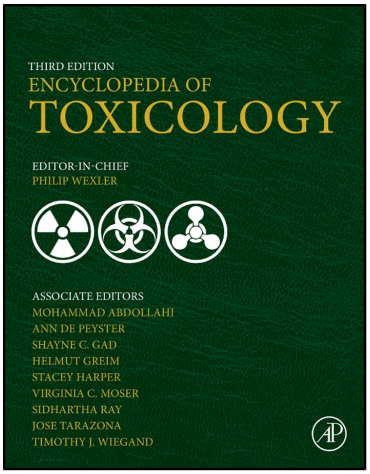

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Bases *see* Alkalies

Batrachotoxin

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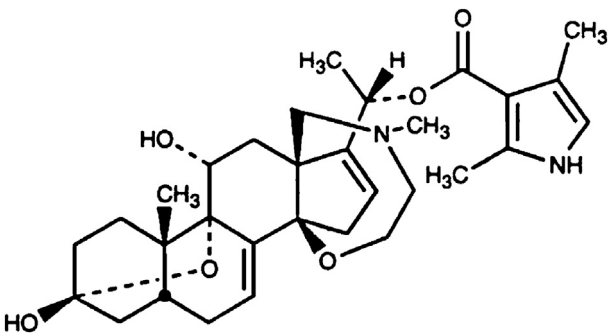
- Representative Chemicals: Batrachotoxin; Homobatrachotoxin; Batrachotoxinin-A; and several other batrachotoxinin-A congeners
- Chemical Abstracts Service Registry Number: CAS 23509-16-2 (Batrachotoxin)
- Synonyms: *Phyllobates* toxin, *Pitohui* toxin, *Ifrita* toxin, and poison dart frog toxin
- Chemical/Pharmaceutical/Other Class: Steroidal alkaloid neurotoxin
- Molecular Formulas:
  - Batrachotoxin: $C_{31}H_{42}N_2O_6$
  - Homobatrachotoxin: $C_{32}H_{44}N_2O_6$
  - Batrachotoxinin-A: $C_{24}H_{35}NO_5$
- Chemical Structure:



Background

Batrachotoxins are a class of steroidal alkaloid neurotoxins originally found in Colombian poison dart frogs of the genus *Phyllobates* (family Dendrobatidae). The frogs have special skin glands that store and secrete the toxins, and these glands are most densely packed on the frog's back behind the head. Evidence suggests that the frogs acquire the toxins from a dietary source; however, no potential source of these frog poisons has been identified. Of all of the so-called poison dart frogs, only three species of poison dart frogs were actually used by Native Americans for poisoning dart tips, and these 'true poison dart frogs' were all members of the genus *Phyllobates* that carry batrachotoxins as their major toxic element responsible for poisoning. More recently, batrachotoxins were found in New Guinean birds of the genus *Pitohui* and *Ifrita*. In birds, the toxins are most concentrated in the skins and feathers.

In both birds and frogs, batrachotoxins are thought to provide some protection against natural enemies. The most toxic *Phyllobates* frogs are brightly colored in comparison to other congeners, and the same is true for the most toxic *Pitohui* species. It is presumed that the bright colors act as warning or aposematic signal to visual predators. Limited experiments have shown that the toxins may be an arthropod repellent and reduce the life span of arthropod pests such as lice, and that natural predators show aversive reactions to the these toxins.

Several naturally occurring batrachotoxins have been identified from frog and bird extracts. The most common are batrachotoxin and homobatrachotoxin, which contain a pyrrole moiety. These occur in frogs in roughly equal proportions and have an LD_{50} in mice of $\sim$2 to 3 $\mu g\,kg^{-1}$ (subcutaneous injection). Toxicity via other routes has not been well studied. The pyrrole can be manipulated in nature and in the laboratory to give the non-pyrrole form, called batrachotoxinin-A, which is about 1/500th as toxic as batrachotoxin or homobatrachotoxin. Several other congeners have been identified in nature, but the pharmacology of most of these remains unstudied. These include batrachotoxinin-A *cis*-crotonate, an allylically rearranged 16-acetate, batrachotoxinin-A 3-hydroxypentanoate, and multiple mono- and dihydroxylated derivatives.

Experiments suggest that both birds and frogs may sequester toxins from dietary sources. When brought into captivity, frogs slowly loose their toxicity, and when raised in captivity on nontoxic diets, frogs fail to produce batrachotoxins. When fed batrachotoxins in their diet, frogs readily accumulate the toxins in their skin. Although it is widely believed that ants may be the source of toxins for dendrobatid frogs, this has yet to be demonstrated for batrachotoxins in *Phyllobates* frogs. Although other frog poisons have been found in ants, no ant species has yet been found to contain batrachotoxins, and ants represent a smaller portion of the overall diet for the larger *Phyllobates* frogs than for the smaller dendrobatid frog species. In New Guinea, a small beetle (genus *Choresine*, family Melyridae) has been shown to carry significant quantities of batrachotoxins and also been shown to be eaten by toxic *Pitohui* birds. Thus, *Choresine* beetles represent a putative source of dietary toxins for the New Guinea birds. Recently, several other dendrobatid frog toxins have been found in soil mites in the family Oribatidae, and these represent a potential ultimate source of these toxins for frogs, beetles, and birds.

Toxin Uses

Batrachotoxin is an important research tool in pharmacology because of its action of holding voltage-gated sodium channels open as well as its specific effects at other ligand-binding sites. It was commonly used in ion channel and ligand research.

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Batrachotoxin has no current clinical uses for two primary reasons. First, batrachotoxin is highly toxic and dangerous to use for medical purposes. Synthetic forms with altered properties would have to be developed for clinical trials. Second, there are no commercially available sources of batrachotoxins or commercially viable synthetic pathways. Most available stocks of batrachotoxin were collected from wild-caught *Phyllobates* frogs by John Daly many years ago. Work in relevant regions of Colombia is currently difficult or impossible, so these stocks cannot be replenished. No commercially viable sources of batrachotoxin are known from New Guinea, but additional research on the ultimate source of batrachotoxins may elucidate new sources.

Human Use of Frog and Bird Secretions Containing Batrachotoxins

Very small amounts of frog secretions from *Phyllobates terribilis*, *P. bicolor*, and *P. aurotaenia* have been used by Choco and Embera Indians to poison dart tips. These poisoned darts are reportedly effective at immobilizing a variety of animals including jaguar, bear, deer, and humans. A single *P. bicolor* or *P. terribili*s frog can effectively poison 20–30 darts. Frog toxin levels are high enough that merely holding the frogs can be dangerous, and human poisonings have been reported.

In New Guinea, traditional hunters are aware that *Pitohui* and *Ifrita* birds carry neurotoxins. Toxins are more diffuse in these birds than in the frogs; however, in some populations, even a single feather, if tasted, can cause a burning sensation in the mouth that may last for several minutes to hours. Handling the birds can cause allergy-like reactions such as itchy watery eyes, running nose, and sneezing. There have been no known human deaths or serious poisonings due to bird ingestion, as it is generally recognized as inedible, and an unpleasant burning sensation sets in before much of the toxin is ingested. No anthropologists have reported local New Guineans using the toxins to immobilize prey, but bird tissues are used in some local medicinal concoctions.

Exposure Routes and Pathways

From *Phyllobates* frogs, exposure occurs through ingesting skin and flesh of the frogs. Toxin quantities can be high enough to make even handling these frogs dangerous, so presumably some absorption can occur through skin. Exposure to the toxins may occur by subcutaneous injection, such as a puncture from a poisoned dart tip. From birds, exposure can occur by eating flesh; however, even handling the birds can cause local irritation and 'allergic-like' reactions such as itchy eyes, runny nose, sneezing, and tingling around buccal membranes. These latter reactions are believed to be caused by powder or tiny feather fragments released from toxic feathers. Batrachotoxins are lipid soluble and soluble in a variety of organic solvents such as methanol, chloroform, and ethanol.

Toxicokinetics

Batrachotoxin can be absorbed through skin as well as from the gastrointestinal tract. Effects can occur within 10 min and can last for several hours to more than a day.

Mechanism of Action and Toxicity

Batrachotoxins bind specifically to voltage-gated sodium channels in nerve and muscle membranes and significantly alter channel function in four primary ways that have been documented. First, batrachotoxin significantly shifts the activation gating 30–50 mV toward hyperpolarization. Thus a batrachotoxin-bound channel will activate more readily, even at membrane resting potentials. Second, batrachotoxin eliminates or reduces both fast and slow inactivation gating, which holds the activated channels in the open conformation for hours or longer. Third, batrachotoxin can reduce single channel conductance by up to 50%. And fourth, batrachotoxin can alter the ion selectivity of the voltage-gated sodium channel.

In short, batrachotoxins activate voltage-gated sodium channels and stabilize the channel in its open conformation. This allows sodium ions to flow freely across the membrane and depolarize membrane. This causes local tingling, irritation, and numbness in peripheral nervous tissue. In higher concentrations or systemic doses, batrachotoxin will cause convulsions, paralysis, and cardiac or pulmonary failure. Because a relatively small proportion of activated channels can depolarize the membrane, batrachotoxins are highly toxic. Because batrachotoxins bind strongly to sodium channel proteins, binding is often referred to as 'irreversible,' although light exposure (resulting in local tingling or numbness) generally subsides within a few minutes to 24 h.

Acute and Short-Term Toxicity (or Exposure)

Human

Very little is known about the toxicity of batrachotoxins in humans. If it is assumed that human and mouse toxicity are roughly equivalent (at $\sim 2.5\ \mu g\ kg^{-1}$ injected subcutaneously), then a median lethal dose for a 68-kg human would be ~170 μg of batrachotoxin. Other studies show that mice are less susceptible to neurotoxins than humans, so another estimate can be based on toxicity relationships of batrachotoxin to aconitine, digitoxin, and strychnine and their toxicity in humans. Using these relationships, it is expected that a dose as small as 2–10 μg of purified batrachotoxin injected subcutaneously may be lethal to humans. Likewise, ingested amounts of as little as 120–500 μg are expected to be lethal. These are certainly rough estimates, and few, if any, human poisonings have been reported in medical literature. However, purified toxins as well as frog skin secretions should be handled with extreme care.

Only direct toxic effects on voltage-gated sodium channels have been studied. Other mechanisms of toxicity (e.g., chronic toxicity, immunotoxicity, genotoxicity, carcinogenicity, etc.) have not been investigated.

Clinical Management

No antidote is available.

See also: Animals, Poisonous and Venomous.

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