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Review

Potential therapeutic uses of mecamylamine and its stereoisomers

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ABSTRACT

Mecamylamine (3-methylaminoisocamphane hydrochloride) is a nicotinic parasympathetic ganglionic blocker, originally utilized as a therapeutic agent to treat hypertension. Mecamylamine administration produces several deleterious side effects at therapeutically relevant doses. As such, mecamylamine's use as an antihypertensive agent was phased out, except in severe hypertension. Mecamylamine easily traverses the blood–brain barrier to reach the central nervous system (CNS), where it acts as a nicotinic acetylcholine receptor (nAChR) antagonist, inhibiting all known nAChR subtypes. Since nAChRs play a major role in numerous physiological and pathological processes, it is not surprising that mecamylamine has been evaluated for its potential therapeutic effects in a wide variety of CNS disorders, including addiction. Importantly, mecamylamine produces its therapeutic effects on the CNS at doses 3-fold lower than those used to treat hypertension, which diminishes the probability of peripheral side effects. This review focuses on the pharmacological properties of mecamylamine, the differential effects of its stereoisomers, S(+)- and R(−)-mecamylamine, and the potential for effectiveness in treating CNS disorders, including nicotine and alcohol addiction, mood disorders, cognitive impairment and attention deficit hyperactivity disorder.

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Abbreviations: ACh, acetylcholine; ADHD, attention deficit hyperactivity disorder; ANOVA, analysis of variance; BSA, bovine serum albumin; CNS, central nervous system; DA, dopamine; dr, dose ratio; FDA, United States Food and Drug Administration; nAChR, nicotinic acetylcholine receptor; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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1. Introduction

The cholinergic neurotransmitter system plays a diverse role in numerous physiological processes of the central nervous system (CNS), including arousal, sleep, pain and cognitive function (Gotti and Clementi, 2004; Hogg et al., 2003), as well as in pathological conditions, including Alzheimer's disease, Parkinson's disease, depression and addiction (Newhouse et al., 1997; Picciotto and Zoli, 2008; Shytle et al., 2002e). Cholinergic signals are recognized and mediated by two pharmacologically distinct receptor classes: muscarinic and nicotinic acetylcholine receptors (nAChRs). Muscarinic receptors mediate numerous central and peripheral nervous system functions (Eglen, 2005), the manipulation of which can lead to severe side effects. As a consequence, effort has focused on the discovery of both novel agonists and antagonists as therapeutic agents which target nAChRs (Arneric et al., 2007; Bencherif and Schmitt, 2002; Dwoskin and Bardo, 2009; Dwoskin and Crooks, 2001; Gotti et al., 2006; Levin and Rezvani, 2000).

One of the first widely-used therapeutic agents targeting nAChRs was the noncompetitive antagonist mecamylamine (Banerjee et al., 1990; Martin et al., 1989). Mecamylamine was introduced originally by Merck & Co., Inc. as an antihypertensive agent (Stone et al., 1956). Although similar to the ganglionic blocker and quaternary ammonium compound hexamethonium, mecamylamine, a secondary amine, is unique among antihypertensive agents. Mecamylamine is rapidly and completely absorbed from the gastrointestinal tract, and has both a fast onset (37 min) and a relatively long duration of action (22 h; Ford et al., 1956). Unfortunately, mecamylamine lacks nAChR subtype selectivity, and thus exerts antagonist activity at parasympathetic ganglionic receptors, which at therapeutic doses results in undesirable side effects, including constipation, urinary retention and dry mouth and skin (Shytle et al., 2002a). However, unlike other ganglionic blockers, mecamylamine easily traverses the blood–brain barrier, allowing inhibition of nAChRs in the CNS (Martin et al., 1989; Suchocki et al., 1991). More recent studies report that the central effects of mecamylamine are obtained at 3-fold lower doses than those used to treat hypertension (2.5–10 mg/day versus 30–90 mg/day), resulting in fewer and more manageable peripheral side effects (Shytle et al., 2002a,d,e). Since nAChRs play a major role in numerous physiological and pathological processes, it is not surprising that mecamylamine has been evaluated as a potential therapeutic agent for a wide variety of disorders that affect the CNS.

Targacept, Inc., which secured the intellectual property, regulatory documentation, contracts and inventory related to mecamylamine from Layton Biosciences, Inc., received approval from the United States Food and Drug Administration (FDA) to test the effectiveness of mecamylamine in treating Tourette's syndrome, a neurological disorder characterized by involuntary movements (Sanberg et al., 2000). In 2002, Targacept, Inc. obtained use patents for the pure stereoisomers, S(+)- and R(−)-mecamylamine, for the treatment of a wide range of clinical conditions, including addiction, schizophrenia, hypertension and cancer (Shytle et al., 2002b,c). Additional use patents were secured for mecamylamine (racemic and stereoisomeric forms) to treat depression, bipolar disorder, obsessive compulsive disorder, attention deficit hyperactivity disorder (ADHD) and Alzheimer's disease (Sanberg et al., 2005). While to date the only FDA-approved use of mecamylamine is for “the management of moderately severe hypertension and uncomplicated cases of malignant hypertension”, these patents have generated renewed excitement and investment in mecamylamine as a potential therapeutic agent for numerous CNS disorders.

In this review, we present an overview of the proposed therapeutic uses for mecamylamine, and both positive and negative results from preclinical and clinical studies. Also, results herein show an interaction between mecamylamine and nicotine, which likely will have an important impact on the development of mecamylamine in terms of doses employed and the conditions necessary to reveal efficacy. Future clinical studies should consider tobacco smoking status when selecting mecamylamine doses to be employed to obtain maximal efficacy for its proposed therapeutic uses.

2. Neuropharmacology

2.1. Mechanism of action

Mecamylamine (3-ethylaminoisocamphane hydrochloride; Fig. 1, left) is a secondary amine that acts as a noncompetitive antagonist to all known nAChR subtypes (Connolly et al., 1992; Varanda et al., 1985). Interestingly, early studies reported that mecamylamine-induced inhibition of parasympathetic neurons from rat submandibular ganglia was the result of a competitive mechanism of action (Ascher et al., 1979; Gurney and Rang, 1984). However, mecamylamine inhibition of agonist-induced receptor activation could not be fully reversed, even after a 60-min washout, suggesting noncompetitive antagonism. In later studies utilizing cultures of parasympathetic neurons and medullary chromaffin cells, mecamylamine was shown to inhibit acetylcholine-evoked currents in a voltage-dependent manner, supporting a noncompetitive channel-blocking mechanism of action (Fieber and Adams, 1991; Nooney et al., 1992). Studies using cell expression systems, such as *Xenopus* oocytes expressing either rat or human nAChR subtypes, have demonstrated that mecamylamine inhibits both neuromuscular and neuronal

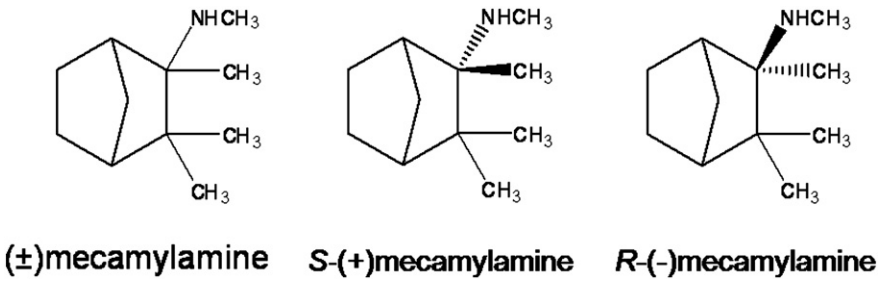

Fig. 1. Chemical structures of racemic mecamylamine, S(+)-mecamylamine and R(−)-mecamylamine.