REVIEW

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Toxicological mechanisms of *Aconitum* alkaloids

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The toxic effects of *Aconitum* alkaloids are known to affect mainly the central nervous system, heart and muscle tissues. Their toxicological mechanisms may involve interaction with voltage-dependent Na^+ channels, modulation of neurotransmitter release and related receptors, promotion of lipid peroxidation and induction of cell apoptosis in heart, liver or other organs. Of them, the mechanism of interaction with voltage-dependent Na^+ channels is quite well known, but the other factors are still unclear, and need to be further studied. This review focuses on the toxicological mechanisms of *Aconitum* alkaloids.

1. Introduction

In recent years, the use of phytomedicine, including natural products and traditional herbal medicine, is gaining worldwide popularity. However, until recently little was known about toxicological mechanisms of natural products. Aconite tuber, roots of aconite (*Aconitum carmichaeli* or *A. kusnezofii*), is an oriental herbal medicine used traditionally for centuries in China and other countries to therapeutically increase the peripheral temperature, relieve rheumatic pain and treat neurological disorders (Sato et al. 1979). The pharmacological effects of *Aconitum* alkaloids have been described as positive inotropic effects (Honerjager and Meissner 1983), analgesic, anti-inflammatory and antirheumatic activity (Hikino et al. 1980) and neurological indications (Herzog et al. 1964).

Herb-induced aconitine poisoning is encountered in both Asia and western countries (Lin et al. 2004). The risk is higher with inadequately processed aconite roots or with large doses. The toxic effects of aconitine and its structurally related analogs are known to affect mainly the central nervous system and the heart (Benn and Jacyno 1983). It is well known that aconitine produces flutter and fibrillation of cardiac and skeletal muscles, and analgesia in the neural system (Honerjager et al. 1982; Sato et al. 1979). Thus, in heart research aconitine has been widely used as an experimental tool to induce experimental tachyarrhythmias (Lévy et al. 1998). Symptoms of intoxication include dizziness, systemic paralysis, followed by sand-blindness, dyslogia, dysphoria, stomachache and diarrhea, nausea and vomiting, palpitation, and ultimately analgesia, dyspnoea, hypotension, arrhythmia, shock, coma and death (Bisset 1981).

This review focuses on the toxicological mechanisms of *Aconitum* alkaloids, and discusses several possible toxicological mechanisms of *Aconitum* alkaloids in recent studies.

2. Interaction with voltage-dependent sodium channels

The toxicological mechanism of *Aconitum* alkaloids on the nerve, heart and muscle system appears to be quite well known in terms of its relationship with voltage-dependent Na^+ channels (Nilius et al. 1986).

2.1. Voltage-gated Na^+ channels and neurotoxin receptor sites

Voltage-gated Na^+ channels are heteromeric membrane glycoproteins responsible for the generation of action potentials (AP), whose physiological function is fulfilled by the α-subunit in Na^+ channels of the brain and heart (Fozzard and Hanck 1996). A number of diverse neurotoxins target voltage-gated Na^+ channels in their primary actions. These toxins promote Na^+ channel opening and closing, induce depolarization and repolarization of the resting membrane potential, and thus drastically affect the excitability and contractility of nerve, cardiac and muscular tissues (Wang and Wang 2003).

The effect of aconitine (AC) on the electrophysiological properties of the rat brain type IIA α-subunit expressed heterologously has been studied in the whole-cell patch-clamp configuration. The results show that the AC-binding site is located in the region close to the cytoplasmic mouth of the α-subunit of the Na^+ channel pore. The AC-modified sodium currents are completely inactivated, although with slower kinetics. It is suggested that the AC-binding site resides in the pore region of the α-subunit, and that the presence of the β-subunit is not essential for AC-binding (Rao and French 2000). The membrane topology of the voltage-gated Na^+ channel α- and β_1-subunit shown in Fig. 1.

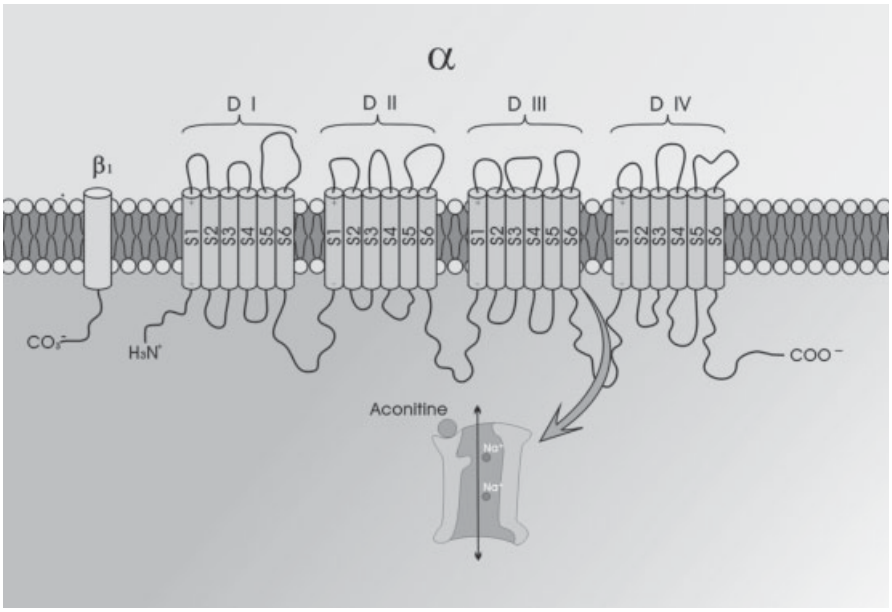


Fig. 1:
Membrane topology of the voltage-gated Na^+ channel α- and β_1-subunit. Transmembrane segments (S1-S6) and homologous domains (D1−D4) are labeled within the α-subunit

2.2. Interaction with Na^+ channel and toxicity

Aconitine is well known to be an activator of the Na^+ channel and has often been used as an experimental tool in physiological research to investigate the function of voltage-dependent Na^+ channels (Schmidt and Schmitt 1974). Recent studies imply that the neural, cardiac and muscular toxicity of aconitine has been elucidated as shifting the voltage-dependence of the voltage-dependent Na^+ channel towards the hyperpolarized direction, thereby leading to a permanent activation of the channel (Faber and Rudy 2000).

Aconitum alkaloids have been investigated to elucidate their binding to the Na^+ channel epitope site 2, alterations in synaptosomal Na^+ and Ca^{2+} concentration ($[Na^+]i$, $[Ca^{2+}]i$), arrhythmogenic action in the isolated heart, and antinociceptive, inotropic and acute toxic action in mice. The study revealed the alkaloids of the group binding with high affinity to site 2 induce an increase in synaptosomal $[Na^+]i$ and $[Ca^{2+}]i$, are antinociceptive, provoke tachyarrhythmia and are highly toxic, whereas low affinity alkaloids reduce $[Ca^{2+}]i$, induce bradycardia and are less toxic. These results suggest that the *Aconitum* alkaloids can be grouped as sodium channel activating or blocking compounds (Friese et al. 1997). Aconitine is known to activate the voltage-dependent Na^+ channel, while lappaconitine has been reported to block this channel (Ameri and Simmet 1999a). The structure-activity relationship shows that alkaloids that activate or block Na^+ channels have a benzoyl ester side chain in the C-14 or C-4 positions respectively, whereas the other compounds lack this group (Gutser et al. 1998; Ameri and Simmet 1999b). Aconitine is assumed to reach its Na^+ channel receptor through the lipophilic part of the membrane (Grishchenko et al. 1983).

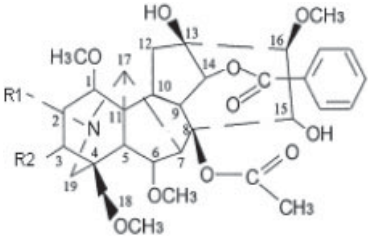
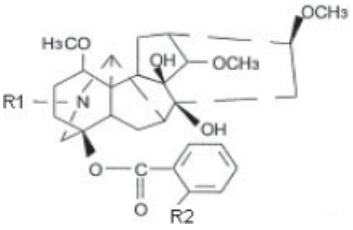
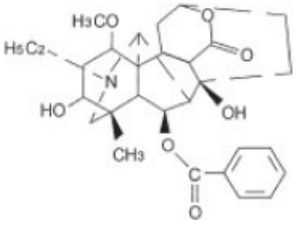
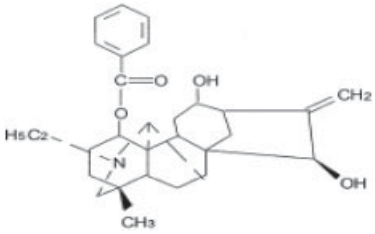
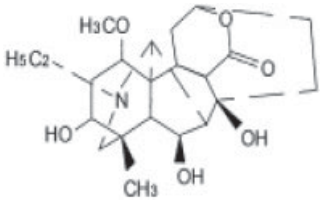
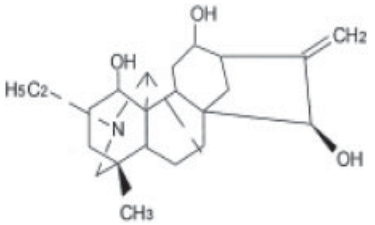
It appears to be the benzoylester group and its position that determine the interaction with the binding site on the α-subunit of the Na^+ channel protein. Aconitum alkaloids can be separated into three groups, which are shown in the Table (Ameri 1998).

Aconitine has been reported to have analgesic properties *in vivo* (Bisset 1981; Ono and Satoh 1988, 1990) and inhibitory effects on neuronal activity in rat hippocampal slices *in vitro* (Ameri et al. 1996a, b). The structurally related aconitine and lappaconitine inhibit the orthodromic and antidromic population spike in the hippocampal area in a frequency-dependent manner. Aconitine (1 μmol/l) completely suppressed epileptiform activity induced by omission of Mg^{2+} as well as normal neuronal activity, whereas lappaconitine (10 μmol/l) and 6-benzoylheteratisine (10 μmol/l) diminished epileptiform activity by sparing normal neuronal activity, which is related to Na^+ channels (Ameri et al. 1996a). The aconitine-induced inhibition of neuronal excitability recorded extracellularly in hippocampal slices does not differ from the inhibition evoked by veratridine, which also activates the Na^+ channel. However, marked differences in the action of both alkaloids become obvious after their washout. The potentiation of hippocampal excitability was sustained over several hours and the amount of increase was dependent on the aconitine concentration (0.1–1 μmol/l) (Ameri et al. 1996).

The effect of aconitine on neuronal excitability in hippocampal slices of adult and juvenile rats was also investigated. The inhibitory action of aconitine was shown to be significantly stronger and was obtained after a shorter latency in slices of juvenile rats as compared with slices of adult rats; a prolonged application of aconitine evoked an increase in spike amplitude of up to 15% in slices of juvenile but not of adult rats, and the latency of recovery was also significantly shorter in slices of juvenile rats. These observations indicate that juvenile hippocampi have a higher susceptibility to the effect of aconitine, but also provide a partial protective mechanism (Ameri et al. 1996).

Aconitine is a highly toxic compound, causing severe acute arrhythmias leading to death. Na^+ overload of cardiac cells can accompany various pathologies and are induce fatal cardiac arrhythmias. Some results suggest that intracellular Na^+ loading plays an important role in aconitine-induced delayed after – depolarization (DAD) and transient inward currents in low Ca^{2+} solution (Sawanobori et al. 1987). The effects of elevated intracellular Na^+ on cardiac AP and on intracellular Ca^{2+} have been investigated. By slowing AP depolarization and shortening APD, Na^+-overload acts to enhance inducibility of reentrant arrhythmias. Shortened APD with elevated $[Ca^{2+}]i$ also predisposes the myocardium to arrhythmogenic DAD (Gregory and Yoram 2000). Using the cell-attached con-

Table: Different groups of *Aconitum* alkaloids and properties (Ameri 1998)

Components			Structure difference	Toxicity	Interaction with Na^+ channel
Group one:					
			Ester bound at C8 and C14	higher	Na^+ channel activators
	R_1	R_2			
Aconitine,	C_2H_5	OH			
Mesaconitine,	CH_3	OH			
3-Acetylaconitine	C_2H_5	CH_3COO			
Group two:					
			Benzoylester side chain at C4, C6 and C1	less	Na^+ channel blocking
	R_1	R_2			
Lappaconitine,	C_2H_5	NH_2			
N-Deacetyllappaconitine	C_2H_2	$NHCOCH_3$			
					
6-Benzoylheteratisine	1-Benzoylnapelline				
Group three:					
			Lacking a benzoylester side chain	least	Different affinity to various subtypes of the α-subunit of the Na^+ channel
Heteratisine	Napelline				

figuration of the patch clamp technique, the single channel activities of the L-type Ca^{2+} channel were recorded before and after addition of three drugs, aconitine, the Ca^{2+} channel blocker verapamil or the Ca^{2+} channel activator BAY K8644. The results show the blocking effect of aconitine on L-type Ca^{2+} channels. Its mechanism may be relevant to the decrease in both open state probability and the mean open time of the Ca^{2+} channel (Chen et al. 1995).

Disturbances in cellular Na^+-Ca^{2+} homeostasis may play a central role in the pathogenesis of ventricular arrhythmias and cell damage induced by the aconitine alkaloid. To test this hypothesis *in vivo*, the effects on aconitine-induced arrhythmias of intravenous pretreatment with R56865 (a Na^+-Ca^{2+} overload inhibitor) in anesthetized rats were observed. The results suggest that intracellular Na^+ loading plays an important role in aconitine-induced ventricular arrhythmias; the Ca^{2+}-overload after Na^+ loading elicited by aconitine is not likely to be mediated by increased Ca^{2+} influx through a slow channel (Lu and Clerck 1993). However, the effects of NCX blockers on ventricular arrhythmias are still controversial. One simulation study indicates that inhibition of NCX may be ineffective to suppress aconitine-induced activity in isolated cardiac ventricular myocytes (Shah et al. 2004).

A recent study was designed to test the hypothesis that anesthesia may increase susceptibility to ventricular arrhythmia caused by aconitine due to the inhibition of arterial baroreflex. There was a significant difference in the lethal dose of aconitine between anaesthetized and conscious rats; anesthesia was found to increase the susceptibility of rats to ventricular arrhythmias following aconitine (Shu et al. 2004). Furthermore, another study aimed to investigate the influence of chronic administration of aconitine in experimental animal models. Surprisingly, the

frequency of arrhythmias decreased remarkably with time and repeated administration of aconitine. These results suggest two possibilities. First, an increase in the activity of aconitine metabolism. Second, a decrease of effectiveness of action on the heart following long-term administration of aconitine (Wada et al. 2005).

It is well known that the property of aconitine in prolonging Na^+ influx during the action potential leads to a positive inotropic effect, thus confirming the importance of Na^+ influx for the regulation of myocardial contractility (Honerjager et al. 1983). In skeletal muscle, excitability and contractility depend on the transmembrane distribution of Na^+ and K^+ and the membrane potential, which in turn are determined by the operation of the Na^+-K^+ pump. When the Na^+-K^+ pump cannot readily restore the Na^+-K^+ gradients, working muscle cells often undergo net loss of K^+ and gain of Na^+ (Clausen 2003a). Reduced Na^+-K^+ pump content leads to loss of contractility and endurance. Increasing excitation-induced Na^+ influx by augmenting the open-time or the content of Na^+ channels reduces contractile endurance. Excitability and contractility depends on the ratio between passive Na^+-K^+ leaks and Na^+-K^+ pump activity, the passive leaks often playing a dominant role (Clausen 2003b).

From all these studies, we can see that disturbed interaction with voltage-dependent Na^+ channels of the Aconitum alkaloids lead to dysfunction of the central nervous system, heart and muscle systems.

3. Modulation of neurotransmitter release

It is shown that the analgesic and arrhythmic action of the Aconitum alkaloids involves the noradrenaline and acetylcholine system, however, the mechanisms of their interaction remain unclear.

3.1. Effect on acetylcholine system

Life-threatening arrhythmias can occur after the consumption of aconitine. In experiments, aconitine produced directly arrhythmogenic and cardiotoxic effects on the myocardium combined with indirect cardiotropic effects mediated via activation of extracardial nerves. Aconitine demonstrated pronounced cholinolytic properties and blocked vagal arrhythmogenic effect (Sheikh-Zade et al. 2000). A study investigated whether peripherally administered aconitine increases spontaneous acetylcholine (ACh) release from the frontal cerebral cortex in freely moving rats. The results indicate that the cortical ACh release caused by peripherally administered aconitine does not occur through activation of the central muscarine receptor, and thus its ACh release may not be concerned with the occurrence of bradycardia (Kimura et al. 1996).

The mechanisms of neuromuscular blockade by hypaconitine and aconitine were investigated in isolated phrenic nerve-diaphragm muscles of mice. The results indicate that the neuromuscular blockade produced by hypaconitine and aconitine was caused by reducing the evoked quantal release. The mechanism of this effect was attributed mainly to blocking of the nerve compound action potential (Muroi et al. 1990). Another reason is that aconitine increases and then decreases electrical stimulation-evoked ACh release from the motor nerve through prolonged activation of Na^+ channels. Further activation of the channels enhances spontaneous release and the subsequent complete inactivation of quantal release may be due to blocking Ca^{2+} influx (Okazaki et al. 1994).

3.2. Effect on noradrenaline system

The effect of the *Aconitum* alkaloids aconitine, 3-acetylaconitine, lappaconitine, and *N*-desacetyllappaconitine to inhibit [^{3}H]noradrenaline uptake was investigated in rat hippocampal synaptosomes. Aconitine and 3-acetylaconitine, which are known to activate Na^+ channels, had comparable inhibitory potency. In contrast, lappaconitine and *N*-desacetyllappaconitine failed to inhibit [^{3}H]noradrenaline uptake. When either lappaconitine or *N*-desacetyllappaconitine was applied in combination with aconitine, [^{3}H]noradrenaline uptake was not affected. The Na^+ channel blocker tetrodotoxin (TTX) enhanced [^{3}H]nora-drenaline uptake, whereas uptake was completely blocked in Na^+-free incubation medium. The inhibitory action of aconitine and 3-acetylaconitine on [^{3}H]noradrenaline uptake was blocked by addition of TTX. It is concluded that the blockade of [^{3}H]noradrenaline uptake evoked by aconitine and 3-acetylaconitine is mediated indirectly by an increased Na^+ concentration in the synaptosomes (Seitz and Ameri 1998). The effect of mesaconitine on noradrenaline uptake and on neuronal activity was also examined in rat hippocampus. Mesoconitine inhibited [^{3}H]noradre-naline uptake in a concentration-dependent manner. In a further series of experiments, the effects of mesaconitine on the extracellularly recorded population spike were investigated in rat hippocampal slices. It is concluded that mesoconitine increased excitability in rat hippocampal pyramidal cells by a mechanism involving the noradrenergic system, with at least one mechanism being inhibition of noradrenaline uptake leading to an enhanced extraneuronal noradrenaline level (Ameri and Seitz 1998).

The antinociceptive action of aconitine administered intracerebroventricularly to mice was reduced by pretreatment with antagonists of noradrenergic receptors, indicating an interaction of the alkaloids with the endogenous central noradrenergic pathways (Lu et al. 1998; Ono and Satoh 1992).

The potential mechanism of the action of *Aconitum* alkaloids on neurotransmitter release can be seen in Fig. 2.

4. Promotion of lipid peroxidation

The changes of phospholipid fatty acid composition of the viscera were investigated in a model of aconitinic arrhythmia in rats by the GC method. Aconitinic arrhythmia leads to a reduction in the proportion of polyenic fatty acids (arachidonic, docosahexaenoic) and to an increase in that of saturated acids (palmitic and stearic acids) in visceral phospholipids, as a result of respiratory and circulatory hypoxia developed, and to activation of lipid peroxidation. The most hypoxia-sensitive phospholipids are those of the heart and brain. The ratio of saturated to polyunsaturated fatty acids is the most informative marker of lipid peroxidation in aconitinic arrhythmia (Skrupskii and Plaksin 1994).

The effects of free polyunsaturated fatty acids (PUFA) on the binding of ligands to receptors on voltage-sensitive Na^+ channels of neonatal rat cardiac myocytes have been assessed. The PUFA were shown to be antiarrhythmic, whereas saturated fatty acids had no antiarrhythmic effects. Enrichment of the myocyte membrane with cholesterol neither affected [^{3}H]BTXB binding when compared with control cells nor altered the inhibitory effects of PUFA on [^{3}H]BTXB binding bracket (Kang and Leaf 1996a). PUFA binding to the Na^+ channel site is reversi-

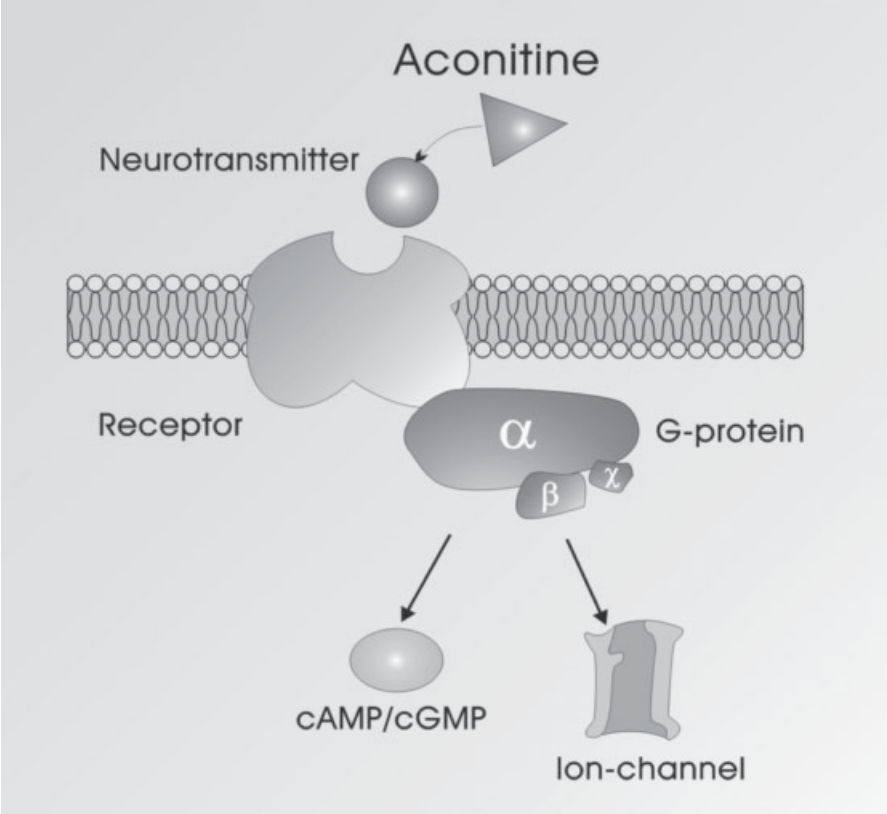


Fig. 2:
The effect of aconitine alkaoids on neurotransmitter release and act on the G-protein, cAMP/cGMP and ion channel

ble and occurs at concentrations close to those required for apparent antiarrhythmic effects, suggesting that PUFA binding at the site relates to their antiarrhythmic action (Honore et al. 1994; Schmitt and Meves 1995).
A neonatal rat cardiac myocyte preparation was used to assay individual fatty acids for antiarrhythmic activity because slowing of the beating or heart rate correlates well with antiarrhythmic capability (Kang and Leaf 1996b).

5. Induction of cell apotosis

It has been shown in some publications that aconitine poisoning may induce cell apoptosis but further studies need to be carried out. An experimental model of aconitine poisoning in Wistar rats was set up, and a technique for apoptosis detection was used. Standard HE staining and immuno-histochemical staining results were analyzed. The results show that levels of apoptosis in myocardial cells, hepatic cells and renal tubule epithelial cells were much higher in poisoning groups than in control groups at the various stages. In addition the levels of apoptosis in the same organ are different after different durations of poisoning. It has been suggested that when clinical symptoms of aconitine poisoning are not apparent or when poison can not be detected, pathological changes of important organs could be successfully detected through investigation of apoptosis (Lei et al. 2004a, b; Lei and Yi 2005).
A variety of factors lends credence to the association of apoptosis with the progression of cardiomyopathy (Narula et al. 1996). Transient myocardial pressure overload induces the expression of proto-oncogenes, leading to compensatory hypertrophy of myocytes (Takahashi et al. 1992; Sadoshima and Izumo 1993). However, the persistence of growth factors may also result in apoptosis (Orrenius et al. 1989). Furthermore, increased sarcoplasmic Ca^{2+} concentration, which is a consistent feature of dilated cardiomyopathy (Gwathmey and Morgan 1985), may activate endonucleases involved in the apoptotic cascade. In cardiomocytes, increases in the concentrations of Ca^{2+}, cyclic AMP, and calcium ionophore have been shown to induce apoptosis (Orrenius et al. 1989; Evan 1992). In addition to the persistent expression of proto-oncogenes and intracellular Ca^{2+} overload, relative hypoxia of myocytes due to left ventricular hypertrophy or dilatation may also perpetuate apoptosis (Marcus et al. 1981). However, the mechanism for the induction of cell apoptosis by aconitine is still unknown.

6. Summary

Taken as a whole, the toxic effects of aconitine and its structurally related analogs are known mainly in relation to the central nervous system, heart and muscle systems. The toxicological mechanisms of *Aconitum* alkaloids may consist of these aspects (Fig. 3): 1. Interaction with voltage-dependent Na^+ channels, shifting the voltage-dependence of the voltage-dependent Na^+ channel towards the hyperpolarized direction, thereby leading to a permanent activation of the channel; 2. Modulation of neurotransmitter release and related receptors, especially involving the noradrenaline and acetylcholine systems; 3. Acceleration of the lipid peroxidation of the cardiac system, that may lead to heart arrhythmia; 4. Inducion of cell apoptosis of the heart, liver or other organs. The mechanism of interaction with voltage-dependent Na^+ channels is quite well known, but the other factors still remain unclear, and need to be further studied.

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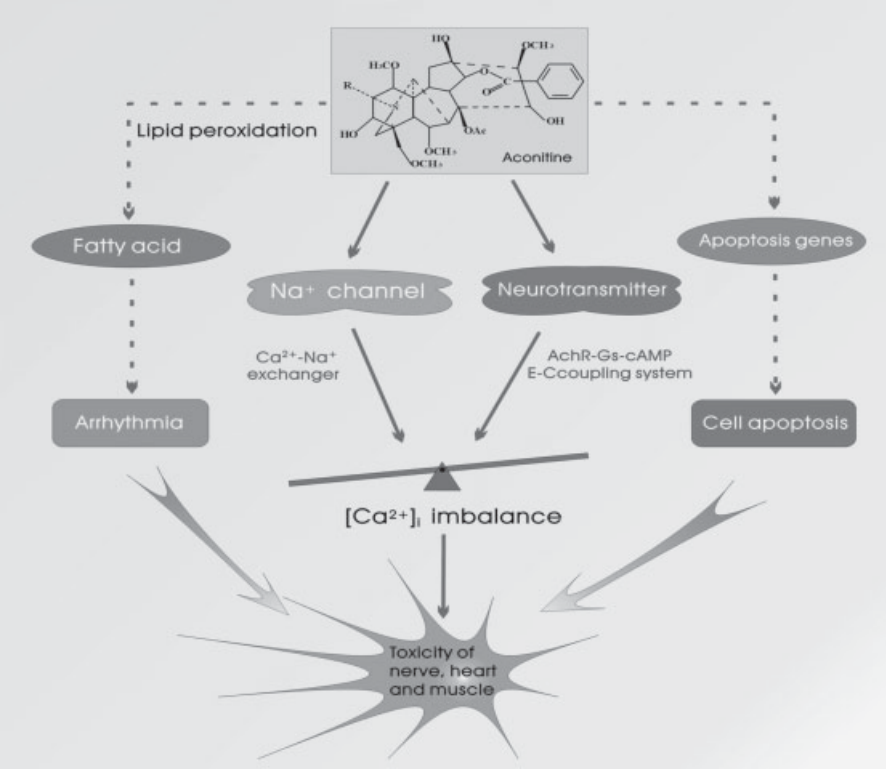

Fig. 3:
Several toxicological mechanisms of *Aconitum* alkaloids

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