Ricin

Not to be confused with raisin.

Ricin /ˈraɪsɪn/ is a highly toxic, naturally occurring lectin (a carbohydrate-binding protein) produced in the seeds of the castor oil plant, *Ricinus communis*. A dose of purified ricin powder the size of a few grains of table salt can kill an adult human.[1] The median lethal dose (LD_{50}) of ricin is around 22 micrograms per kilogram of body weight (1.78 milligram for an average adult). For comparison, a standard acetaminophen (Tylenol) tablet contains 500 mg of acetaminophen and a low dose aspirin contains 81 mg of aspirin.[2] Oral exposure to ricin is far less toxic, and an estimated lethal dose in humans is approximately 1 milligram per kilogram.[2]

1 Toxicity

Castor beans

Ricin is very poisonous if inhaled, injected, or ingested. It acts as a toxin by inhibiting protein synthesis.[3] It prevents cells from assembling various amino acids into proteins according to the messages it receives from messenger RNA in a process conducted by the cell's ribosome (the protein-making machinery)—that is, the most basic level of cell metabolism, essential to all living cells and thus to life itself. Ricin is resistant, but not impervious, to digestion by peptidases. By ingestion, the pathology of ricin is largely restricted to the gastrointestinal tract, where it may cause mucosal injuries. With appropriate treatment, most patients will make a full recovery.[4][5]

Because the symptoms are caused by failure to make protein, they emerge only after a variable delay from a few hours to a full day after exposure. An antidote has been developed by the UK military, although it has not yet been tested on humans.[6][7] Another antidote developed by the U.S. military has been shown to be safe and effective in lab mice injected with antibody-rich blood mixed with ricin, and has had some human testing.[8] Symptomatic and supportive treatments are available. Survivors often develop long-term organ damage. Ricin causes severe diarrhea, and victims can die of circulatory shock. Death typically occurs within 3–5 days of exposure.[9]

The seeds can be crushed in an oil press to extract castor oil. This leaves behind the spent crushed seeds, called variously the "cake", "oil cake", and "press cake". While the oil cake from coconut, peanuts, and sometimes cotton seeds can be used as either cattle feed and/or fertilizer, the toxic nature of castor precludes them from being used as feed unless the ricin is first deactivated by autoclaving.[10] Accidental ingestion of *Ricinus communis* cake to be used as fertilizer has been reported to be responsible for fatal ricin poisoning in animals.[3][11]

Deaths from ingesting castor plant seeds are rare, partly because of their indigestible capsule, and because the body can, although only with difficulty, digest ricin.[12] The pulp from eight beans is considered dangerous to an adult.[13] Rauber and Heard have written that close examination of early 20th century case reports indicates that public and professional perceptions of ricin toxicity "do not accurately reflect the capabilities of modern medical management".[14]

1.1 Overdose

Most acute poisoning episodes in humans are the result of oral ingestion of castor beans, 5–20 of which could prove fatal to an adult. However, there was one case of a 37-year-old female ingesting 30 beans in the United States in 2013 who survived.[15] Victims often manifest nausea, diarrhea, tachycardia, hypotension, and seizures persisting for up to a week.[3] Blood, plasma, or urine ricin or ricinine concentrations may be measured to confirm diagnosis. The laboratory testing usually involves immunoassay or liquid chromatography-mass spectrometry.[16]

2 Biochemistry

Ricin is classified as a type 2 ribosome-inactivating protein (RIP). Whereas type 1 RIPs are composed of a single protein chain that possesses catalytic activity, type 2 RIPs, also known as holotoxins, are composed of two different protein chains that form a heterodimeric complex. Type 2 RIPs consist of an A chain that is functionally equivalent to a type 1 RIP, covalently connected by a single disulfide bond to a B chain that is catalytically inactive, but serves to mediate transport of the A-B protein complex from the cell surface, via vesicle carriers, to the lumen of the endoplasmic reticulum (ER). Both type 1 and type 2 RIPs are functionally active against ribosomes *in vitro*, however only type 2 RIPs display cytoxicity due to the lectin-like properties of the B chain. In order to display its ribosome-inactivating function, the ricin disulfide bond must be reductively cleaved.[17]

2.1 Biosynthesis

Ricin is synthesized in the endosperm of castor oil plant seeds.[18] The ricin precursor protein is 576 amino acid residues in length and contains a signal peptide (residues 1–35), the ricin A chain (36–302), a linker peptide (303–314), and the ricin B chain (315–576).[19] The N-terminal signal sequence delivers the prepropolypeptide to the endoplasmic reticulum (ER) and then the signal peptide is cleaved off. Within the lumen of the ER the propolypeptide is glycosylated and a protein disulfide isomerase catalyzes disulfide bond formation between cysteines 294 and 318. The propolypeptide is further glycosylated within the Golgi apparatus and transported to protein storage bodies. The propolypeptide is cleaved within protein bodies by an endopeptidase to produce the mature ricin protein that is composed of a 267 residue A chain and a 262 residue B chain that are covalently linked by a single disulfide bond.[18]

2.2 Structure

The quaternary structure of ricin is a globular, glycosylated heterodimer of approximately 60–65 kDa.[12] Ricin toxin A chain and ricin toxin B chain are of similar molecular weights, approximately 32 kDa and 34 kDa, respectively.

- **Ricin A chain** (RTA) is an N-glycoside hydrolase composed of 267 amino acids.[20] It has three structural domains with approximately 50% of the polypeptide arranged into alpha-helices and beta-sheets.[21] The three domains form a pronounced cleft that is the active site of RTA.
- **Ricin B chain** (RTB) is a lectin composed of 262 amino acids that is able to bind terminal galactose residues on cell surfaces.[22] RTB forms a bilobal, barbell-like structure lacking alpha-helices or beta-sheets where individual lobes contain three subdomains. At least one of these three subdomains in each homologous lobe possesses a sugar-binding pocket that gives RTB its functional character.

Many plants such as barley have the A chain but not the B chain. People do not get sick from eating large amounts of such foods, as ricin A is of extremely low toxicity as long as the B chain is not present.

2.3 Entry into the cytoplasm

Ricin B chain binds complex carbohydrates on the surface of eukaryotic cells containing either terminal N-acetylgalactosamine or beta-1,4-linked galactose residues. In addition, the mannose-type glycans of ricin are able to bind cells that express mannose receptors.[23] RTB has been shown to bind to the cell surface on the order of $10^6 - 10^8$ ricin molecules per cell surface.[24]

The profuse binding of ricin to surface membranes allows internalization with all types of membrane invaginations. The holotoxin can be taken up by clathrin-coated pits, as well as by clathrin-independent pathways including caveolae and macropinocytosis.[25][26] Intracellular vesicles shuttle ricin to endosomes that are delivered to the Golgi apparatus. The active acidification of endosomes is thought to have little effect on the functional properties of ricin. Because ricin is stable over a wide pH range, degradation in endosomes or lysosomes offers little or no protection against ricin.[27] Ricin molecules are thought to follow retrograde transport via early endosomes, the trans-Golgi network, and the Golgi to enter the lumen of the endoplasmic reticulum (ER).[28]

For ricin to function cytotoxically, RTA must be reductively cleaved from RTB in order to release a steric block of the RTA active site. This process is catalysed by the protein PDI (protein disulphide isomerase) that resides in the lumen of the ER.[29][30] Free RTA in the ER lumen then partially unfolds and partially buries into the ER membrane, where it is thought to mimic a misfolded membrane-associated protein.[31] Roles for the ER chaperones GRP94,[32] EDEM[33] and BiP[34] have been proposed prior to the 'dislocation' of RTA from the ER lumen to the cytosol in a manner that utilizes components of the endoplasmic reticulum-associated protein degradation (ERAD) pathway. ERAD normally removes misfolded ER proteins to the cytosol for their destruction by cytosolic proteasomes. Dislocation of RTA requires ER membrane-integral E3 ubiquitin ligase complexes,[35] but RTA avoids the ubiquitination that usually occurs with ERAD substrates because of its low content of lysine residues, which are the usual attachment sites for ubiquitin.[36] Thus, RTA avoids the usual fate of dislocated proteins (destruction that is mediated by targeting ubiquitinylated proteins to the cytosolic proteasomes). In the mammalian cell cytosol, RTA then undergoes

triage by the cytosolic molecular chaperones Hsc70 and Hsp90 and their co-chaperones, as well as by one subunit (RPT5) of the proteasome itself, that results in its folding to a catalytic conformation,[32][37] which de-purinates ribosomes, thus halting protein synthesis.

2.4 Ribosome inactivation

RTA has rRNA N-glycosylase activity that is responsible for the cleavage of a glycosidic bond within the large rRNA of the 60S subunit of eukaryotic ribosomes.[38] RTA specifically and irreversibly hydrolyses the N-glycosidic bond of the adenine residue at position 4324 (A4324) within the 28S rRNA, but leaves the phosphodiester backbone of the RNA intact.[39] The ricin targets A4324 that is contained in a highly conserved sequence of 12 nucleotides universally found in eukaryotic ribosomes. The sequence, 5'-AGUACGAGAGGA-3', termed the sarcin-ricin loop, is important in binding elongation factors during protein synthesis.[40] The depurination event rapidly and completely inactivates the ribosome, resulting in toxicity from inhibited protein synthesis. A single RTA molecule in the cytosol is capable of depurinating approximately 1500 ribosomes per minute.

2.5 Depurination reaction

Within the active site of RTA, there exist several invariant amino acid residues involved in the depurination of ribosomal RNA.[27] Although the exact mechanism of the event is unknown, key amino acid residues identified include tyrosine at positions 80 and 123, glutamic acid at position 177, and arginine at position 180. In particular, Arg180 and Glu177 have been shown to be involved in the catalytic mechanism, and not substrate binding, with enzyme kinetic studies involving RTA mutants. The model proposed by Mozingo and Robertus,[21] based on X-ray structures, is as follows:

1. Sarcin-ricin loop substrate binds RTA active site with target adenine stacking against tyr80 and tyr123.
2. Arg180 is positioned such that it can protonate N-3 of adenine and break the bond between N-9 of the adenine ring and C-1' of the ribose.
3. Bond cleavage results in an oxycarbonium ion on the ribose, stabilized by Glu177.
4. N-3 protonation of adenine by Arg180 allows deprotonation of a nearby water molecule.
5. Resulting hydroxyl attacks ribose carbonium ion.
6. Depurination of adenine results in a neutral ribose on an intact phosphodiester RNA backbone.

3 Therapeutic applications

Although no approved therapeutics are currently based on ricin, it does have the potential to be used in the treatment of tumors, as a so-called "magic bullet" to destroy targeted cells.[27] Because ricin is a protein, it can be linked to a monoclonal antibody to target malignant cells recognized by the antibody. The major problem with ricin is that its native internalization sequences are distributed throughout the protein. If any of these native internalization sequences are present in a therapeutic agent then the drug will be internalized by, and kill, untargeted non-tumorous cells as well as targeted malignant cells.

Modifying ricin may sufficiently lessen the likelihood that the ricin component of these immunotoxins will cause the wrong cells to internalize it, while still retaining its cell-killing activity when it is internalized by the targeted cells. However, bacterial toxins, such as diphtheria toxin, which is used in denileukin diftitox, an FDA-approved treatment for leukemia and lymphoma, have proven to be more practical. A promising approach for ricin is to use the non-toxic B subunit (a lectin) as a vehicle for delivering antigens into cells, thus greatly increasing their immunogenicity. Use of ricin as an adjuvant has potential implications for developing mucosal vaccines.

4 Regulation

In the U.S., ricin appears on the select agents list of the Department of Health and Human Services,[41] and scientists must register with HHS to use ricin in their research. However, investigators possessing less than 100 mg are exempt from regulation.[42]

5 Chemical or biological warfare agent

A metal vial containing ricin from the 2003 ricin letters

The United States investigated ricin for its military po-

tential during World War I.[43] At that time it was being considered for use either as a toxic dust or as a coating for bullets and shrapnel. The dust cloud concept could not be adequately developed, and the coated bullet/shrapnel concept would violate the Hague Convention of 1899 (adopted in U.S. law at 32 Stat. 1903), specifically Annex §2, Ch.1, Article 23, stating "... it is especially prohibited ... [t]o employ poison or poisoned arms".[44] World War I ended before the United States weaponized ricin.

During World War II the United States and Canada undertook studying ricin in cluster bombs.[45] Though there were plans for mass production and several field trials with different bomblet concepts, the end conclusion was that it was no more economical than using phosgene. This conclusion was based on comparison of the final weapons, rather than ricin's toxicity (LCt_{50} ~40 mg·min/m^3). Ricin was given the military symbol **W** or later **WA**. Interest in it continued for a short period after World War II, but soon subsided when the U.S. Army Chemical Corps began a program to weaponize sarin.

The Soviet Union also possessed weaponized ricin. There were speculations that the KGB used it outside the Soviet bloc, however this was never proven.

Given ricin's extreme toxicity and utility as an agent of chemical/biological warfare, it is noteworthy that the production of the toxin is rather difficult to limit. The castor bean plant from which ricin is derived is a common ornamental and can be grown at home without any special care.

Under both the 1972 Biological Weapons Convention and the 1997 Chemical Weapons Convention, ricin is listed as a schedule 1 controlled substance. Despite this, more than 1 million tonnes of castor beans are processed each year, and approximately 5% of the total is rendered into a waste containing negligible concentrations of undenatured ricin toxin.[46]

Ricin is several orders of magnitude less toxic than botulinum or tetanus toxin, but the latter are harder to come by. Compared to botulinum or anthrax as biological weapons or chemical weapons, the quantity of ricin required to achieve LD_{50} over a large geographic area is significantly more than an agent such as anthrax (tons of ricin vs. only kilogram quantities of anthrax).[47] Ricin is easy to produce, but is not as practical or likely to cause as many casualties as other agents.[4] Ricin is inactivated (the protein changes structure and becomes less dangerous) much more readily than anthrax spores, which may remain lethal for decades. Jan van Aken, a German expert on biological weapons, explained in a report for The Sunshine Project that Al Qaeda's experiments with ricin suggest their inability to produce botulinum or anthrax.[48]

6 Developments

A biopharmaceutical company called Soligenix, Inc. has licensed an anti-ricin vaccine called RiVax™ from Vitetta et al. at UT Southwestern. The vaccine is safe and immunogenic in mice, rabbits, and humans. It has completed two successful clinical trials.[49]

7 Incidents

Main article: Incidents involving ricin

Ricin has been involved in a number of incidents. In 1978, the Bulgarian dissident Georgi Markov was assassinated by Bulgarian secret police who surreptitiously shot him on a London street with a modified umbrella using compressed gas to fire a tiny pellet contaminated with ricin into his leg.[4][50] He died in a hospital a few days later and his body was passed to a special poison branch of the British Ministry of Defence (MOD) that discovered the pellet during an autopsy. The prime suspects were the Bulgarian secret police: Georgi Markov had defected from Bulgaria some years previously and had subsequently written books and made radio broadcasts that were highly critical of the Bulgarian communist regime. However, it was believed at the time that Bulgaria would not have been able to produce the pellet, and it was also believed that the KGB had supplied it. The KGB denied any involvement, although high-profile KGB defectors Oleg Kalugin and Oleg Gordievsky have since confirmed the KGB's involvement. Earlier, Soviet dissident Aleksandr Solzhenitsyn also suffered (but survived) ricin-like symptoms after an encounter in 1971 with KGB agents.[51]

Several terrorists and terrorist groups have experimented with ricin and caused several incidents of the poisons being mailed to U.S. politicians. For example, on May 29, 2013 two anonymous letters sent to New York City Mayor Michael Bloomberg contained traces of it.[52] Another was sent to the offices of Mayors Against Illegal Guns in Washington DC. A letter containing ricin was also alleged to have been sent to American President Barack Obama at the same time. An actress, Shannon Richardson, was later charged with the crime, to which she pled guilty that December.[53] On July 16, 2014, Richardson was sentenced to 18 years in prison plus a restitution fine of $367,000.[54]

8 Popular culture

Ricin has often been used as a plot device in the television series *Breaking Bad* (Season 2, Season 4 and Season 5), *The Mentalist* (Season 2, Episode 15), on *NCIS* (Season 7, Episode 21), *ER* (Season 15, episode 2), and the TV film

Complicit. It is also intended as the assassination weapon of Kim Jong-un in *The Interview*.

9 See also

- Abrin is similar to ricin but even more toxic
- European Mistletoe
- Lily of the Valley
- Incidents involving ricin

10 References

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11 External links

- Studies showing lack of toxicity of castor oil from the US Public Health Service
- Castor bean information at Purdue University
- ricin information at Cornell University
- Medical research on ricin at BBC
- Ricin - Emergency Preparations at CDC
- Emergency Response Card - Ricin at CDC

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12.1 Text

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Williams III, Jessicalynneguyton, Antiqueight, Chilllls, Drlectin, Helpful Pixie Bot, Alex.brazier, JohnSRoberts99, BG19bot, Juro2351, Doctaduck, Exercisephys, AdventurousSquirrel, Aisteco, Rob Hurt, A2-33, BattyBot, Citing, Rohansingh.31, Nero the red dragon, Ignacio.Agulló, JZNIOSH, Lugia2453, Dyehard321, Canralph, Jcatki, Sbalfour, SomeFreakOnTheInternet, Spider55555, Jdylanparker, Havensfire, American In Brazil, HediBougghanmi2014, Jakec, Hernandovoters, Xyproto, DLC601, Jshelt0n1, Laurencebeck, Shaun9876, Ginsuloft, Conversar, HediBougghanmi2015, EtymAesthete, Leleffyouwikirofl, Vparekhpi, Mrhomerjaysimpson, Monkbot, Fish storm, Goblinshark17, Z White Guy, Qbork, Okey721, Clicksm and Anonymous: 531

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