many different DOR agonists have been developed, and some are already in phase II [9]. The deltorphins are a family of neuropeptides with a high affinity for the DOR receptor; deltorpin is selective δ-opioid receptor agonist (IC50 = 0.21 nM) [10-11]. Deltorphin B is also known as a positive

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modulator of morphine's analgesic effect: the mediation of this synergistic effect of morphine has been proved to be a result of stimulating the DOR receptors as this effect could be counteracted by a specific DOR antagonist [12]. Deltorphin though has not been tested yet in humans for its analgesic properties. Given the peptide structure, the most appropriate route of administration for all three neuroactive peptides from Kambo would be via an intrathecal infusion system [13].

Conclusion

Kambo is a very special mix of bioactive peptides. Its ritual use in the West since the beginning of our age is increasing. Users of Kambo report healing effects and sometimes explicite effects on symptoms, such as chronic pain. Kambo contains a great many interesting compounds, among which at least 3 peptides with painkilling activity. Especially dermorphin and cerulein might hold promise for future studies, since these peptides have already be tested for their efficacy and safety in patients. From the point of the anesthesiologist, the most suited indication would be intrathecal delivery of these two pepides in case of sever chronic cancer or postoperative pain.

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