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A0005

Homobatrachotoxin

John P Dumbacher

P0005 • Representative Chemicals: Batrachotoxin; Homobatrachotoxin; Batrachotoxinin A; and several other batrachotoxinin A congeners

P0010 • Chemical Abstracts Service Registry Number: CAS 23509-16-2 (Batrachotoxin)

P0015 • Synonyms: *Phyllobates* toxin; *Pitohui* toxin; *Ifrita* toxin; poison dart frog toxin

P0020 • Chemical/Pharmaceutical/Other Class: Steroidal alkaloid neurotoxin

P0025 • Molecular Formulas:

P0030 Batrachotoxin: $C_{31}H_{42}N_2O_6$

P0035 Homobatrachotoxin: $C_{32}H_{44}N_2O_6$

P0040 Batrachotoxinin-A: $C_{24}H_{35}NO_5$

S0005

Background Information

P0045 Batrachotoxins are a class of steroidal alkaloid neurotoxins 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 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. Interestingly, of all of the so-called poison dart frogs, only three species of *Phyllobates* were actually used by Native Americans for poisoning dart tips, and the major toxic element responsible for poisoning are the batrachotoxins. More recently, identical toxins were found in New Guinean birds in the genus *Pitohui* (family Pachycephalidae) and *Ifrita* (family Cinclosomatidae). The toxins are most concentrated in the skins and feathers of birds.

P0050 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 and LD_{50} in mice of approximately 2–3 $\mu g\,kg^{-1}$ (subcutaneous injection). Toxicity via other routes has not been well studied. The pyrrole can be manipulated in nature and in the lab to give the non-pyrrole form, called batrachotoxinin-A, which is approximately 1/500th as toxic as batrachotoxin or homobatrachotoxin. Several other congeners have been identified in nature, but the pharmacology of many of these remains unstudied.

S0010

Exposure Routes and Pathways

P0055 From *Phyllobates* frogs, exposure occurs through ingesting skin and flesh of the frogs. Toxin quantities can be high enough that even handling these frogs can be 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 'allergic' like reactions such as itchy eyes, runny nose, sneezing, and tingling around buccal membranes. These 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.

S0015

Toxicokinetics

P0060 Batrachotoxin can be absorbed through skin as well as from the gastrointestinal tract. Effects can occur within 10 minutes and can last for several hours to more than a day.

S0020

Mechanism of Toxicity

P0065 Batrachotoxins bind specifically to voltage-gated sodium channels in nerve and muscle membranes. Once activated, bound batrachotoxins stabilize the channel in its open conformation. This allows sodium ions to flow freely across the membrane, and depolarizes the membrane, causing local tingling, irritation, and numbness, and in higher concentrations can cause convulsions, paralysis, and cardiac or pulmonary failure. Because a relatively small proportion of activated channels can depolarize the membrane, batrachotoxins are highly toxic. Batrachotoxins bind strongly to sodium channel proteins, so 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.

S0025

Acute and Short-Term Toxicity (or Exposure)

S0030

Human

P0070 Very little is known about toxicity of batrachotoxins in humans. If we assume that human and mouse

toxicity are equivalent (at about 2.5 μg kg^{-1} subcutaneously), then a median lethal dose for a 68 kg human would be about 170 μg of batrachotoxin. Other studies show that mice are less susceptible to neurotoxins than humans, so another estimate can be based upon 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 the medical literature. This is an important cautionary note, however, as purified toxins as well as frog skin secretions should be handled with extreme care.

S0035 **Human Use of Frog Secretions Containing Batrachotoxins**

P0075 Very small amounts of frog secretions from *Phyllobates terribilis*, *P. bicolor*, and *P. aurotanea* can be used to poison dart tips, which are reportedly effective at immobilizing a variety of animals including jaguar, bear, deer, and humans. A single *P. bicolor* or *P. terribilis* can effectively poison 20–30 darts.

S0040 **Human Knowledge of *Pitohui* and *Ifrita* Birds Containing Batrachotoxins**

P0080 In New Guinea, traditional hunters are aware that *Pitohui* and *Ifrita* birds carry neurotoxins. Local names for these birds often reflect the fact that they are bitter or contain burning chemicals. Toxins in these birds are more diffuse than in the frogs, but even a single feather, if tasted, can cause an acute burning sensation that may last for several minutes to hours. Handling the birds can cause allergic-like reactions such as itchy watery eyes, running nose, and sneezing. I know of no 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 eaten. No anthropologists have reported local New Guineans using the toxins to immobilize prey.

S0045 *In-Vitro* Toxicity Data

P0085 Batrachotoxin is an important research tool because of its action holding voltage-gated sodium channels open as well as its specific effects at other ligand-binding sites. It was previously commonly used in research channel and ligand research. There are no commercially-available stocks of batrachotoxins, however, and work in Colombia is currently difficult or impossible, so these chemicals are used less and less frequently in research.

Clinical Management S0050

No antidote is available. P0090

See also: Animals, Poisonous and Venomous (00075). AU:1

Further Reading

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