THE EFFECTS OF ACONITUM ALKALOIDS ON THE CENTRAL NERVOUS SYSTEM

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Abstract—Preparations of Aconitum roots are employed in Chinese and Japanese medicine for analgesic, antirheumatic and neurological indications. The recent surge in use of phytomedicine derived from traditional Chinese medicine as well as increasing concerns about possible toxic effects of these compounds have inspired a great deal of research into the mechanisms by which certain Aconitum alkaloids may act on the central nervous system. The pharmacological effects of preparations of Aconitum roots are attributed to several diterpenoid alkaloids. The main alkaloid of these plants is aconitine, a highly toxic diterpenoid alkaloid which is known to suppress the inactivation of voltage-dependent Na⁺ channels by binding to neurotoxin binding site 2 of the α-subunit of the channel protein. In this article the pharmacology of several structurally related Aconitum alkaloids is highlighted and their therapeutic vs toxic potential is discussed. Neurochemical and neurophysiological studies will be reviewed with emphasis on the effects of the alkaloids in regions of the brain that have been implicated in pain transmission and generation of epileptic activity. Considering the chemical structure of the Aconitum alkaloids as well as their mechanism of action, a subdivision in three groups becomes obvious: the first group comprises such alkaloids which possess high toxicity due to two ester bondings at the diterpene skeleton. The members of this group activate voltage-dependent sodium channels already at resting potential and inhibit noradrenaline reuptake. Activation of sodium channels and in consequence excessive depolarization with final inexcitability and suppression of pain transmission account for their antinociceptive properties. The second group comprises less toxic monoesters which have been shown to possess strong antinociceptive, antiarrhythmic and antiepileptiform properties due to a blockade of the voltage-dependent sodium channel. Electrophysiological studies have revealed a use-dependent inhibition of neuronal activity by these alkaloids. They seem to be competitive antagonists of the group I-alkaloids. The third group of Aconitum alkaloids are lacking an ester side chain in the molecule. Toxicity is markedly reduced when compared with the two other groups. They fail to affect neuronal activity, but are reported to have antiarrhythmic actions suggesting that they may have different affinities to various subtypes of the α-subunit of the Na⁺ channel in brain and heart.

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1. INTRODUCTION

In the recent years, the use of phytomedicine, including natural products of traditional Chinese medicine, is gaining wide popularity in Europe. However, until recently few was known about the ingredients and their mechanisms of action. Therefore the increasing popularity of phytomedicine derived from traditional Chinese medicine has also produced uncertainty about their toxicity and their active compounds [for review see Chan (1995)].

For centuries, preparations of various species of Aconitum have been widely used by various civilizations as sources of both arrow poisons and medicines. At first glance, it seems surprising that aconitine and related alkaloids are employed as medicinals, since aconitine is a highly potent neurotoxin. Indeed, preparations from certain species of Aconitum (Ranunculacea) of Chinese and Japanese origin are an indispensable material in Eastern medicine. The pharmacological effects can be attributed to various diterpenoid alkaloids. In a large number of cases in the literature, these therapeutic effects have not been correlated with the primary mechanism of action. On the other hand, aconitine, the main alkaloid of these plants, is well known to be an activator of the Na⁺ channel and was used often as an experimental tool in physiological systems, in order to investigate the function of voltage-dependent Na⁺ channels. In more recent times, the mechanisms of action of various structurally related Aconitum alkaloids have been elucidated. These recent studies imply a differential interaction with the voltage-dependent Na⁺ channel depending on the chemical structure of the alkaloids. Since aconitine and related alkaloids can reasonably be expected to be a highly potent neurotoxin, it is pertinent to question whether it has desirable properties for the neuropharmacologist.

The present review covers both previously published results obtained from in vivo studies and more recently published findings from electrophysiological in vitro studies, in order to give an overview of an emerging research field.

2. ACONITUM ALKALOIDS—MEDICAL USE VS TOXICITY

2.1. Definition

What is an alkaloid? Alkaloids are a class of natural products processing an enormous variety of structures. At present > 5000 alkaloids of all structural types are known. The various structural types of alkaloids are discussed in Pelletier (1983), who suggests that alkaloids should be defined simply as naturally occurring cyclic organic compounds containing nitrogen in a negative oxidation state. The present review is restricted on class C19 and C20 diterpenoid alkaloids which occur in plants of the Aconitum genus. A diterpenoid alkaloid is understood to be a nitrogenous base or derivative, whose nitrogen-functionalized skeleton is formed from some C20-terpenoid precursors. The Aconitum plants contain many constituents classified chemically, some of which are shown in Fig. 1. Within the set of diterpenoid alkaloids thus defined, not all have been subjected to toxicological and pharmacological studies. Thus, the present review summarizes what is known for some 12 compounds, natural alkaloids and chemical transformation products thereof (Fig. 1).

2.2. Toxicity and Its Prevention

The medical use of Aconitum spans many centuries. In context of scientific research, single alkaloids have been isolated and their action has been investigated in vivo and, more recently, in vitro. The chemistry and importance of diterpenoid alkaloids in Eastern medicine was previously reviewed (Benn and Jacyno, 1983). The tubers of certain species of Aconitum (Ranunculacea) of Chinese and Japanese origin are an indispensable material in Eastern medicine. The pharmacological effects can be attributed to various diterpenoid alkaloids. In a large number of cases in the literature, these therapeutic effects have not been correlated with the primary mechanism of action. On the other hand, aconitine, the main alkaloid of these plants, is well known to be an activator of the Na⁺ channel and was used often as an experimental tool in physiological systems, in order to investigate the function of voltage-dependent Na⁺ channels. In more recent times, the mechanisms of action of various structurally related Aconitum alkaloids have been elucidated. These recent studies imply a differential interaction with the voltage-dependent Na⁺ channel depending on the chemical structure of the alkaloids. Since aconitine and related alkaloids can reasonably be expected to be a highly potent neurotoxin, it is pertinent to question whether it has desirable properties for the neuropharmacologist.

The present review covers both previously published results obtained from in vivo studies and more recently published findings from electrophysiological in vitro studies, in order to give an overview of an emerging research field.
The electrophysiological mechanism of the arrhythmogenic effect of aconitine is a delay in the final repolarization phase of the action potential which initiate premature or triggered excitations. These, in turn, are due to a removal of inactivation of voltage-dependent Na⁺ channels (see below) (Schmidt and Schmidt, 1974; Honerjäger and Meissner, 1983; Nilius et al., 1986). The arrhythmic activity of aconitine alkaloids has been tested in mice and has been shown to be correlated with the presence of a benzoylester side chain at C14 position explaining the common arrhythmic and toxic effects of such compounds as aconitine, mesaconitine and 3-acetylaconitine, which are the most toxic Aconitum alkaloids (Table 1). The potency of arrhythmia induction was found to be of the order: mesaconitine > aconitine > 3-acetylaconitine (Zhou et al., 1984).

However, regarding the high toxicity of the already mentioned alkaloids, it is intriguing that certain diterpenoid alkaloids isolated from the plant species Aconitum are less toxic and have cardiac effects quite opposite to those of aconitine, mesaconitine and 3-acetylaconitine. Members of this group of Aconitum alkaloids are lappaconitine, N-desacetyllappaconitine, 6-benzoylheteratisine, lappaconidine, heteratisine and napelline (Fig. 1). Despite their structural relationship with aconitine these alkaloids are reported to have a lower toxicity (Table 1) and even to possess antiarrhythmic properties (Dzhakhangirov and Sadritinov, 1985a,b; Sokolov et al., 1988; Abdalla et al., 1989).

Aconitum alkaloids which lack a benzoylester side chain, such as napelline, heteratisine and lappaconidine, have the lowest toxicity among the group of
compounds and have been reported to possess antiarrhythmic effects, too (Dzhakhangirov and 
Sadritinov, 1977; Benn and Jacyno, 1983).

The high toxicity is attributed to the acetyl group 
at C8, the hydroxyl group at C13, four methoxyl 
groups at C1, C6, C16 and C18, and the benzoylest-
er group at C14. At the present, only processed 
aconitine is used clinically because the alkaloid con-
tent is in part decomposed during the preparation 
process. In practice, processing is performed by 
steaming raw aconite roots under high pressure of 
an autoclave. During the processing a greater part 
of toxic aconitine-like alkaloids are largely con-
verted into much less poisonous alkaloids. (Hikino 
et al., 1977; Yang, 1985; Kimura et al., 1988). It has 
been shown that, when raw aconite tubers are heat-
processed, the content of the aconitine-like alkaloids 
is gradually diminished and the toxicity reduced 
rapidly (Hikino et al., 1977), a fact which confirms 
that raw tubers become far less toxic by means of 
sufficient heating. Previously, it was found that 
during heat-processing of the Aconitum roots, the 
aconitine alkaloids of the diester-type were trans-
formed to the benzoylaconines or aconines (Katz 
and Rudin, 1984; Murayama et al., 1991; Isono et 
al., 1994).

Taken together, with respect of the toxicity of 
different Aconitum alkaloids it is obvious that the 
LD<sub>50</sub> values of those compounds characterized by a 
lack of diester boundings is comparatively low 
(Table 1). In contrast, the toxicity of those alkaloids 
which represent diester bases with an acetoxy resi-
due at C8 and benzoylester residue at C14, such as 
aconitine, mesaconitine and 3-acetylaconitine is very 
high.

### 3. PHARMACOLOGY

#### 3.1. Analgesic Effects

Various plant extracts and preparations containing Aconitum alkaloids have been reported to pos-
sess analgesic activity, but the experimental 
methodology and results have been somewhat in-
consistent. This was complicated by the fact, that 
aconitine and mesaconitine often are collocalized in 
certain subspecies of Aconitum napellus. These two 
alkaloids have a very closely related structure and 
were difficult to separate in the past (Benn and 
Jacyno, 1983). Although the analgesic activity of 
Aconitum roots was thought to be due to the pre-
sence of aconitine, the data currently available on 
this subject do not clearly indicate an analgesic ac-
tivity of aconitine (Hikino et al., 1979). However, 
several widely occurring alkaloids in the roots of 
various Aconitum species were demonstrated to pos-
sess antinociceptive properties in different test 
models. Among these are the alkaloids mesaconi-
tine, 3-acetylaconitine, lappaconitine and N-deace-
tylappaconitine which have been reported to induce 
antinociception in visceral pain models as well as in 
models of somatosensory pain.

Various nociceptive test models for testing analge-
sic activity are based on the production of pain by 
thermoreceptors (tail-flick test and hot-plate test), 
mechanoreceptors (scratching, biting and licking 
behaviour) or by visceral chemoreceptors (writhing 
test). A painful ‘writhing’ syndrome induced by an 
intraperitoneal injection of a number of chemical 
agents, for example, bradykinin, histamine and 
acetic acid, has been shown to exhibit some degree of 
selectivity for screening analgesic agents [for

### Table 1. Pharmacological effects of various Aconitum alkaloids

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; (mg kg&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>Antinociceptive effect (ED&lt;sub&gt;50&lt;/sub&gt;)</th>
<th>Cardiovascular effect</th>
<th>Antiinflammatory effect (mg kg&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aconitine</td>
<td>0.12–0.2 (s.c.)</td>
<td>0.06 (s.c.)</td>
<td>Arrhythmogenic</td>
<td>0.1 (p.o.)</td>
<td>Benn and Jacyno (1983); Honerjäger and Meissner (1983); Murayama et al. (1991); Sato et al. (1979); Benn and Jacyno (1983); Murayama et al. (1991); Sato et al. (1979); Tang et al. (1984, 1986); Dzhakhangirov and Sadritinov (1985a,b); Liu et al. (1987)</td>
</tr>
<tr>
<td>Mesaconitine</td>
<td>0.20 (s.c.)</td>
<td>0.04 (s.c.)</td>
<td>Arrhythmogenic</td>
<td>0.2–0.5 (p.o.)</td>
<td>Benn and Jacyno (1983); Murayama et al. (1991); Sato et al. (1979); Benn and Jacyno (1983); Murayama et al. (1991); Sato et al. (1979); Tang et al. (1984, 1986); Dzhakhangirov and Sadritinov (1985a,b); Liu et al. (1987)</td>
</tr>
<tr>
<td>3-Acetylaconitine</td>
<td>0.87 (s.c.)</td>
<td>0.4 (s.c.)</td>
<td>—</td>
<td>0.18–0.3</td>
<td>Dzhakhangirov and Sadritinov (1977)</td>
</tr>
<tr>
<td>Lappaconitine</td>
<td>5.9–11.5 (i.v.)</td>
<td>1.2–3.8 (s.c.)</td>
<td>Antiarhythmic</td>
<td>6–8 (s.c.)</td>
<td>Dzhakhangirov and Sadritinov (1977)</td>
</tr>
<tr>
<td>N-Deacetyl-lappaconitine</td>
<td>23.5 (i.p.)</td>
<td>7.1 (s.c.)</td>
<td>Antiarhythmic</td>
<td>10–15 (s.c.)</td>
<td>Dzhakhangirov and Sadritinov (1977)</td>
</tr>
<tr>
<td>6-Benzoyl heteratisine</td>
<td>30.0 (i.v.)</td>
<td>—</td>
<td>Antiarhythmic</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Heteratisine</td>
<td>180.0 (i.v.)</td>
<td>—</td>
<td>Antiarhythmic</td>
<td>—</td>
<td>Benn and Jacyno (1983); Dzhakhangirov and Sadritinov (1977)</td>
</tr>
<tr>
<td>Napelline</td>
<td>87.5 (i.v.)</td>
<td>—</td>
<td>Antiarhythmic</td>
<td>—</td>
<td>Benn and Jacyno (1983); Dzhakhangirov and Sadritinov (1977)</td>
</tr>
</tbody>
</table>

All data in the table were obtained in experiments with mice. The route of administration of the drugs were subcutan 
(s.c.), intravenous (i.v.), intraperitoneal (i.p.) or per os (p.o.). Numbers represent authors reporting results referenced 
below.
Mesaconitine is like aconitine a predominant alkaloid in certain subspecies of *Aconitum napellus*. This compound has been proven to possess potent antinociceptive activity in writhing-assay and tail flick test (Hikino and Murayama, 1985; Murayama, et al. 1984; Oyama et al., 1994). When tested in mice with tail-flick experiments at a dose of ca one-quarter the amount of the LD$_{50}$ value (20 mg kg$^{-1}$ s.c.), mesaconitine (0.06 mg kg$^{-1}$ s.c.) elevates pain threshold by a factor 1.5 as compared with the normal level (Hikino et al., 1979). The analgesic activity of mesaconitine was much greater than that of morphine as judged by the ED$_{50}$ values in both the tail-flick and the acetic acid-induced writhing method. However, the opioid receptor antagonist levallorphan does not affect the analgesic activity of mesaconitine, suggesting that this effect is not mediated by stimulation of opioid receptors (Murayama et al., 1984). To evaluate the possibility that mesaconitine exerts its analgesic action via the central nervous system, the alkaloid was administered intracerebral (Murayama et al., 1984). Dose-dependent analgesic activity was observed, indicating that mesaconitine did elicit analgesic activity by a mechanism through the central nervous system. It is well known that the descending inhibitory system plays an important role in pain modulation and analgesia. The organization of this endogenous antinociceptive system has been recently reviewed (Behbehani, 1995; Sandkuhler, 1996; Willis and Westlund, 1997).

Structures involved in the descending analgesia system include the periaqueductal gray, nucleus raphe magnus, reticular formation, thalamus, cerebral cortex and several components of the limbic system (Fig. 2). Activation of the descending system inhibits the mean discharge rates of the nociceptive neurons in the dorsal horn of the spinal cord. These descending effects were mediated by neurotransmitters such as noradrenaline and serotonin. There is evidence that the antinociceptive action of mesaconitine is closely related to responses involving the central catecholaminergic system, particularly the noradrenergic system, because the mesaconitine-induced antinociception can be potentiated by β-adrenoceptor stimulation and reduced by β-adrenoceptor inhibition (Murayama and Hikino, 1985). In order to clarify the active sites in the central nervous system, mesaconitine (50–100 ng per rat) was microinjected into the nucleus reticularis gigantocellularis and the nucleus reticularis paragigantocellularis in the lower brain stem and the periaqueductal gray in the upper brain stem of rats (Murayama and Hikino, 1985). In addition mesaconitine was injected into the lumbar enlargement in the spinal cord through a catheter inserted into the spinal subarachnoid space. After these injections, the response latency measured by means of the tail immersion test in rats was increased in a dose-dependent manner. In contrast, microinjections of mesaconitine into neighbouring sites, the nucleus parvocellularis, the nucleus originis nervi abducentis and the fasciculus longitudinals medialis, elicited no significant effect. Inhibitory neurons descending from the nucleus reticularis gigantocellularis, which include noradrenergic neurons, project to lamina V of the lumbar enlargement and modulate the transmission of the noxious stimuli. It has been shown by Hikino and Murayama (1985) that mesaconitine when injected in combination with β-adrenoceptor antagonists into the nucleus reticularis gigantocellularis failed to induce antinociception. Thus, central sites are involved in the analgesic activity of mesaconitine, and the antinociceptive effect of mesaconitine administered into the nucleus reticularis gigantocellularis seems to be elicited by activation of the inhibitory noradrenergic neurons from the nucleus reticularis gigantocellularis, in particularly via β-adrenoceptor-mediated effects of noradrenaline. Moreover, the mesaconitine-induced antinociception could be significantly potentiated by adenosine 3′,5′-cyclic monophosphate [cAMP; Murayama and

![Fig. 2. Schematic drawing of the nociceptive system with ascending and descending fibers.](image)
Hikino (1985)). The phosphodiesterase inhibitor theophylline also significantly potentiated the antinociceptive effect produced by mesaconitine. Furthermore, mesaconitine-induced antinociception was markedly enhanced by isoproterenol, a β-adrenoceptor agonist, and reduced by propranolol, a β-adrenoceptor antagonist (Murayama and Hikino, 1985). Apparently, the antinociceptive action of mesaconitine is potentiated through cAMP and occurs via stimulation of the central β-adrenoceptor system.

More recently, it has been shown that the antilumbar effect of mesaconitine is blocked by the selective 2α-adrenoceptor antagonist idazoxan as well as by the 5-hydroxytryptamine (5-HT) receptor antagonist methysergide (Isono et al., 1994). Taken together, these findings imply that mesaconitine activates descending inhibitory 2α-adrenoceptor and serotonergic neurons which project from the brainstem to the spinal cord and which are known to inhibit nociception transmission at the spinal level (Dray et al., 1994). As recently has been reviewed by MacDonald et al. (1997), it is the 2αα-adrenoceptor subtype which acts as a mediator of the antinociceptive effect produced by 2α-adrenoceptor agonist.

3.1.2. 3-Acetylaconitine

3-acetylaconitine is the main alkaloid of the Chinese plant Aconitum fleum and is used for the treatment of rheumatic arthritis and rheumatic pain in the northwestern of China. There are only spare experimental evidences about the mode of its pharmacological action. The antinociceptive effect of 3-acetylaconitine has been reported to be about five times higher than that of morphine in hot plate and tail flick tests at rat and mice (Tang et al., 1986). The analgesic action of 3-acetylaconitine is not antagonized by the opioid receptor antagonist naloxone. In contrast, reserpine, which depletes the stores of catecholamines and serotonin, blocks the antinociceptive action of 3-acetylaconitine, whereas it is enhanced by the 5-HT receptor antagonist haloperidol (Tang et al., 1986; Zheng and Yang, 1988). In marked contrast to morphine, daily treatment of mice with 3-acetylaconitine neither induces tolerance nor physical dependence, and long-term treatments of monkeys fails to produce morphine-like abstinence syndromes after a sudden withdrawal (Tang et al., 1986). Although these findings suggest some involvement of the monoamine system in the antinociception induced by 3-acetylaconitine, they do not provide convincing evidences for the mechanism of action involved. Nevertheless, they show clearly that opioid receptors are not involved in the analgesic action produced by 3-acetylaconitine. However, taking the results of acute toxicity and antinociceptive efficacy into account, 3-acetylaconitine as well as mesaconitine cannot be considered as therapeutic useful analgesic drugs, because of their small therapeutic indices (LD50 ED50).

3.1.3. Lappaconitine and N-Deacetyllappaconitine

Lappaconitine, a C19 diterpenoid alkaloid occurring in several species of Aconitum and Delphinium, is until now the best investigated compound among the Aconitum alkaloids. This is probably due to its lower toxicity in comparison with aconitine and mesaconitine (Table 1). A toxicological study with this compound showed it to be ca 40 times less toxic than aconitine on intravenous administration to mice (Benn and Jacyno, 1983). Lappaconitine has been reported to exhibit potent analgesic efficacy when examined after oral or subcutaneous (s.c) administration to mice and rats in the hot-plate, tail-immersion and acetic acid-induced writhing tests (Tang et al., 1983; Ono and Satoh, 1988) and has been shown to be effective for post-operative analgesia with epidural injection (Chen et al., 1995). In order to determine whether the analgesic action of lappaconitine is either peripheral or central, Ono and Satoh (1988) have compared its effects with those of morphine, indometacin and acetylsalicylic acid. The analgesic activity of per os (p.o) lappaconitine against heat, pressure and chemical stimuli has been found to be greater than those of indometacin and acetylsalicylic acid, but was as potent as morphine (Ono and Satoh, 1988). In the s.c. route, lappaconitine is about two to five times less potent than morphine. However, in contrast to morphine, lappaconitine is equipotent in the tail-immersion test, when either given orally or s.c. The therapeutic indices of lappaconitine, calculated from the p.o. LD50 (35.5 mg kg−1 p.o.) and p.o. ED50 (1–4 mg kg−1 p.o.) values in mice, are three to five times and two to four times larger than those of indometacin and acetylsalicylic acid, respectively (Ono and Satoh, 1988). When tested in the Randall–Selitto method, lappaconitine raised the pain threshold of both the inflamed and the normal paw, like morphine, whereas the analgesic effects of indometacin and acetylsalicylic acid were observed only on the inflamed paw. The Randall–Selitto test demonstrates that centrally acting analgesics affect the pain threshold of the normal paw as well as that of the inflamed paw, whereas peripheral analgesics have no effect on the threshold of the normal paw. Thus, the findings of Ono and Satoh (1988) indicate that lappaconitine has an analgesic action in which probably the central nervous system is involved. The analgesic action of centrally acting analgesics such as morphine is mediated by the dorsal horn, reticular formation, nucleus reticularis paragigantocellularis, nucleus raphe magnus and periaqueductual gray matter (for review see Yaksh et al. (1988) and Yaksh (1997)). Since binding at the opioid receptor appears as the first step of the antinociceptive action of opioids and opiates, the action of these drugs is antagonized by the opioid receptor antagonist naloxone. However, it has been shown that the analgesic effect after systemic, intracerebroventricular (i.c.v.) or intrathecal (i.t.) application of lappaconitine is not antagonized by naloxone (Ono and Satoh, 1989, 1990) indicating that it is not mediated by opioid receptors. Moreover, when lappaconitine has been administered for up to 92 days to monkeys, no signs of physiological dependence were observed during this period and no withdrawal symptoms were evoked by injection of the opioid receptor antagonist nalorphine (Tang et al., 1983) supporting the lack of affinity to opioid receptors.
It is a well known fact that, when morphine is co-administered at two separate sites in the central nervous system, supraspinal and spinal sites, a multiplicative interaction for antinociception occurs (Roerig and Fujimoto, 1989). Concurrent i.c.v. and i.t. application of lappaconitine produces also an multiplicative interaction suggesting, that lappaconitine acts at a supraspinal level to inhibit nociceptive transmission or to block the spinal action of nociceptive neurotransmitters via descending pathways (Ono and Satoh, 1991a,b). This is supported by the finding that antinociception produced by s.c. and i.c.v. administration of lappaconitine was markedly reduced by pretreatment with the \( \beta \)-adrenoceptor antagonist timolol, and the 5-HT2 antagonist ketanserin, whereas antinociception produced by i.t. administration of the drug was reduced by the \( \alpha \)-adrenoceptor antagonist phenoxybenzamine and by the 5-HT1 antagonist mianserin, whereas antinociception produced by i.t. administration of mesaconitine administered i.c.v. to mice was reduced by pretreatment with the \( \beta \)-adrenoceptor antagonist timolol, and the 5-HT1 antagonist ketanserin, whereas antinociception produced by i.t. administration of mesaconitine in the spinal cord and \( \beta \)-adrenoceptors and 5-HT1 receptors in the brain.

N-Deacetyllappaconitine is an alkaloid which occurs together with lappaconitine in plants of the species *Aconitum* and *Delphinium* and has been reported to have antinociceptive properties, too (Liu et al., 1987; Guo and Tang, 1990, 1991). A previous study (Guo and Tang, 1990) has demonstrated in rat tail flick tests that i.c.v. administration of lappaconitine (20–40 \( \mu \)g per rat) has no analgesic effect, whereas i.c.v. administration of N-deacetyllappaconitine (20–60 \( \mu \)g per rat) elicits a dose-dependent analgesic action. These authors have concluded that lappaconitine may not directly act on the central nervous system. This conclusion has been supported by an investigation of the metabolism of lappaconitine. The metabolic products of lappaconitine in rat urine and human urine have been separated and characterized by high-performance liquid chromatography (Xie et al., 1990a,b). The results show that N-deacetyllappaconitine is a metabolite of lappaconitine. The urine level of lappaconitine decreased gradually over a period of 48 hr following intravenous administration of the drug, whereas the level of N-deacetyllappaconitine increased relative to that of lappaconitine. It has been concluded that lappaconitine is metabolized to N-deacetyllappaconitine by N-deacetylation. Taking these results into consideration, N-deacetyllappaconitine is proposed to be an active metabolite of lappaconitine in rats (Xie et al., 1990b) and in humans (Xie et al., 1990a).

### 3.2. Anti-Inflammatory Effects

The curative effect of rheumatism is one of the reputed therapeutic effects of extracts prepared from *Aconitum* roots in traditional Chinese and Japanese medicine. The *Aconitum* alkaloids mesaconitine (Hikino et al., 1982) and 3-acetylaconitine (Tang et al., 1984) have been shown experimentally to possess anti-inflammatory activity in addition to their above described antinociceptive effect.

Both mesaconitine and 3-acetylaconitine have been shown to inhibit the increased vascular permeability induced by acetic acid in mouse peritoneal cavity and by histamine in rat intradermal sites. The anti-inflammatory effect of both alkaloids were observed in sham-operated mice as well as adrenalectomized mice, confirming that the anti-inflammatory activity was not mediated by glucocorticoids secreted as a result of stimulation of the hypophysis-adrenal system. Mesoacitine prevented hind-paw edema induced by carrageenin or by subcutaneous injection of histamin, serotonin and prostaglandin E1 (Hikino et al., 1982). This indicates that mesaconitine is effective at an early, exudative stage of inflammation.

It is well known that non-steroidal anti-inflammatory agents in general are potent inhibitors of prostaglandin biosynthesis. In opposite to non-steroidal anti-inflammatory agents, mesaconitine fails to inhibit the biosynthesis of prostaglandins in either guinea pig lung homogenate or rat peritoneal activated macrophages (Hikino et al., 1982), indicating that prostaglandin biosynthesis does not participate in the anti-inflammatory actions exerted by this compound.

However, the traditional view, that the analgesic action of non-steroidal anti-inflammatory drugs is only a consequence of their inhibition of the peripheral prostaglandin biosynthesis and, thus, their classification as exclusively 'peripherally acting' drugs is no more longer valid (Jurna and Brune, 1990; Jurna, 1991; McCormack, 1994; Cashman, 1996), since they exert their analgesic effect not only through peripheral inhibition of prostaglandin synthesis but also by suppressing the sensory response of the nociceptive system via a central effect that synergistically augments the peripheral mechanisms. There is experimental evidence that the anti-inflammatory activity of mesaconitine might be exerted through a mechanism involving the central nervous system. When injected into the lateral ventricle of the brain, mesaconitine at doses where it produced marked analgesic activity (40–80 \( \mu \)g per mouse) produced dose-dependent anti-inflammatory effects on paw edema produced by carrageenin and on vascular permeability accelerated by acetic acid and agar (Hikino et al., 1982). Thus, in accordance with the analgesic action, the anti-inflammatory activity of mesaconitine seems to involve the central nervous system, but the mode of action remained unknown. A practical significance of the central analgesic effect of this *Aconitum* alkaloid could be that its applicability is not limited only to the treatment of pain, which results from an activation of nociceptors.
3.3. Antiepileptiform Effects

More recently, certain *Aconitum* alkaloids have been investigated *in vitro* at rat hippocampal slices and have revealed potent antiepileptiform activity. The hippocampal slice model is a useful model for the investigation of putative anticonvulsant drugs. Spontaneous or stimulus-evoked epileptiform activity can be recorded by extracellular microelectrodes in the pyramidal cell layer of area CA3 or CA1, respectively. At the control state, an electrical stimulus to the afferents (i.e. Schaffer collateral fibers) produces a single population spike [Fig. 3(A)] reflecting nearly simultaneous discharge of a few hundred pyramidal neurons. Epileptiform activity can be induced in the hippocampal slice by the addition of convulsants which interfere with the inhibitory transmission such as bicuculline (Campbell and Holmes, 1984; Herron and Collingridge, 1985; Ault and Wang, 1986; Chagnac-Amitai and Connors, 1989) or by exposure to a nominally Mg$^{2+}$-free perfusate in order to activate N-methyl-D-aspartate (NMDA) receptor-mediated responses (Coan and Collingridge, 1985; Mody et al., 1987; Tancredi et al., 1990). After pharmacological induction of epileptiform activity, the electrical stimulus evokes synchronized population bursts, each consisting of multiple spike discharges. Significant components of the epileptiform burst discharge include the presynaptic fiber spike, the first postsynaptic spike and succeeding spikes which define epileptiform activity. In hippocampal area CA3, spontaneously occurring epileptiform discharges can be elicited in absence of electrical stimulation by perfusion of an artificial cerebrospinal fluid (ACSF) which is nominal Mg$^{2+}$-free and has an elevated K$^+$-concentration [Fig. 3(B)].

As shown recently, certain *Aconitum* alkaloids, such as lappaconitine (Ameri et al., 1996c; Ameri, 1997b), 6-benzoylheteratisine (Ameri, 1997a,d), 1-benzoylnapelline (Ameri, 1997e) and mesaconitine (Ameri, 1998b) inhibited the experimentally induced

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**Fig. 3.** Extracellular recording of epileptiform activity in the hippocampal slice. (A) Stimulation of the Schaffer collaterals (sch) evokes a population spike which can be recorded in the CA1 pyramidal cell layer. In control perfusate, neurons discharged synchronously only once, producing one postsynaptic population spike. The postsynaptic spike is preceded by the presynaptic fiber spike which reflects the stimulus-evoked activity of the Schaffer collaterals. After perfusion of the slices by a nominal Mg$^{2+}$-free perfusate, the same stimulus elicits multiple population spike representing epileptiform activity. (B) Perfusion of the slice by a perfusate which is Mg$^{2+}$-free and contains an elevated K$^+$ concentration evokes spontaneous epileptiform bursting which can be recorded in the CA3 pyramidal cell layer.
epileptiform activity. Lappaconitine (Fig. 4) has been shown to selectively suppress the later population spikes in the epileptiform burst, which represent pathological activity, while sparing the first postsynaptic spike, which represent normal neuronal activity (Ameri et al., 1996c). These findings are consistent with the interpretation that lappaconitine inhibits selectively excessive neuronal activity, thus blocking the generation and spread of aberrant activity by sparing normal activity.

In a recent study, the effects of the Aconitum alkaloid mesaconitine on both stimulus-triggered and spontaneous epileptiform activity in rat hippocampal slices has been described (Ameri, 1998b). Both stimulus-triggered epileptiform activity (Fig. 5) and spontaneous epileptiform activity (Fig. 6) was attenuated by mesaconitine in a concentration-dependent manner (0.03–1 μM). Frequency, duration and amplitude of the burst were decreased by the alkaloid. The α-adrenoceptor antagonist yohimbine (1 μM) antagonizes the antiepileptiform effect of mesaconitine when both compounds were applied together, whereas the β-adrenoceptor antagonist timolol has no effect on the mesaconitine-evoked antiepileptiform action (Figs 5 and 6). These findings provide clear evidence for an involvement of α-adrenoceptor activation in the inhibitory action of mesaconitine on experimentally induced epileptiform activity in the hippocampus. Noradrenaline is known to exert a variety of effects at α- as well as β-adrenoceptors in the hippocampus. The hippocampus has been reported to receive a diffuse pro-

![Aconitum alkaloids on the CNS](image)
Fig. 5. Effect of the *Aconitum* alkaloid mesaconitine (MES, 30 nM) on stimulus-evoked epileptiform activity recorded extracellularly in CA1 pyramidal cell layer. Epileptiform activity was induced by a nominal Mg\(^{2+}\)-free perfusate. (A) The \(\beta\)-adrenoceptor antagonist timolol (TIM, 1 \(\mu\)M) did not affect the antiepileptiform activity of mesaconitine, whereas (B) the \(\alpha\)-adrenoceptor antagonist yohimbine (YOH, 1 \(\mu\)M) prevented this effect. Neither antagonist affected the extracellular recorded population spikes prior to the addition of mesaconitine [taken from Ameri (1998b)].
Fig. 6. Inhibition of spontaneously occurring epileptiform activity in hippocampal area CA3 by mesaconitine (MES, 30 nM) and its antagonism by the α-adrenoceptor antagonist yohimbine. Epileptiform activity was elicited by a nominal Mg²⁺-free perfusate with elevated K⁺ concentration (5 mM). (A) In presence of the β-adrenoceptor antagonist timolol (TIM, 1 μM), mesaconitine suppressed the spontaneous discharges. (B) The antiepileptic effect of mesaconitine was abolished by the α-adrenoceptor antagonist yohimbine (YOH, 1 μM). Neither timolol nor yohimbine affected the spontaneously occurring epileptiform bursting prior addition to mesaconitine [taken from Ameri (1998b)].
jection of noradrenaline containing fibers which originate in the locus coeruleus (Loy et al., 1980; Mongeau et al., 1997) and activation of these noradrenergic afferents has a profound influence on neuronal activity in the hippocampus (Olpe et al., 1986; Washbourn and Moises, 1989). Noradrenaline, in turn, has been reported to interact with $\alpha$-adrenoceptors to increase hippocampal pyramidal cell excitability and with $\beta$-adrenoceptors to increase cell excitability (Mueller et al., 1981, 1982). Moreover, there is mounting evidence for a role of noradrenaline in long-term plasticity and its contribution in the process of seizure development (Stanton et al., 1992; Gundlach et al., 1995). It has been previously shown, that noradrenaline can have both pro- and anticonvulsive properties in the hippocampal slice (Rutecki, 1993). At higher concentrations ($\geq 10 \mu M$), noradrenaline attenuated spontaneous epileptiform discharges. This effect is mediated by a hyperpolarization due to an activation of a $K^+$ conductance and a reduction in glutamatergic transmission via $\alpha$-adrenergic receptors (Pralong and Magistretti, 1995). Moreover, noradrenaline has been reported to evoke potent antiepileptic effects via $\alpha_2$-adrenoceptors in amygdala-kindled kittens (Shouse et al., 1996a,b). There is evidence that the $\alpha$-adrenoceptor-mediated antiepileptic effect of mesaconitine is mediated by an enhanced neuronal release of noradrenaline. It has been demonstrated that mesaconitine induces contractions of the guinea-pig vas deferens which are due to an increase in the neuronal release of noradrenaline (Sato et al., 1979). The increase in the release of noradrenaline could be reduced by depletion of calcium from the bathing medium and prevented completely by treatment with tetrodotoxin (TTX) or by prior reserpinization of the animal. These effects were interpreted as indicating that mesaconitine caused presynaptic release of noradrenaline and acted postsynaptically in some way that potentiated the effect of the transmitter.

The common antinociceptive (Hikino and Murayama, 1985; Murayama et al., 1984; Oyama et al., 1994) and antiepileptiform effect of the Aconitum alkaloid mesaconitine (Ameri, 1998b) seems to be intriguing in view of the fact that novel antiepileptic drugs, such as lamotrigine, have been reported to be effective in the treatment of chronic pain (Canavero and Bonicalzi, 1996; Hunter et al., 1997; Zakrzewska et al., 1997).

3.4. Other Pharmacological Effects

Apart from the broad range of pharmacological effects of aconitine and its derivatives in the central nervous system (CNS), attention has been focused on the cardiovascular effects of this group of compounds. As mentioned already, the Aconitum alkaloids aconitine, 3-acetylccamine and mesaconitine induce tachyarrhythmia. In contrast, the alkaloids, lappaconitine, N-deacetyllappaconitine, 6-benzoylheteratisine, heteratisine and napelline have been reported to possess antiarrhythmic effects (Dzhakhangirov and Sadritdinov, 1985a,b; Sokolov et al., 1988; Abdalla et al., 1989). The ED$_{50}$ value for the antiarrhythmic action of lappaconitine comprised 0.05 mg kg$^{-1}$ after intravenous injection to rats (Dzhakhangirov and Sadritdinov, 1985a,b). The therapeutic use of lappaconitine for the treatment of arrhythmia in humans has already been investigated in clinical studies (Sokolov et al., 1988; Abdalla et al., 1989). Certain diterpenoid alkaloids isolated from plant species Aconitum and Delphinium have hypotensive and bradycardic actions which may be due to an activation of autonomic reflexes. Recently, it was reported that lappaconitine as well as N-deacetyllappaconitine are capable to reduce arterial blood pressure and lower heart rate when given at a dose of 0.15 mg kg$^{-1}$ i.v. to dogs (Chiao et al., 1995) suggesting that both alkaloids may be useful in the treatment of hypertension. It is known that stimulation of cardiac reflex receptors and stimulation of arterial baroreceptors will cause an increase in cardiac vagal afferent nerve activity and a decrease in cardiac sympathetic nerve activity (Rebagay and Calwell, 1992). Thus, the ability of lappaconitine and N-deacetyllappaconitine to alter cardiac vagal afferent nerve activity and cardiac sympathetic activity implies that these effects are due to activation of cardiac reflex receptors.

4. MECHANISMS OF ACTION OF CERTAIN ACONITUM ALKALOIDS

4.1. Interaction with the Voltage-Dependent Na$^+$ Channel

The mechanism of action of aconitine at least at nerve and muscle seems to be rather well known. Electrophysiological experiments have revealed further insight into the mode of interaction of aconitine with central neurons by investigating synchronously discharging action potentials (population spikes) in the CA1 pyramidal cell layer as well as voltage-dependent Na$^+$ currents in cultivated neurons of the rat hippocampus (Ameri et al., 1996a,b; Ameri and Peters, 1996). Moreover, recent experimental data obtained with the same methods at the same preparations allow a comparison of the action of the structural related alkaloids with those of aconitine (see below).

4.1.1. The Voltage-Dependent Na$^+$ Channel and Its Neurotoxin Binding Sites

The alkaloid aconitine is one of the most powerful modulators of the voltage-dependent Na$^+$ channel. The physiological function of the Na$^+$ channel is fulfilled by the $\alpha$-subunit [for review see Catterall (1992) and Fozzard and Hanck (1996)]. In brain, two additional subunits ($\beta_1$ and $\beta_2$) are associated with the $\alpha$-subunit. It is still controversial, if the cardiac Na$^+$ channel includes any $\beta$-subunit. Four distinct but highly homologous ($>85\%$ sequence identity) primary structures of Na$^+$ channel $\beta$-subunits have been cloned from the rat brain (type I, II, IIA and III) and one from the rat heart (Noda et al., 1984; Auld et al., 1988; Kayano et al., 1988; Rogart et al., 1989). The splice variant type IIA is abundant in the adult rat brain. The brain type IIA $\beta$-subunit consists of four homologous domains (I–IV), each composed of six membrane-spanning
hydrophobic sequences (S1–S6) and connecting intra- and extracellular loops [Fig. 7(A)].

Several natural occurring toxins alter the normal functioning of the Na⁺ channel protein (Catterall, 1988, 1992; Adams and Olivera, 1994). At least five binding sites for toxins have been identified [Fig. 7(B)]. Neurontoxin receptor site 1 is thought to be located near the extracellular opening of the ion-conducting pore. The water-soluble heterocyclic guanidines TTX and saxitoxin bind to this site and block the influx of Na⁺ ions independent from the channel conformation. This binding site is located on the S5–S6 linker of domain I. Cardiac Na⁺ channels bind TTX with 200-fold lower affinity than brain Na⁺ channels. Site-directed mutagenesis and toxin assays have made residue 385 of the α-subunit essential for high affinity TTX binding.

Neurontoxin receptor site 2 is localized in the transmembrane region and lipophilic toxins, including batrachotoxin, aconitine and veratridine have high affinity to this site (Catterall, 1988, 1992; Adams and Olivera, 1994). These toxins cause per-

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**Fig. 7.** The sodium channel and its neurotoxin binding sites. (A) Proposed transmembrane folding of the α-subunit of the sodium channel. The repeats 1 to IV are membrane-spanning domains each consisting of six hydrophobic α-helices. The cytoplasmatic loop (h) is the putative inactivation gate. The fourth segment is positively charged and thought to be the voltage sensor [modified from Catterall (1992)]. (B) Schematic drawing of the neurotoxin binding sites on the sodium channel. Four toxin sites are shown for tetrodotoxin (TTX), aconitine (ACO), α-scorpion toxin (α-ScTx) and β-scorpion toxin (β-ScTx). Local anaesthetics are thought to bind within the pore [adapted from Catterall (1992) and Wann (1993)].
sistent activation of Na\textsuperscript{+} channels at the resting membrane potential by blocking Na\textsuperscript{+} channel inactivation and shifting the voltage-dependence of the channel activation to a more negative membrane potential. As the site 2-selective toxins also alter the ion selectivity of the Na\textsuperscript{+} channel, this receptor site is likely to be in a region of the \(\alpha\)-subunit which is involved in voltage-dependent activation and inactivation, and allosterically linked to the transmembrane pore of the channel. As these toxins are large molecules, their multiple effects can also result from an interaction at several microsites of the \(\alpha\)-subunit (Zamponi and French, 1994). Several local anaesthetics, anticonvulsants (phenytoin and lamotrigine) and antiarrhythmic agents (class 1) have been shown to inhibit neuronal excitability by interacting with neurotoxin receptor site 2 of the Na\textsuperscript{+} channel (Catterall, 1987; Rogawski and Porter, 1990). This inhibition is likely to result from indirect allosteric coupling between the receptor site 2 and the receptor site for these drugs. The molecular site of local anaesthetic block is thought to be in the ion conductance pathway, near the inactivation gate and the selectivity filter.

Neurotoxin receptor site 3 binds polypeptide toxins which slow or block Na\textsuperscript{+} channel inactivation and enhance persistent activation induced by neurotoxins acting at site 2 through allosteric interactions (Catterall, 1992). Receptor site 3 is likely to be located on a hydrophobic region of the \(\alpha\)-subunit that undergoes a conformational change during voltage-dependent channel activation. Neurotoxin receptor site 4 binds \(\beta\)-scorpion toxin which shift the voltage-dependent activation of the channel to more negative potentials leading to transient repetitive activity and blockage of ion influx. Channel inactivation is unaltered. Brevetoxins and ciguatoxins, two classes of polyethertoxins, bind to neurotoxin receptor site 5 which is presumed to be located at the extracellular site of the \(\alpha\)-subunit. They cause repetitive firing of nerves, block inactivation and shift the voltage-dependence of activation to more negative potentials. They enhance allosterically the binding and action of neurotoxins acting at site 2 and 4.

### 4.1.2. Activation of the Voltage-Dependent Na\textsuperscript{+} Channel

In membranes of rat brain and of cardiac myocytes, aconitine has been found to inhibit \([^3]H\)batrachotoxinin A 20 \(\beta\)-benzoate (BTX) binding with a \(K_I\) value of 1.12 and 1.7 \(\mu M\), respectively (Shimidzu et al., 1997). Binding of aconitine to site 2, leads to sustained activation of the channel by blocking channel inactivation (Catterall, 1988). Activation threshold of the Na\textsuperscript{+} current is shifted ca. 50 mV towards more hyperpolarized potentials, and maximum inward current is reduced (Schmidt and Schmidt, 1974; Grischenko et al., 1983). In consequence, aconitine-modified Na\textsuperscript{+} channels open at more negative membrane potentials than normal Na\textsuperscript{+} channels. Due to the suppression of inactivation of the Na\textsuperscript{+} channel, aconitine depolarizes neuronal membranes. Nodal membranes of myelinated nerve fibers of Xenopus laevis are depolarized by 10–15 mV (Schmidt and Schmidt, 1974).

Since aconitine activates Na\textsuperscript{+} channel already at resting membrane potential, it evokes a transient enhancement in excitability which has been previously observed as a sudden and transient increase in amplitude of extracellular recorded population spikes in rat hippocampal slices at a concentration of 1 \(\mu M\) (Ameri et al., 1996d). Due to the massive influx of Na\textsuperscript{+} ions, the excitation is followed by complete inexcitability of nerve cells (Schmidt and Schmidt, 1974; Onur et al., 1995, Ameri et al., 1996d). The onset of inhibitory action has been reported to be critically dependent on frequency of electrical stimulation rather than on duration of its application (Ameri et al., 1996a,d) suggesting an use-dependent mode of action. This finding is in line with a previous report demonstrating a frequency-dependent action of aconitine (1 \(\mu M\)) at isolated guinea-pig papillary muscle (Honerjäger and Meissner, 1983). The prolonged Na\textsuperscript{+} influx during the action potential was shown to cause a TTX-sensitive positive inotropic effect preceding the arrhythmogenic phase of the aconitine action. Activation of Na\textsuperscript{+} channels may also account for the antinoceptive properties as demonstrated for aconitine by writhing and tail flick test (Hikino et al., 1979). Since aconitine blocks neuromuscular transmission of isolated phrenic nerve-diaphragm muscle without affecting the contraction of the muscle itself (Muroi et al., 1990; Onur et al., 1995), permanent neuronal depolarization may induce a blockage of neuronal conductance which seems to be responsible for the suppression of pain transmission as described above. However, it cannot be excluded, that due to the low doses for toxic effects of aconitine the behavioural studies may be confounded by other actions of this alkaloid.

The aconitine-induced inhibition of neuronal excitability recorded extracellularly in hippocampal slices does not differ from the inhibition evoked by veratridine, which also activates Na\textsuperscript{+} channel (Ameri et al., 1996d). However, marked differences in the action of both alkaloids become obvious after their washout. It has been recently reported, that during washout of 1 \(\mu M\) aconitine the amplitude of the ortho- and antidromic population spike recorded in CA1 region of hippocampal slices was markedly enhanced (up to 150\%) compared with the control value prior to addition of the alkaloid (Ameri and Peters, 1996). This potentiation of hippocampal excitability was sustained during an observation period of several hours and the amount of increase was dependent on the aconitine concentration (0.1–1 \(\mu M\)). Since veratridine failed to evoke an enhancement of the spike amplitude, this finding implies that different mechanisms might be involved in the action of both alkaloids. Furthermore, this study has demonstrated, that the aconitine-induced enhancement of population spike amplitude is prevented:

1. by lowering the Ca\textsuperscript{2+} concentration of the bathing medium during the application of aconitine (Fig. 8); and
2. in the presence of inhibitors of protein kinase C and Ca\textsuperscript{2+}/calmodulin-dependent protein kinase II.
CaCl₂), the CaCl₂ concentration of the perfusate was low-
perfusate with standard calcium concentration (2.5 mM
hibition was still observed. (B) After a control period in a
aconitine evokes an increase in intracellular Ca²⁺
pressed recovery from the aconitine-induced inhi-
bation. Taken together, these findings suggest that
CD₂⁺ which failed to affect the antidromic popu-
lation spike prior to addition of aconitine, not only
mediated the sustained increase in excitability which
becomes obvious after reversion of the acute aconi-
tine-induced inhibition. This conclusion raises the
question by which way Ca²⁺ may enter the cell.
Since aconitine is known to change the selectivity of
the Na⁺ channel in so far that it becomes temporarily
permeable for divalent cations (Nilius et al., 1986; Frelin et al., 1986) it has been proposed that
Ca²⁺ as well as Cd²⁺ can enter the Na⁺ channel,
the former activating protein kinases leading to the
sustained potentiation in excitability, the latter
inhibiting the channel (Ameri and Peters, 1996). An
additional way of Ca²⁺ entrance into the cell has
been suggested to occur via a reversion of the Na⁺ /
Ca²⁺ exchanger (Onur et al., 1995).

There are several examples of apparent mis-
matches between the results obtained with electrophysiological methods at different preparations.
First, it is intriguing that aconitine affects the Na⁺
current at neuroblastoma cells only at a concen-
tration of at least 300 μM (Grischenko et al., 1983),
whereas Na⁺ currents in single cells isolated from
mouse ventricular myocardium are modified by aco-
nitine in a concentration of 1 μM (Nilius et al.,
1986). A concentration-dependent inhibition of
extracellularly recorded population spikes evoked by
electrical stimulation in slices of the rat hippo-
campus was observed in a concentration range of
0.01–1 μM (Ameri et al., 1996b). Second, aconitine-
modified Na⁺ channels in frog nerve have been
shown to inactivate incompletely (Schmidt and
Schmidt, 1974), whereas heart cell Na⁺ channels
inactivate both completely and fast at membrane
potentials positive to −40 mV, but extremely slowly
at membrane potentials negative to −40 mV (Nilius et al., 1986). Moreover, in patch clamp experiments
at neuroblastoma cells performed in the outside–out
mode, aconitine completely failed to affect the Na⁺
current even in concentration of up to 200 μM
(Negulayev et al., 1990). This findings suggest that
the interaction of aconitine with the Na⁺ channel is
promoted by cytosolic factors which are absent in
outside–out patches (Negulayev et al., 1990).
Nevertheless, it cannot be excluded that the different
preparations differ in their in response to aconitine.
Aconitine might interact differentially with various
channel subtypes occurring in various preparations
or in different developmental stages. This view is
supported by the recent observation of age-depen-
dent differences in sensitivity to aconitine in rat hip-
PCampal slices (Ameri, 1996). The results of this
study demonstrate that aconitine exerts a stronger
inhibition of stimulus-evoked population spikes in
hippocampal slices prepared from juvenile rats (20–
25 days) than in slices from adult rats (45–50 days).
In has been concluded that the higher susceptibility
might reflect different affinities of aconitine to the
three subtypes of the z-subunit of the Na⁺ channel
which are known to show a different temporal ex-
pression pattern during postnatal development
(Beckh et al., 1989; Brysch et al., 1991).

With respect to the relation of chemical structure
it is not surprising that the alkaloid 3-acetylaconi-
tine which has recently been investigated by electrophysiological methods in the slice preparation and
on cultivated neurons of rat hippocampus shows a
similar mechanisms of action as aconitine (Ameri,
1997c). Following a transient period of epileptiform
hypereexcitability, 3-acetylaconitine (0.01–1 μM)
diminished the orthodromic and the antidromic
population spike recorded extracellularly in area

Fig. 8. Calcium dependence of the aconitine-evoked
enhancement of the antidromic population spike recorded
extracellularly in hippocampal area CA1. (A) Aconitine
(1 μM) was applied in a perfusate which contains 2.5 mM
CaCl₂. When washout of aconitine was performed by a
perfusion which contained only 1.25 mM CaCl₂, the poten-
tiation was still observed. (B) After a control period in a
perfusate with standard calcium concentration (2.5 mM
CaCl₂), the CaCl₂ concentration of the perfusate was low-
ered to 1.25 mM. The inhibitory effect of aconitine (1 μM)
was unchanged when added to this low calcium perfusate,
but recovery from the initial aconitine effect was attenu-
ated and the enhancement of the spike amplitude abol-
ished. Application of aconitine is indicated by the black
bar, application of the low calcium perfusate by the
hatched bar (taken from Ameri and Peters (1996)].
CA1 of hippocampal slices in a concentration-dependent manner. The latency of onset of the inhibition was accelerated by increased stimulation frequency indicating an activity-dependent mode of action. As shown in Fig. 9, whole-cell patch clamp recordings on cultivated hippocampal pyramidal cells revealed that 3-acetylaconitine (1 μM) activates voltage-dependent Na⁺ currents already at resting membrane potentials due to a shift of the activation threshold in hyperpolarized direction without affecting the peak amplitude of the current (Ameri, 1997c). This shift is consistent with the hyperexcitability which was observed in the hippocampal slices immediately after addition of the alkaloid. Despite the fact that both aconitine and 3-acetylaconitine have a similar chemical structure and share the same mechanism of action, it is intriguing that 3-acetylaconitine completely failed to induce a Ca²⁺-dependent long-lasting increase in population spike amplitude which became obvious after washout of aconitine. These differences in the action of aconitine and 3-acetylaconitine could result from an interaction with different subdomains of the alkaloid-binding region on the α-subunit of the Na⁺ channel.

4.1.3. Inhibition of the Voltage-Dependent Na⁺ Channel

In marked contrast to the Aconitum alkaloids aconitine and 3-acetylaconitine the mechanism of action of other structurally related alkaloids aconitine and 3-acetylaconitine could result from an interaction with different subdomains of the alkaloid-binding region on the α-subunit of the Na⁺ channel.

Fig. 9. Effect of 3-acetylaconitine (3-AC, 1 μM) on voltage-dependent sodium-current in hippocampal pyramidal cells. (A) Sodium currents evoked by a voltage-step from −90 to −70 mV (left) and to −55 mV (right). The currents were blocked by 0.5 μM TTX. (B) Current–voltage relationship of peak sodium currents in the absence (●) and in the presence of (○) 1 μM 3-acetylaconitine. Peak currents are plotted as function of membrane potential (V_m). Cells were maintained at a holding potential of −90 mV. Data points represent the mean ± SD of five experiments [taken from Ameri (1997c)].
past. However, especially these less toxic alkaloids are obtained during heat processing of crude *Aconitum* tubers and thus merit more interest.

Lappaconitine has been previously reported to exert an inhibitory effect on inward TTX-sensitive Na⁺ currents when applied at concentrations from 1–10 μM to neurons isolated from rat trigeminal ganglion and cardiomyocytes (Valeev et al., 1990). This is supported by a recent finding which shows that both lappaconitine and its main metabolite N-deacetyllappaconitine have an inhibitory effect on the voltage-dependent Na⁺ channel in rat hippocampal neurons at a concentration of 10 μM (Seitz and Ameri, 1998). In contrast to aconitine and 3-acetylaconitine, lappaconitine and N-deacetyllappaconitine do not evoke a shift in the activation threshold of the Na⁺ current towards hyperpolarized potentials but reduce the peak amplitude of the current (Fig. 10). Moreover, the effects of lappaconitine on neuronal excitability were compared with the effects of N-deacetyllappaconitine and the structurally related alkaloid lappaconidine in rat hippocampal slices (Ameri, 1997b). At concentrations of 1–100 μM, both lappaconitine and N-desacetyllappaconitine were shown to inhibit the orthodromic and antidromic population spikes elicited by stratum radiatum and alvear stimulation, respectively, as well as the field excitatory postsynaptic potential (Fig. 10).

**Fig. 10.** Inhibitory effect of lappaconitine (LAP, 10 μM) on the voltage-dependent sodium current in hippocampal pyramidal cells. (A) Sodium currents evoked by voltage steps from −80 mV at control (left) and in presence of lappaconitine (right). (B) Current–voltage relationship of peak sodium currents in the absence () and in the presence of (○) 10 μM lappaconitine. Peak currents are plotted as function of membrane potential (V_m). Cells were maintained at a holding potential of −80 mV. Data points represent the mean ± SD of five experiments [taken from Seitz and Ameri (1998)].
aptic potential (EPSP) recorded in the dendrite layer of CA1 stratum radiatum. The drug-induced depression of the evoked field potential responses was increased with increasing stimulus frequency indicating an use-dependent mode of action. Moreover, this study revealed that the effect of N-deacetyllappaconitine on each parameter measured was significantly stronger than the effect of lappaconitine. This finding is in line with previous results of in vivo studies which demonstrated that the cardiovascular effects of N-deacetyllappaconitine were stronger than those of lappaconitine (Chiao et al., 1995). Despite the structural relationship with the two aforementioned compounds, the alkaid lappaconidine, which does not bear a benzoylster side chain at the diterpene skeleton, failed to affect neuronal excitability at concentrations below 100 μM (Ameri, 1997b). Both lappaconitine and N-deacetyllappaconitine have been shown to diminish the antidromic population spike, that is, the compound action potential of the neurons recorded from, also when synaptic transmission was suppressed by either CNQX or by perfusion of a Ca²⁺-free ACSF. A recent report provided evidence that the Aconitum alkaloids 6-benzoylheteratisine and 1-benzoylnapelline share the actions of lappaconitine and N-deacetyllappaconitine determined by extracellular recording from normal and epileptiform hippocampal slices (Ameri, 1997a,d,e). 6-Benzoylheteratisine (0.01–10 μM) and 1-benzoylnapelline (1–100 μM) exerted a concentration-dependent inhibition of both the orthodromic and the antidromic population spike. The inhibition was markedly enhanced by increasing the frequency of electrical stimulation. At a concentration of 10 μM both compounds were capable to suppress epileptiform burst discharges in the hippocampal slice. The structurally related alkaloids heteratisine and napelline, however, were shown to evoke a diminution of the orthodromic spike and the field EPSP in concentrations of at least 10 and 100 μM, respectively. It is intriguing that lappaconidine, heteratisine and napelline, which lack a benzoylster group at the diterpene skeleton (Fig. 1) attenuated the synaptically evoked field potentials, but completely failed to affect the antidromic spike which is elicited by direct, averse stimulation of the CA1 pyramidal cells. Furthermore, the effect of the latter three compounds was independent on stimulation frequency. From these evidences it seems likely that these compounds affect predominantly synaptic transmission. Nevertheless, in regard to the rather high concentrations necessary to exert an inhibitory effect on the synaptically evoked field potentials, independent on stimulation frequency, this action might include nonspecific mechanism due to their lipophilic nature.

Taken together, the group of alkaloids which contains lappaconitine, N-deacetyllappaconitine, 6-benzoylheteratisine and 1-benzoylnapelline inhibits aberrant excessive activity which occurs during excessive excitability, thereby blocking the generation and spread of aberrant activity by sparing normal neuronal activity. The activity-dependent effects of these alkaloids may be important for filtering high frequency bursts of action potentials characteristic for epileptiform activity. It is concluded that the activity-dependent fashion of these alkaloids contributes to the therapeutic actions of these agents (Ameri, et al., 1996c; Ameri, 1997b). This finding indicates that both compounds inhibit predominantly excitability of the afferents and, in consequence, neurotransmission at the dendrites. This assumption is supported by a previous report which has shown that lappaconitine does not affect currents activated by various neurotransmitters such as glutamate, γ-aminobutyric acid (GABA), glycine, taurine and adenosine 5′-triphosphate (ATP) in trigeminal neurons (Valeev et al., 1990). Moreover, there is a large body of evidence for Na⁺ channels in the dendrites of pyramidal cells which actively propagate information within the dendritic tree of pyramidal neurons and contribute to an amplification of synaptic potentials (Stuart and Sakmann, 1994, 1995). Since lappaconitine is known to block voltage-dependent sodium channels (Valeev et al., 1990; Seitz and Ameri, 1998), it thereby could suppress amplification of the EPSPs at a dendritic level. As described already, both lappaconitine and N-deacetyllappaconitine have been shown to exert antiepileptiform activity in rat hippocampal slices (Ameri et al., 1996a,c; Ameri, 1997b). This effect is in line with the activity-dependent and Na⁺ channel blocking properties of these alkaloids. Use-dependent block of voltage-dependent Na⁺ channels is a common action of local anaesthetics, antiaarrhythmic agents (class I) and of anticonvulsants like, for example, phenytoin-like drugs. This, in turn, explains their antiepileptic and neuroprotective effects (for review see Taylor and Meldrum (1995)). Moreover, it is well known, that Na⁺ channels underlie detrimental influx of Na⁺ ions in neurons during the pathophysiological state of seizures (Sashihara et al., 1992). With consideration of the Na⁺ channel blocking effect of lappaconitine and N-deacetyllappaconitine it is concluded that the high-frequency discharges of action potentials as they can occur for instance during seizure activity could be a prerequisite for the blocking action of these two drugs. This mode of action would explain the previous reported antiaarrhythmic effect of lappaconitine (Dzhakhangirov and Sadrizinov, 1985a,b; Sokolov et al., 1988; Abdalla et al., 1989) as well as the recently reported antiepileptiform activity of lappaconitine and N-deacetyllappaconitine (Ameri, 1996, 1997b).
reflects their accumulation in open Na⁺ channels as described for conventional phenytoin-like anticonvulsants and class I-antiarrhythmics (Catterall, 1987; Ragsdale et al., 1991; Taylor and Meldrum, 1995).

4.2. Interaction with the Noradrenergic System

Although there is strong evidence from in vivo studies that the analgesic action of the Aconitum alkaloids involves the noradrenergic system, the mechanisms of this interaction are still unknown. However, recently, the first in vitro studies have been performed in order to examine this question. The effect of aconitine, 3-acetylaconitine, lappaonitine and N-deacetyllappaconitine to inhibit [³H]noradrenaline uptake has been investigated in synaptosomes prepared from rat hippocampus (Seitz and Ameri, 1998). This study revealed that both aconitine and 3-acetylaconitine are capable to inhibit [³H]noradrenaline uptake in a concentration-dependent manner (Fig. 11). Furthermore, this study has shown that the inhibition of [³H]noradrenaline uptake by these two alkaloids was antagonized by the Na⁺ channel blocker TTX. It has been concluded that the blockade of the [³H]noradrenaline uptake evoked by both compounds is mediated indirectly by an increased Na⁺ concentration in the synaptosomes. It is known that the energy for reuptake of noradrenaline, which is often against the concentration gradient, is derived from the cotransport of Na⁺ (Lester et al., 1994). An increase in the intracellular Na⁺ concentration and, in turn, a decrease in the electrochemical gradient attenuates the uptake of noradrenaline. Since aconitine and 3-acetylaconitine activate the Na⁺ channel already at resting membrane potential, the Na⁺ gradient and consequently the noradrenaline uptake is disturbed. The dependence of the noradrenaline transporter on Na⁺ channel activity is supported by the finding that the Na⁺ blocker TTX enhances [³H]noradrenaline uptake (Seitz and Ameri, 1998). These results are in line with the analgesic action of 3-acetylaconitine, since blockade of noradrenaline uptake by specific uptake blockers, such as desipramine, is known to potentiate the antinociceptive action of endogenous noradrenaline (Sawynok and Reid, 1996).

In contrast, lappaonitine and N-deacetyllappaconitine, which both inhibit Na⁺ channels have been reported to exert no effect on [³H]noradrenaline uptake (Seitz and Ameri, 1998) due to a blockade of uptake (Ameri and Seitz, 1998). However, both these alkaloids were shown to antagonize the ability of aconitine and 3-acetylaconitine to inhibit [³H]noradrenaline uptake into synaptosomes. This antagonism is likely to be a consequence of the different effects at the voltage-dependent Na⁺ channels and must might reflect a competitive antagonism at the same binding site at the channel protein.

Recently, mesaconitine has been shown to also interact with the noradrenergic system (Ameri, 1998a). At low concentrations (≤10 nM), mesaconitine evoked long-lasting excitations, which were manifested as an enhancement of the extracellularly recorded population spike in the hippocampal area CA1 as well as the appearance of multiple epileptiform spikes following the first postsynaptic spike. The magnitude of paired-pulse facilitation was not affected by mesaconitine indicating that the drug does not alter the probability of transmitter release. At an intermediate concentration range (30–100 nM), mesaconitine evoked a biphasic effect, that is an excitation followed by an inhibition. At concentrations above 100 nM, the alkaloid suppressed the population spikes. The enhancement of the population spike by mesaconitine and the appearance or multiple spikes were blocked by pretreatment with the β-adrenoceptor antagonists propranolol and timolol [Fig. 12(A)] and mimicked by the β-adrenoceptor agonist isoproterenol, whereas the inhibitory effect was blocked by the z-adrenoceptor antagonists yohimbine and phentolamine [Fig. 12(B)]. The latter result is in line with the finding of an z-adrenoceptor-mediated antiepileptiform effect of mesaconitine (Ameri, 1998b) as described in Section 3.3. Coupled with the fact that mesaconitine failed to alter the magnitude of paired-pulse facilitation, these findings imply a postsynaptic locus of action leading to the long-lasting enhancement of pyramidal cell excitability. Moreover, this study (Ameri, 1998a) has shown that the mesaconitine-evoked persistent enhancement of neuronal excitability is mediated via an increase in cAMP, because the alkaloid has no effect after pretreatment of the slices with the selective inhibitor of the cAMP-dependent protein kinase A, H-89 and no additional effect after pretreatment with the stimulator of adenylate cyclase, forskolin. However, the question remains whether mesaconitine interact directly with the noradrenergic receptors. Assuming that mesaconitine, like aconitine and 3-acetylaconitine, is capable of activating voltage-dependent Na⁺ chan-
Fig. 12. Action of mesaconitine and adrenoceptor antagonists on the amplitude of the orthodromic population spike in area CA1 of hippocampal slices. (A) Pretreatment with the β-adrenoceptor antagonist timolol (TIM, 1 μM) demasked the inhibitory effect of mesaconitine (MA, 30 nM), but abolished its excitatory effect. (B) Pretreatment of the slices with the α-adrenoceptor antagonist yohimbine (YOH, 1 μM) caused mesaconitine (MA, 30 nM) to exert a sustained enhancement of the population spike and to evoke multiple epileptiform spikes. The black bars above the graphs indicate the application of mesaconitine, the hatched bars the application of the adrenoceptor antagonists [taken from Ameri (1998a)].
nells, it seems likely that it can induce blockade of noradrenaline uptake as reported for the two latter alkaloids. On the other hand, there is evidence that mesaconitine evokes release of noradrenaline as reported for the mesaconitine-induced contractions of the guinea-pig vas deferens (Sato et al., 1979).

4.3. Interaction with the Cholinergic System

Aconitine has been reported to block neuromuscular transmission and induces depolarization in the frog (Nanasi et al., 1990) and mouse (Muroi et al., 1990) skeletal muscles. Moreover, aconitine is reported to block the end-plate potential without affecting the amplitude of miniature end-plate potentials but by reducing the evoked quantal release (Muroi et al., 1990). At low concentrations, aconitine increased electrically evoked [3H]acetylcholine release from motor nerve terminals of the mouse diaphragm, while at higher concentrations the evoked [3H]acetylcholine release was decreased (Okazaki et al., 1994). More recently, it has been shown that the aconitine-induced neuromuscular blockade is mainly due to presynaptic mechanisms which can be explained by excessive presynaptic depolarization which leads to the blockade of nerve action potentials and end-plate potentials (Onur et al., 1995). However, methyllycaconitine, a derivative of aconitine which occurs mainly in plants of Delphinium species, has been described as a potent competitive antagonist at the nicotinic acetylcholine receptors and thereby blocking the nicotinic responses (Alkondon et al., 1992; Hardick et al., 1996; Yum et al., 1996). Methyllycaconitine is remarkable in being highly selective for the subclass of the neuronal nicotinic acetylcholine receptor that are sensitive to the snake toxin z-bungarotoxin-sensitive (Hardick et al., 1996; Yum et al., 1996). Moreover, it has been shown that aconitine can be converted into a potent nicotinic ligand, comparable to methyllycaconitine, with concomitant loss of TTX-sensitive Na⁺ channel activation, by addition of a 2-(methylsuccinimido)benzoyl side chain (Hardick et al., 1995). This finding indicates a major step towards the rational design of receptor subtype-selective drugs derived from Aconitum alkaloids.

5. STRUCTURE–ACTIVITY RELATIONSHIP

With respect to the findings obtained with electrophysiological methods, it is intriguing that those Aconitum alkaloids, which lack the benzoyl ester side chain in the steroid skeleton of the molecule differ markedly from the alkaloids bearing this group: first, their inhibitory potency was lower. Second, and more important, they diminished only the orthodromic population spike but completely failed to alter the size of the antidromic spike. Third, the inhibition was independent from stimulation frequency. These differences underline the importance of the benzoyl ester as an essential group for interaction with the binding site at voltage-dependent Na⁺ channels. Furthermore, aconitine and 3-acetylaconitine which are known to suppress inactivation of Na⁺ channel and to activate the current already at resting potential have a benzoyl ester side chain in C14-position. Thus, it seems to be the benzoyl ester group and its position which determine the interaction with the binding site on the α-subunit of the Na⁺ channel protein.

Considering the chemical structure of the Aconitum alkaloids reported in this review as well as their mode of action a subdivision in three groups becomes obvious: the first group comprises the alkaloids aconitine, mesaconitine and 3-acetylaconitine. The common structural properties of these alkaloids primarily responsible for the high toxicity are the ester boundings at C8 and C14. Removal of these ester groups by hydrolysis is known to cause sharp decrease in toxicity (Katz and Rudin, 1984; Zhou et al., 1984; Yang, 1985; Murayama et al., 1991; Isono et al., 1994). These compounds are reported to evoke arrhythmia and to be potent analgeses. At least aconitine and 3-acetylaconitine have been reported to be Na⁺ channel activators. Activation of Na⁺ channels and in consequence excessive depolarization with final inexcitability and suppression of pain transmission may account for the antinociceptive properties of this group of alkaloids.

The second group comprises the less toxic alkaloids lappaconitine, N-deacetyllappaconitine, 6-benzoyletheratsine and 1-benzoylenapelline. The most striking difference in the chemical structure of these alkaloids and group I-alkaloids is the lack of ester boundings at C8 and C14, whereas they possess a benzoyl ester side chain at C4, C6 and C1, respectively. While aconitine and 3-acetylaconitine completely abolish both normal neuronal activity and epileptiform activity, these compounds attenuate epileptiform activity in the hippocampal slice stronger than normal neuronal activity. Due to its Na⁺ channel blocking properties, the antinociceptive activity of lappaconitine, demonstrated previously with various models such as tail pinch, hot plate and acetic acid-induced writhing assay (Ono and Sato, 1990) and its antiarrhythmic activity in animals (Dzakhkhangirov and Sadritinov, 1985a,b) and humans (Sokolov et al., 1985; Abdulla et al., 1989) may be explained by a mechanism of action similar to local anaesthetics and class I-antiarrhythmics, respectively. Despite the lipophilic nature an integration of lappaconitine into the cell membranes as primary mechanism of action seems to be unlikely. This assumption is supported by the recent findings that lappaconitine evoked a use-dependent inhibition on population spikes in rat hippocampal slices (Ameri et al., 1996c). This implies a specific interaction of lappaconitine to channel proteins rather than an unspecific membrane intercalation. Furthermore, a number of antidepressant and anti-convulsant drugs, including amitriptyline, desipramine and carbamazepine have been useful in treating central pain (Deffois et al., 1996). These drugs block voltage-dependent Na⁺ channels and are likely to block pain-generating ectopic activity in the brain (Dray et al., 1994).

The third group is represented by laconitine, heteratisine and napelline. It is intriguing that these are such alkaloids which are lacking a benzoyl ester side chain in the molecule, underlining the physiological importance of this group for the interaction
with the binding site at the Na⁺ channel protein. Toxicity is markedly reduced when compared with the group I and II alkaloids (Table 1). It is intriguing that napelline and heteratisine have been reported to have an antiarrhythmic effect (Dzhakhangirov and Sadritinov, 1977; Benn and Jacyno, 1983), although there was no activity-dependent inhibition of neuronal activity in the hippocampus slice (Ameri, 1997d,e). These findings imply that at least napelline and heteratisine might have different affinities to various subtypes of the α-subunit of the Na⁺ channel in brain and heart.

It is emphasized that the action of the various Aconitum alkaloids observed in vivo can be compared with their electrophysiological action reported recently. Assuming that, based on their lipophilic nature, the alkaloids distribute easily from plasma to tissues and reach about the same concentration in tissue as in plasma, then brain concentration after doses near the ED₅₀ values of the various alkaloids (Table 1) would be in the range of concentration employed in the electrophysiological experiments at hippocampal slices, thus, allowing a comparison of the in vivo and in vitro effects.

6. CONCLUDING REMARKS
As outlined in the present review, the Aconitum alkaloids represented in Fig. 1 are subdivided in three groups according to their chemical structure, toxicity and mechanism of action. The presence of the benzoylsterol side chain and its position at the diterpene skeleton is likely to determine pharmacological effect as well as toxicity. The compounds of group I (aconitine-like alkaloids) and group II (lappaconitine-like alkaloids) induce their pharmacological effects via different modes of interaction with the voltage-dependent Na⁺ channel, that is, activation and use-dependent blockage of the channel, respectively. With respect to the growing trend towards natural products of traditional Chinese medicine it should be emphasized that a therapeutic use of aconitine-like group I-alkaloids is at an early stage, recent findings showing valuable clues as to how rational drug design could provide new Na⁺ blockers for analgesic, antiarrhythmic and antiepileptic indications. The compounds of group II-alkaloids is at an early stage, recent findings showing valuable clues as to how rational drug design could provide new Na⁺ blockers for analgesic, antiarrhythmic and antiepileptic indications.

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