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Perspective Green tobacco sickness: Mecamylamine, varenicline, and nicotine vaccine as clinical research tools and potential therapeutics

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Abstract

Introduction: Green tobacco sickness occurs from transdermal absorption of chemicals from freshly harvested, green tobacco leaves. Signs and symptoms include nausea, vomiting, headache, and abdominal cramps. Prevalence has shifted from the United States and Europe to China, India, and Brazil. Worldwide 8 million individuals are afflicted, including women and children.

Areas covered: Mecamylamine (Inversine®, Vecamyl®), a nicotinic acetylcholine receptor (nAChR) antagonist, should be tested as a remedy for green tobacco sickness. Mecamylamine is approved as an oral tablet for the treatment of hypertension, is safe, and is off-patent. Mecamylamine attenuates many of the effects of nicotine and tobacco including seizures, thereby supporting its use as an effective pharmacotherapy for tobacco dependence. Varenicline (Chantix®) and cytisine (Tabex®) are low efficacy (i.e., intrinsic activity) nAChR agonists, are used as smoking cessation aids, and are viable options to test as remedies against green tobacco sickness. Nicotine immunization strategies may provide further options for future testing.

Expert commentary: Efforts to demonstrate reversal and/or prevention of green tobacco sickness by mecamylamine will underscore the importance of nicotine in this illness and highlight a new medication for effective treatment of tobacco poisoning.

Keywords

nicotine; mecamylamine; green tobacco sickness; nicotine poisoning; tobacco

1. Green tobacco sickness: History and incidence

Tobacco (*Nicotiana tabacum*) is grown and cultivated in over 100 countries; China, Brazil, India, United States, Malawi, and Indonesia account for two-thirds of all production

Declaration of Interest

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worldwide [1]. An estimated 30 million farmers are involved in the production of tobacco. Green tobacco sickness is an occupational hazard associated with tobacco production. The existing literature shows a large variance in prevalence, with 8.2–47% of tobacco handlers afflicted with the sickness. Freshly cut green, tobacco leaves secrete an aqueous material containing alkaloids such as nicotine. Nicotine can be absorbed through the skin; from there it enters the blood and is distributed throughout the body including brain. Heat and humidity are optimal for tobacco growth, and harvesting often occurs when plants are wet; perspiration mixed with the dew and sap from tobacco leaves and stems facilitates exposure of skin to the chemicals in tobacco.

Green tobacco sickness was first documented in the United States medical literature during the early 1970s; those afflicted were farm workers seeking medical attention at a clinic in Lafayette county located in north central Florida [2]. However, the condition had been well known among tobacco farmers long before this report appeared in the medical literature. Some speculated that the cause was due to absorption of a chemical in tobacco through the skin during the process of picking and securing leaves between the arm and torso. Case reports and patient surveys obtained from tobacco harvesters in eastern North Carolina corroborated the sickness described in the Florida report [3]. The signs and symptoms, in order of prevalence, included vomiting, pallor, weakness, dizziness, light-headedness, headache, increased sweating, abdominal pain, cold, chills, and increased salivation. The sickness was isolated to the process of having direct contact with tobacco leaves, because other steps not involving direct contact with tobacco (e.g., breathing air in a storage facility) did not appear related to the illness. However, the large amounts of nicotine measured in the air of some facilities merits caution regarding potential harmful effects in exposed workers [4],

Gehlbach and colleagues were among the first to systematically measure nicotine and its primary metabolite cotinine in the dew from tobacco leaves, and from the urine and sweat of tobacco harvesters [5]. Relatively large nicotine amounts were measured from tobacco leaf dew (34–84 μg/ml) and from the perspiration collected from the clothing of laborers who picked tobacco leaves (58–98 μg/ml). Cotinine, a metabolite with a more stable *in vivo* half-life than nicotine (2 versus 20 h, respectively; [6]), was measured at much higher levels in the urine of tobacco harvesters (89 μg/100 mg creatinine) as compared to the stringers who tied tobacco leaves to a pole for curing (23 μg/100 mg creatinine), tractor drivers (11 μg/100 mg creatinine), and non-exposed controls (4 μg/100 mg creatinine). Smoking status and other tobacco use were carefully monitored to control for nicotine exposure unrelated to the act of harvesting. Overall, these results provided empirical support for an important role for nicotine in green tobacco sickness [5]. These and other data [7] illustrate the potential utility of using nicotine and cotinine in urine, saliva, and/or blood to diagnose green tobacco sickness. However, levels to define poisoning have not been established, and universal application of such testing may not be feasible.

A case-control, retrospective study of tobacco harvesters in south-central Kentucky described a constellation of signs and symptoms with an onset of ten hours and duration of 2.4 days [8]. Respondents reported the following during the illness: weakness, nausea, vomiting, dizziness, abdominal cramps, headache, and labored respiration. Prevalence

appeared to vary with age; younger respondents (less than 30 years of age) were more likely to report the illness than older respondents. Increased incidence in the young has been corroborated in additional studies [9, 10]. The greater prevalence of the illness in younger workers may reflect attrition, i.e., younger individuals susceptible to the illness are believed to quit tobacco farming, whereas those resistant to the illness continue to farm tobacco. There also appeared to be a non-significant relationship with smoking status in the Kentucky study, with smokers being somewhat protected from green tobacco illness as compared with non-smokers. While reports indicate that smokers are afflicted with green tobacco sickness, symptoms appear to be less in smokers as compared with non-smokers. This is potentially due to smokers having acquired tolerance to nicotine's effects, within the blood nicotine concentrations typically achieved from smoking. This would suggest that current users of other nicotine products (e.g. smokeless tobacco, electronic cigarette, or nicotine replacement therapy) may also have some protection from green tobacco sickness via a similar mechanism.

The extent to which tobacco use (i.e., cigarette smoking) protects against green tobacco sickness is equivocal. Smokers were reported to be less susceptible to green tobacco sickness than non-smokers in cases reported in Florida [2], Kentucky [8] and North Carolina [3, 5]. The implication is that tolerance to tobacco from cigarette smoking produces cross-tolerance to the effects of chemicals absorbed from tobacco leaves. In both cases the chemical to which tolerance develops is very likely to be nicotine. However, even cigarette smokers become ill with green tobacco sickness; urine nicotine measured in afflicted smokers can exceed nicotine measured in smokers who are not ill [11]. Protection in cigarette smokers is not universally reported or accepted. Some accounts even suggest that the prevalence of green tobacco sickness is greater in smokers as compared with non-smokers [12, 13]. This has led some to question whether the behaviorally active tobacco alkaloids normally inhaled in cigarette smoke are the main causal factor in green tobacco illness. Some chemical insecticides sprayed onto tobacco plants, such as organophosphate and carbamate, have been identified as possible causes of reported symptoms. Some insecticides contain nicotine and related chemicals that target nAChRs [14], which could potentially be a source of nicotine and nicotine-like poisoning in tobacco farm workers. Nicotine poisoning from insecticide exposure has been documented previously [6]. However, green tobacco sickness is reported to occur on farms that do not use insecticides [3].

Production of tobacco outside of the United States has increased rapidly in the last two decades. Developing countries such as China, Brazil, and India, are now producing more tobacco products than the United States. Farming conditions around the world vary, with some growers relying on mechanized equipment for harvesting, which eliminates much of the need for human contact with tobacco leaves. However, green tobacco sickness continues to be reported in farm operations around the world, e.g., Brazil [15] Korea [16], and Thailand [17]. Because workers are still relied upon for harvesting in many places, those workers are not consistently protected from contact with green tobacco leaves, and the sickness can be severely debilitating for several days, there is a need to disseminate knowledge about the illness to protect workers as much as possible.

The use of personal protective equipment, i.e., water-resistant clothing, chemical-resistant gloves, plastic aprons, and rain-suits with boots are reported to decrease the incidence of green-tobacco sickness [18, 19, 20, 21]. In hot, humid climates, however, compliance with personal protective equipment can be problematic, especially when such equipment is not lightweight and breathable. In health care facilities serving tobacco farmers, dissemination of knowledge about signs and symptoms of green tobacco sickness are essential to improve diagnosis. Green tobacco sickness has been misdiagnosed and treated as heat stroke or dizziness, and in many regions green tobacco sickness is not even recognized. While diagnostic screens based on the amounts of nicotine and cotinine in urine and saliva are possible, the cost and infrastructure required to efficiently implement such testing is not always feasible for rural and poor communities. Such diagnostic tests might not be definitive anyhow, as the amounts of nicotine and cotinine measured in individuals who may be afflicted with green tobacco sickness are less than the amounts measured in heavy cigarette smokers. Currently there are no official, universally accepted treatments for patients who present with symptoms of green tobacco sickness. Some combination of rest, rehydration, and pharmacotherapy to achieve symptom reduction is the usual course of action. Drugs include various antiemetics and antihistamines such as dimenhydrinate and diphenhydramine.

2. Mecamylamine (Inversine®, Vecamyl®): Clinical research tool and potential therapeutic against green tobacco sickness

The signs and symptoms of green tobacco sickness are similar to, though not clearly identical with, overdose and poisoning resulting from dermal absorption of nicotine solutions [22]. Moreover, the data and observations surrounding green tobacco sickness are not entirely consistent with nicotine exposure being the sole explanatory factor. There is little evidence to support the notion that tolerance develops to the adverse effects associated with green tobacco sickness, or that smokers are protected, as implied in the earliest reports. In contrast, tolerance very clearly develops to a number of effects of nicotine in controlled laboratory studies in humans and non-human animals [23, 24]. If nicotine were the primary cause of green tobacco sickness, then some degree of tolerance to the effects of repeated exposure to dermal application of nicotine would be expected; moreover, some protection agonist green tobacco sickness in heavy cigarette smokers would be expected. The time course of the illness is also not entirely consistent with nicotine's pharmacokinetics. The effects of nicotine are typically short in duration, even when large doses of nicotine are applied, although nicotine poisoning attributed to ingestion can last 1–2 days [25]. The mean estimated duration of green tobacco sickness (2.4 days) seems inconsistent with a condition solely attributable to nicotine, which is rapidly metabolized and cleared [26]. Perhaps accumulation of nicotine in skin and prolonged release from skin depots, the production of nicotine metabolites, or longer-acting tobacco alkaloids are involved.

Mecamylamine (3-methylaminoisocamphane hydrochloride or Inversine®) is a secondary amine that targets nicotinic acetylcholine receptors (nAChRs). Mecamylamine acts within the nAChR ion channel pore, but not at the nicotine binding site of nAChRs. Mecamylamine blocks the effects of nicotine but does not displace nicotine binding [27, 28]. This type of

antagonism is referred to as non-competitive, and can be insurmountable. This means that at a sufficiently large dose of mecamylamine, increasing the dose of nicotine will not be able to surmount blockade by mecamylamine. Insurmountable antagonism could be an attractive feature of an approved green tobacco sickness medication.

Mecamylamine's use as an antihypertensive drug began in the 1950s; it remains available by prescription in the United States [29, 30]. High blood pressure treatment with mecamylamine starts initially with relatively small doses to minimize untoward effects such as somnolence, dizziness, and fatigue. Tolerance appears to develop to the untoward effects of mecamylamine, a notion that has not been empirically verified; dose escalation up to 30–90 mg daily presumably enables the pressor effects of mecamylamine to prevail. Under conditions of nicotine poisoning such as that accompanying green tobacco sickness, any adverse effects of mecamylamine would seem minor and not debilitating enough to rule out its potential use to counteract nicotine-induced illness.

Controlled laboratory studies have demonstrated that mecamylamine effectively blocks many of the effects of nicotine. Mecamylamine blocks the psychopharmacological effects of nicotine that presumably drive the repeated use of tobacco, including nicotine's positive reinforcing and discriminative stimulus effects in both non-human and human animals [31, 32, 33, 34, 35, 36]. Because of findings such as these, many have proposed that mecamylamine should be used as a smoking cessation aid. Unlike antagonists from other pharmacological classes, such as naltrexone in opioid-dependent individuals, mecamylamine appears to produce little or no withdrawal from nicotine in cigarette smokers [37]. While not formally recognized as such by the Food and Drug Administration, mecamylamine has been prescribed off-label as a smoking cessation aid [38]. However, the results of small-scale smoking cessation trials with mecamylamine have not been successful enough to warrant larger scale clinical development [39, 40]. One limitation may be that mecamylamine dosing has not been optimized to maximize its effectiveness as a smoking cessation aid.

Studies examining the effectiveness of mecamylamine in blocking the highly toxic effects of nicotine are in agreement with its use as a treatment for green tobacco sickness. Mecamylamine has been demonstrated to block nicotine-induced seizures and lethality in mice [27, 28, 41, 42], nicotine-induced seizures in rats [43, 44, 45], and nicotine-induced seizures in cats [46]. The striking effectiveness of mecamylamine in blocking highly toxic effects of nicotine, including death, provides a compelling case for the use of mecamylamine to counteract nicotine poisoning in tobacco farm workers. Mecamylamine is approved as an oral tablet, it is safe at doses well above those that block the effects of nicotine, and it is off-patent. Efforts to demonstrate reversal and/or prevention of green tobacco sickness by mecamylamine, i.e., relief of signs and symptoms after an oral dose of mecamylamine (30–90 mg), will underscore the importance of nicotine in this illness and highlight a potential new indication for mecamylamine in the treatment of tobacco poisoning.

3. Varenicline and cytisine

Varenicline, a drug approved by the FDA in 2006, is marketed as a low efficacy (i.e., intrinsic activity) nAChR agonist [47], which is proposed to confer a pharmacological

profile that differs from nicotine replacement therapy. Cytisine (Tabex) is another such low efficacy nAChR agonist used as a smoking cessation aid in Central and Eastern Europe. The relatively high nAChR efficacy of nicotine is assumed to produce effects similar to those produced by inhaling nicotine in cigarette smoke. Varenicline also mimics the effects of inhaled nicotine in cigarette smoke. However, as a low efficacy agonist, varenicline can also act to antagonize the effects of nicotine if the two are used together. This therapy is meant to simultaneously reduce craving for cigarettes through its actions as an agonist, as well as diminish the reinforcing effects of smoking through its actions as an antagonist. Nonetheless, there are drawbacks to utilizing varenicline for smoking cessation: varenicline has potentially dangerous side effects that require it to carry a black box warning of depression, suicidal thoughts, and suicidal actions [48]. These side effects are rare, but other side effects are common, including nausea, trouble sleeping, and abnormal dreams. Side effects compromise compliance and can be a trigger for relapse [48, 49, 50, 51, 52]. Because the effectiveness of varenicline as a smoking cessation aid is equal to or greater than that of nicotine replacement, it is a popular choice. Populations susceptible to green tobacco sickness have limited access to varenicline and cytisine as medications. Nevertheless, it would be useful to examine the extent to which varenicline and cytisine protect against green tobacco sickness. Because nicotine use (i.e., cigarette smoking) has an equivocal influence on susceptibility to green tobacco sickness, it is not clear whether lower nAChR efficacy medications would impart a different and perhaps effective profile of protection against green tobacco sickness.

4. Nicotine vaccines

Vaccines for nicotine are immunogens consisting of synthetic drug-derived haptens that are conjugated to immunogenic carriers; these are packaged in adjuvants to increase immunogenicity. Vaccination occurs through an injectable formulation of the conjugate immunogens, which leads to T cell-dependent, B cell activation. This in turn generates polyclonal anti-nicotine antibodies that bind nicotine and prevent nicotine from crossing the blood-brain barrier, thereby preventing access to brain nAChRs. Nicotine vaccines have been shown to block the abuse-related effects of nicotine in pre-clinical studies, but so far no vaccine has been approved for clinical use as a smoking cessation strategy. The development of an effective nicotine vaccine could provide long-lasting, safe, and cost-effective smoking cessation treatments that do not confer the same side effects associated with currently approved drugs such as varenicline (Chantix) and bupropion (Zyban).

Several factors have prevented the successful translation of nicotine vaccines to clinical use. One challenge is obtaining sufficiently high and stable immunogenicity for long periods, although major efforts have been put forth to overcome this challenge by systematically exploring the effectiveness of nicotine-based haptens with varying lengths, polarities, and flexibilities (e.g., [53]). Additional concerns include heterogeneity in responses across subjects, a delay in maximum response (e.g., 1–2 months), and the need for multiple vaccinations over a period of days to weeks to achieve response. The challenges facing use of vaccines for nicotine addiction are perhaps even more problematic when considering green tobacco sickness, where a relatively short (i.e., time-limited) and robust anti-nicotine response would be required.

Vaccination is an “active” immunization strategy that takes advantage of an animal’s natural immune response. Active immunization is a preferred strategy for substance use disorder treatment because it is relatively safe and convenient insofar as the response is sustained after a series of vaccine administrations. “Passive” immunization does not involve an immune response, but rather introduces polyclonal nicotine antibodies directly; this can produce a more robust, immediate anti-nicotine action [54, 55]. Passive immunization could be a viable strategy for reversing or preventing green tobacco sickness. A drawback to monoclonal antibodies is that they are expensive to produce, although improvements in technology are expected to reduce the cost.

5. Expert Commentary

Nicotiana tabacum and *Nicotiana rustica* are the two types of nicotine-based plant that are grown and cultivated. The relatively low nicotine yield of *Nicotiana tabacum* is the preferred choice among most users, thereby creating the widespread popularity of tobacco worldwide. The higher nicotine yield of *Nicotiana rustica* is optimal for extraction, isolation, and purification of the nicotine that is added to replacement products used for smoking cessation and liquids that are now widely used in electronic nicotine delivery systems (i.e., e-cigarettes). Because nicotine’s popularity and widespread use appears stable for many years to come, and perhaps could be growing with newer and assumed to be safer methods of self-administration, farming and production of nicotine-based plants will remain an attractive, especially for poor economies existing in hot and humid climate zones. Large numbers of farm workers will inevitably come into dermal contact with the relatively high amounts of nicotine that presumably cause green tobacco sickness. The reasons for exposure will be multi-factorial: lack of knowledge regarding the risk, lack of access to personal protective equipment, and improper use of such equipment. This article is written to not only highlight and increase awareness of green tobacco sickness, but also to generate the necessary clinical studies to improve health care options to prevent and attenuate green tobacco sickness.

A staggering number of tobacco farm workers, including women and children, are afflicted, i.e., approximately one-quarter. Symptoms (nausea, vomiting, headache, abdominal cramps, hypothermia, breathing irregularities, cardiac arrhythmias, drenching sweats, pallor, chills, and malaise) persist for 2.4 days on average and are often confused with heat exhaustion or insecticide poisoning, though as noted above some insecticides containing nicotine can produce nicotine poisoning. Effective treatments are completely lacking. The approximately 8 million individuals afflicted with green tobacco sickness deserve better treatment.

Mecamylamine (3-methylaminoisocamphane hydrochloride; Inversine, Vecamyl®) is a an nAChR antagonist; it binds to a site in the ion pore of the nAChR that is separate from the nicotine binding site. Mecamylamine produces non-competitive antagonism of nicotine; this means that increasing the amount of nicotine will be unable to “surmount” the antagonism produced by mecamylamine. This very effective, insurmountable antagonism has been shown in numerous pre-clinical studies to result in effective blockade of many different effects of nicotine. Non-competitive antagonism could be a very attractive pharmacological strategy for preventing or reversing green tobacco sickness. Mecamylamine could be prescribed to workers who are susceptible to the illness, perhaps due to insufficient access or

proper use of personal protective equipment. Alternatively, individuals presenting with symptoms of green tobacco sickness could receive mecamylamine; the extent to which symptoms are reduced in those individuals could be measured, and ideally compared to a group of controls that receive the current standard of care (rest and rehydration) and mecamylamine placebo.

Racemic mecamylamine and individual stereoisomers have been tested in clinical trials for various conditions including depression, Tourette's syndrome, and reduction of cigarette smoking. The use of mecamylamine as a blood pressure medication starts at a small dose (e.g., 5 mg p.o.) to minimize its minor untoward effects: somnolence, dizziness, and fatigue observed in less than one-quarter of users. Tolerance develops to the untoward effects, and doses are escalated to 30–90 mg/day p.o.. Mecamylamine (2.5–20 mg p.o.) dose-dependently blocks the psychopharmacological effects of nicotine. In non-humans, mecamylamine blocks many different effects of nicotine, including seizures and death, providing unquestionable and striking evidence of its utility as a nicotine blocker *in vivo*. Similarities between the adverse effects of mecamylamine and symptoms of green tobacco sickness could be problematic, especially if it is found that mecamylamine treatment produces additive effects with nicotine poisoning symptoms. However, the marked anti-nicotine effects of mecamylamine might suggest that this primary action would overshadow the adverse effects; this issue should be carefully monitored and controlled for in clinical assessments.

Mecamylamine is off-patent and therefore a relatively cheap option among those discussed here far for the treatment of green tobacco sickness. Varenicline, cytisine, and perhaps even nicotine (in the form of nicotine replacement products) could be tested for their viability as well. The utility of nicotine itself is questionable because smokers do not appear to be protected from the illness and at least one study suggests that smokers may be more susceptible than non-smokers to green tobacco sickness. This would presumably reflect additive effects of nicotine from smoking and nicotine delivered dermally during the process of tobacco farming. Varenicline and cytisine are low efficacy nAChR agonists, which means they could mimic the actions of nicotine under some conditions and yet antagonize the actions of nicotine under other conditions. To the extent that nicotine antagonism is crucial for reversal of green tobacco sickness, antagonist actions of varenicline and cytisine could be effective against nicotine poisoning. Different from mecamylamine, binding of varenicline and cytisine at nAChRs is at the same site as nicotine; this competitive pharmacological interaction with nicotine could confer a different profile of activity compared to mecamylamine. Clinical studies comparing mecamylamine to varenicline and/or cytisine would be of value in this regard. While immunization of nicotine, either actively through vaccination or passively through direct administration of ant-nicotine antibodies, has shown some promise pre-clinically, these biologic-based approaches have not yet been optimized for large-scale clinical use.

Symptoms of green tobacco sickness resemble those of nicotine poisoning. However, nicotine's role remains debatable. The time course of the sickness appears to be longer than would be expected for nicotine's short half-life, although dermally absorbed nicotine can remain in a skin reservoir and continue to be absorbed into the blood long after direct

contact on the skin surface has ceased. Heavy cigarette smokers do not always appear to be protected against green tobacco sickness. Tolerance develops to many effects of nicotine. If nicotine caused green tobacco sickness, heavy smokers might be expected to be less susceptible than non-smokers. Mecamylamine is approved as an oral tablet, is safe at doses well above those that block the effects of nicotine, is off-patent, and is readily available for use in rural and poor communities. Mecamylamine needs to be tested for its ability to alleviate green tobacco sickness in clinics serving tobacco farmers. Ideally this would involve a placebo-controlled, double blind acute clinical study with mecamylamine in the target population of tobacco field workers. If mecamylamine is shown to be effective at reducing the signs and symptoms of green tobacco sickness, then this would help confirm nicotine's critical involvement. Most importantly, the estimated 8 million tobacco farmers, including women and children, who suffer each year from green tobacco sickness would have access to a simple and potentially life-enhancing remedy.

6. Five-year view

Clinician scientists are challenged to investigate the effectiveness of mecamylamine as a treatment to attenuate the signs and symptoms of green tobacco sickness. An acute clinical trial in tobacco farm workers with an appropriate placebo control is needed. Varenicline should also be tested and compared to mecamylamine. The results of such clinical trials could promote mecamylamine and varenicline as standards of care for this widespread affliction in tobacco farm workers.

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7.

Key issues

- Green tobacco sickness is a debilitating occupational hazard experienced by farm workers whose skin contacts freshly harvested green tobacco leaves.
- The hot humid climate of tobacco farms decreases worker compliance in the use of personal protective equipment; workers come from economically underserved, rural, and often uneducated communities.
- Of the 33 million tobacco farm workers worldwide, approximately 8 million are afflicted with green tobacco sickness.
- Mecamylamine (3-methylaminoisocamphane hydrochloride; Inversine, Vecamyl®) is a non-competitive nAChR antagonist that was originally prescribed for blood pressure control.
- Mecamylamine is an effective blocker of many effects of nicotine in humans and non-humans, including seizures and death in rodents and cats.
- Mecamylamine is approved as an oral tablet, is safe at doses well above those that block the effects of nicotine, is off-patent, and is readily available.
- Varenicline (Chantix), an nAChR agonist with lower efficacy than nicotine at some nAChR subtypes, is a smoking cessation aid that might prove effective against green tobacco sickness.
- Nicotine vaccines and passive immunizations through direct administration of anti-nicotine antibodies, which prevent nicotine from crossing the blood-brain barrier and gaining access to brain nAChRs, offer another possible approach for treating green tobacco sickness.
- If mecamylamine is shown to alleviate green tobacco sickness, nicotine's critical involvement would be confirmed and millions of tobacco farm workers worldwide would be protected from a debilitating illness.