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The Frog Prince – royalty or hallucination?

Poisons of the amphibian skin

Do you remember the old folk-tale about the ugly and slimy frog that turned into a handsome young prince when he was kissed by the pretty princess? The story lives on in many versions, and is certainly remembered by some. In the summer of the year 2002, when the Norwegian princess Märtha Louise (eldest daughter of King Harald V and Queen Sonja of Norway) was about to be married in Trondheim, she went through a "princess test" (together with several hundred not-yet-so-royal young girls). This test included lying on a pile of mattresses with a little pea underneath, to check the delicacy of her skin – just as in Hans Christian Andersen's fairytale (Andersen 1835), to try on the glass slipper in true Cinderella tradition and, not least, to kiss a frog. According to observers in Trondheim, not all the young princess candidates were too enthusiastic about the frog, but Märtha Louise did the right thing and got her loved one. Well, not a prince exactly, but that may not matter.

The folk-tale probably stems from the story about the Frog Prince derived from the Grimm brothers (Grimm & Grimm, 1812/1815). In this tale the rather cocky young princess loses her golden ball into the well, and the ball is retrieved by a slimy amphibian. In exchange for his services, the frog demands to be allowed to sleep in the princess's bed – no less – for the night. Although she originally agrees (to get her ball back), the story suggests rather deep lack of enthusiasm from the princess over this arrangement. However, her father, the wise old king, holds her to her promise to the frog. In the end, as you may expect, the slimy frog turns into a handsome young prince. In the original tale this happens after the princess hurls him into the wall, but anyway. And so they lived happily ever after.

So, where is the kiss in all this? Certainly, the moralistic society following on the period when Grimm's story was first written down couldn't be expected to endorse the keeping of young men, royal or otherwise, in young girls' beds. Therefore, it might have been a wise move to transfer the story out of the bedroom and onto the road – no hanky-panky – although a sisterly kiss may be required for the magic to work.

The toad, *Bufo bufo*.

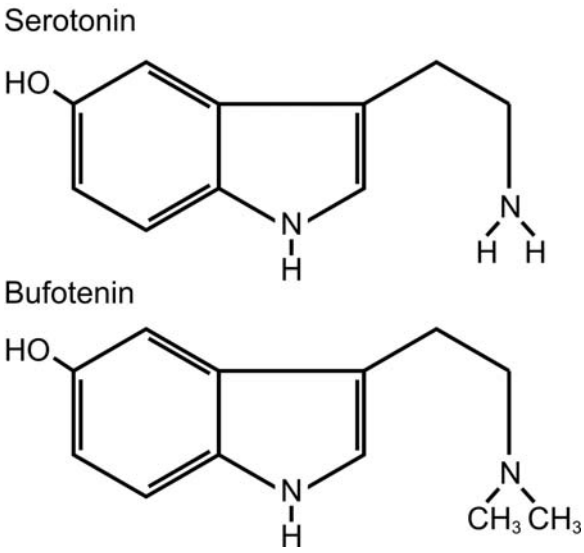
So, that leaves us with the princess walking one day along the road. Deeply dissatisfied, no doubt, with her suitors thus far, and longing in her heart for the True Love in the shape of the proverbial Handsome Prince in dainty tights. Instead, she finds in the middle of the road an ugly frog that stares at her. (Now, please note: personally I don't think that frogs are ugly at all. This is just part of the build-up before The Kiss). The frog says: "Please, beautiful princess, give me a kiss to release the evil spell that turned me from a handsome young prince into the shape of this nasty frog". So, the princess – without hesitation (just like Märtha Louise) – kisses the frog, which promptly turns into the promised royal human shape. And so they lived happily ever after.

Now, all this is of course magic. Outside the realms of Science, wouldn't you say? Well, maybe not quite. Frog skin contains a multitude of very potent chemicals, many of which also act in the transfer of nerve signals in the brain and gut of frogs as well as humans. Some of these compounds are peptides, named in fact after the frog species where they were first demonstrated (bombesin from the frog *Bombina*, litorin from *Litoria*, ranatensin from *Rana*, and so on). I don't know any princesses personally and therefore have no first-hand information regarding their relationship with frogs. Also, it seems likely that quite a bit

of serious licking would be required to ingest enough peptides to even feel light nausea. Let alone turn frogs into princes. No, it seems unlikely indeed that it was a frog that the princess kissed.

However, might it not be possible that our princess was a bit behind on her zoology lessons? Couldn't she mistakenly have classified the ugly amphibian as a frog, while it was in fact an equally repulsive (to the princess) toad?

Toads, belonging to the family Bufonidae, produce skin secretions that are quite toxic. Every year the cane toad, *Bufo marinus*, and some of its toady relatives kill a fair number of dogs and cats that bite into the toxic skin and don't give up fast enough despite the bitter taste. A major group of compounds in the toad skin is the bufotenins, named bufotenin, bufotenidin and bufoviridin.



The detailed mechanisms of action are not well known, but there is a structural relationship between the bufotenins and both serotonin, a neurotransmitter in the central nervous system, and the well-known hallucinogen lysergic acid diethylamide (LSD-25). So, if the princess kissed a toad and not a frog, could it be that the fine-looking young prince was a simple hallucinated figment of her imagination? Maybe but it could have been worse. There are some amphibians with skin secretion toxic enough to poison arrows/darts for hunting with blowpipes (Edström, 1992).

First, a note about blowpipes and poisoned darts. East of the Andes, the poison used for the darts is curare (d-tubocurarin). This is a plant poison prepared from the South American vine *Chondodendron tomentosum*, and is used in a fashion similar to the frog secretions to make poison darts for hunting and warfare. Curare acts by blocking the nicotinic cholinoceptors of the neuromuscular transmission,

rendering the victim immobile and, of course, also incapable of breathing (see below).

Dart-poison frogs of the genera *Phyllobates* ("leaf climber") and *Dendrobates* ("tree climber") live in the (fertile) lush rainforest of northern South America, west of the Andes. These are very pretty little creatures; I believe even the princess of the folk-tale is likely to have agreed. Only a few centimetres long, and with striking colouration, they inhabit the forest canopy where they enthusiastically add to the racket of the tropical night. Their skin secretion is exceptionally toxic, and darts are poisoned by being rubbed against the skin of the frog.

When preparing their darts, the locals are careful not to touch the frog. It has been assumed that the presence of very potent toxins prevents infections by microorganisms of the animal's moist skin (*cf.* Edström, 1992). Also, a predator that tries to taste the extremely

Pilgiftsgroda, *Phyllobates terribilis*

bitter-tasting little frog (and survives!) is unlikely to try again.

The active compounds in the skin of *Phyllobates* species are known as batrachotoxins (batrachos is the Greek word for “frog”). These are complex alkaloids, a group of substances much more prevalent in plants than in animals. It could be noted that poison-dart frogs bred in captivity do not become toxic, suggesting that – indeed – a plant precursor may be essential for the formation of the toxic compounds. The molecular structure of the batrachotoxins somewhat resemble that of steroid hormones, and they act by inhibiting the inactivation of the sodium channel in neurons as well as muscle cells (see later), causing a prolonged, even irreversible, depolarisation (Edström, 1992). This leads to the disruption of nerve function, and also to heart arrhythmia. Another group of frog poisons are the pumiliotoxins. Somewhat simpler and less lethal, these act by enhancing the availability of intramuscular calcium ions released after stimulation. This could produce cramps and convulsions, but most definitely not the creation of any prince.

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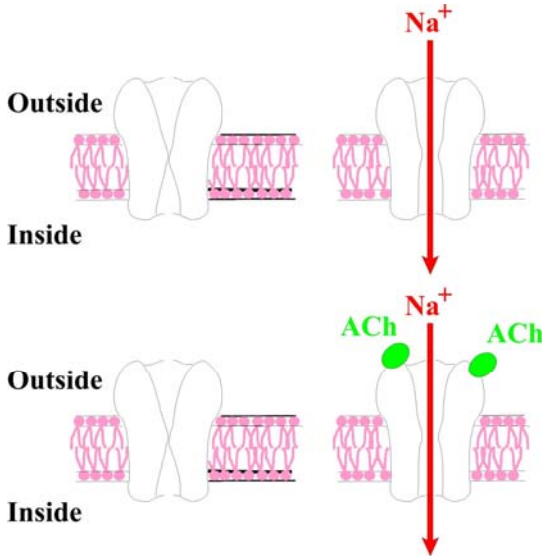
Photos: *Bufo bufo*; Stefan Nilsson; *Phyllobates terribilis*; Claes Andrén.

On receptors and ion channels

A number of toxins of plant or animal origin can affect the function of the (Figure 4) nervous system. These substances are known as neurotoxins. Nerve impulses, or action potentials, rely on exchange of ions such as sodium (Na+) over the nerve cell membrane. If the voltage gradient between the inside and outside of the cell membrane changes due to some kind of stimulation, trans-membrane channels called "voltage-gated sodium channels" will open, and a nerve impulse occurs due to influx of the positively charged sodium ions (top pair of figures). The channel needs to close quickly, to prepare itself for the next impulse to be generated in due course. If the channels are kept open, e.g., due to the action of a neurotoxin such as the batrachotoxins mentioned, the neurons cease to function properly.



Some receptors for neurotransmitters may also trigger the opening of other sodium channels ("ligand-gated sodium channels"), eventually generating action potentials (lower pair of figures). Acetylcholine (ACh) is an example of a neurotransmitter substance that stimulates receptors in neurons and skeletal muscle fibres. In the presence of curare, acetylcholine is blocked from binding to its receptors, causing paralysis of the body muscles.

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