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Commentary

Cytisine for smoking cessation: A research agenda

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Abstract

Cytisine has a molecular structure somewhat similar to that of nicotine and varenicline. The concept for the new smoking cessation drug varenicline was based partly on cytisine. Like varenicline, cytisine is a partial agonist of nicotinic acetylcholine receptors, with high affinity for α4β2 receptors. Cytisine has been used since the 1960s as a smoking cessation drug in Eastern and Central Europe, but has remained largely unnoticed elsewhere. Three placebo-controlled trials, conducted in East and West Germany in the 1960s and 1970s, suggest that cytisine, even with minimal behavioural support, may be effective in aiding smoking cessation. Cytisine tablets are very inexpensive to produce and could be a more affordable treatment than nicotine replacement, bupropion and varenicline. There is however a dearth of scientific research on the properties of cytisine, including safety, abuse liability and efficacy. This paper seeks to identify research priorities for molecular, animal and clinical studies. In particular, new studies are necessary to define the nicotinic receptor interaction profile of cytisine, to establish its pharmacokinetics and pharmacodynamics in humans, to determine whether animals self-administer cytisine, and to ascertain whether cytisine is safe and effective as a smoking cessation drug. Potentially, this research effort, contributing to wider use of an inexpensive drug, could save many lives.

Keywords: Cytisine; Smoking cessation; Tobacco use disorder

1. Introduction

Nicotine replacement therapy and bupropion only help some 5–15% of those who use them to remain long-term abstinent from smoking, depending on the context (Etter et al., 2006; Lancaster et al., 2006). These two treatments have about equal efficacy (Mills et al., 2007). New treatments are needed that are either more effective, can be more widely applied, or treat individuals that are not helped by existing treatments. A new medication, varenicline, has been found to be more effective than placebo (pooled odds ratio from meta-analysis = 2.80) and than bupropion (pooled odds ratio = 1.59), in clinical trials funded by the manufacturer (Gonzales et al., 2006; Jorenby et al., 2006; Nides et al., 2006; Oncken et al., 2006; Tonstad et al., 2006; Mills et al., 2007). Varenicline is a new chemical entity developed partly as an analog of cytisine, a natural insecticide present in several plants, e.g. in *Cytisus laburnum* (Coe et al., 2005). Cytisine has a molecular structure somewhat similar to that of nicotine, and it is a partial agonist of nicotinic acetylcholine receptors (nAChRs) with a high affinity for α4β2-nAChRs (Coe et al., 2005; Papke and Heinemann, 1994; Chandler and Stolerman, 1997). Cytisine has been used since the 1960s as a smoking cessation drug in East and Central European countries, where it is marketed as Tabex, registered for this purpose in 20 countries (Sopharma, Sofia, Bulgaria, www.tabex.net) (Etter, 2006). Despite its widespread use, cytisine has not been available for clinical use outside Eastern and Central Europe. This may in part be explained by limited access to the clinical studies of cytisine, which were conducted in East and Central European countries and were not published in English (Etter, 2006).

Cytisine can be manufactured at a very low cost. For instance in Russia, Poland and Bulgaria, a 25-day course of Tabex is currently 5–15 times cheaper than a 25-day course of the nicotine patch or gum. The use of cytisine for smoking cessation is out

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of patent, so this drug could have an important public health impact in countries and subpopulations where other smoking cessation drugs are too expensive or are otherwise unavailable. Because the clinical pharmacology of cytisine is incompletely characterized, there is a need for state-of-the-art research in this field.

The aim of this paper is to identify priorities for research on cytisine, focusing on its potential use as a tobacco dependence treatment. This paper contains expert opinion and is not a systematic literature review. The authors of this paper cover a broad range of scientific expertise, from basic science to public health.

2. In vitro studies

Cytisine has been used as a template for the design and development of novel nicotinic ligands (Bencherif et al., 1998; Cassels et al., 2005; Coe et al., 2005; Fitch et al., 2005; Slater et al., 2003). This work has been informed by preclinical studies characterizing interactions of cytisine and related compounds with nAChRs, which exist as a diverse family of subtypes (Lukas, 2006). Each subtype is defined by its unique subunit composition and is distinguished by its drug interaction profile. For example, α4β2-nAChRs, composed of α4 and β2 subunits, are the most abundant, high affinity sites for nicotine binding in the brain.

Cytisine, like varenicline, has been classified as a selective, partial agonist at human α4β2-nAChRs (Lukas, 2006). *Selective* means that cytisine activates function of human α4β2-nAChRs at a lower concentration than required to activate some other human nAChR subtypes (cytisine is selective for α4β2-nAChRs, as is nicotine, relative to many nAChR subtypes). Partial agonist means that, in some test systems, the magnitude of the maximal functional responses of α4β2-nAChRs to cytisine is lower than that for the responses to nicotine or acetylcholine, the presumptive native ligand. Cytisine has submaximal functional efficacy, or acts as a partial agonist, at α4β2-nAChRs in in vitro studies, although such action in vivo has not been definitely demonstrated (Chandler et al., 1997).

However, numerous studies suggest that cytisine has a more complex pharmacological profile. Cytisine's affinity for other nAChR subtypes, such as α4β4- or nAChRs-containing α6 subunits is or may be greater than or equal to its affinity for α4β2-nAChRs (Lukas, 2006; Marks et al., 2006; Salminen et al., 2005). Cytisine may interact with more than one form of α4β2-nAChR (i.e., receptors with the stoichiometry $(\alpha4)_2(\beta2)_3$ or $(\alpha4)_3(\beta2)_2$), or more than one class of functional sites on α4β2-nAChRs (Slater et al., 2003). Cytisine's efficacy can vary across studies of the same nAChR subtype from different species and perhaps depending on the experimental system and approach used (Chavez-Noriega et al., 1997; Eaton et al., 2000, 2003; Stauderman et al., 1998). Simple modifications, such as halogenation, markedly affect binding affinities of nAChRs for cytisine analogues (Chellappan et al., 2006; Fitch et al., 2005; Slater et al., 2003). Reciprocally, modest changes in the presumed agonist-binding pocket of nAChRs can alter cytisine's functional potency (Papke et al., 2005). Further studies of cytisine-based compounds are likely to be informative about the ligand-binding pockets on nAChR and molecular mechanisms involved in nicotine dependence. Moreover, these studies are necessary to define the nAChR subtype interaction profile of cytisine, especially in comparison to the in vitro profiles for receptor interactions with bupropion, varenicline, and nicotine itself. Also needed are studies of the effects of longer-term exposure to cytisine on the numbers and function of different nAChR subtypes, as well as on the activity of neurons or other cells expressing nAChRs. Use of cytisine as a smoking cessation medication may involve chronic dosing and will be best informed by an understanding of its long-term effects.

3. Behavioural pharmacology of cytisine: animal studies

Behavioural pharmacological studies have been generally consistent in reporting that the behavioural effects of cytisine in animals are somewhat similar to those of nicotine (Brioni et al., 1994; Chandler and Stolerman, 1997; Craft and Howard, 1988; Pratt et al., 1983; Reavill et al., 1990; Stolerman et al., 1984). However, cytisine does not produce the same degree of behavioural activation as nicotine (measured as ambulatory activity) in animals chronically treated with nicotine (Stolerman et al., 1995). There are few studies of cytisine in direct or indirect measures of reinforcement and reward. Rasmussen and Swedberg (1998) have reported that drug-naïve mice would self-administer cytisine intravenously, which suggests that cytisine has reinforcing effects. However, the acute self-administration model used by Rasmussen et al. may not reflect the chronic reinforcing properties of the drug, and the tail-vein procedure used in this study induces stress, a potential confounding factor. In addition, cytisine can condition a preference for the environment in which it is administered, which is indirect evidence that it has rewarding effects (Museo and Wise, 1994).

The paucity of studies of reinforcement and associated animal behavioural measures that are believed to model drug use in humans suggest the need for experiments to examine the extent to which cytisine (i) will maintain self-administration behaviour compared with nicotine, (ii) will antagonize or otherwise shift/reduce the dose-effect curve for nicotine self-administration, (iii) will reduce the extent of relapse to self-administration behaviour caused by nicotine or re-exposure to the drug-taking environment (or in fact precipitate relapse behaviour), and (iv) will attenuate withdrawal symptoms (or, again, precipitate some withdrawal). Given the recent introduction of varenicline onto the market, the expectation of emerging clinical reports as use of this medication expands, and the limited number of animal studies that have been reported with varenicline, conjoint behavioural pharmacological experiments with varenicline might provide a valuable comparison. These proposed studies are, however, not a necessary precondition to the use of cytisine in humans.

4. Pharmacokinetic and pharmacodynamic studies

The human pharmacology of cytisine buccal films was reported in one Russian study of 78 patients (Ostrovskaia,