Biochemical Pharmacology 82 (2011) 943–951

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Review

Functional brain imaging of nicotinic effects on higher cognitive processes

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ARTICLE INFO

Article history:
Received 14 April 2011
Accepted 2 June 2011
Available online 13 June 2011

Keywords:
Nicotine
fMRI
Mecamylamine
Physostigmine
Attention
Memory
Emotion

ABSTRACT

Significant advances in human functional brain imaging offer new opportunities for direct observation of the effects of nicotine, novel nicotinic agonists and nicotinic antagonists on human cognitive and behavioral performance. Careful research over the last decade has enabled investigators to explore the role of nicotinic systems on the functional neuroanatomy and neural circuitry of cognitive tasks in domains such as selective attention, working memory, episodic memory, cognitive control, and emotional processing. In addition, recent progress in understanding functional connectivity between brain regions utilized during cognitive and emotional processes offers new opportunities for examining drug effects on network-related activity. This review will critically summarize available nicotinic functional brain imaging studies focusing on the specific cognitive domains of attention, memory, behavioral control, and emotional processing. Generally speaking, nicotine appears to increase task-related activity in non-smokers and deprived smokers, but not active smokers. By contrast, nicotine or nicotinic stimulation decreases the activity of structures associated with the default mode network. These particular patterns of activation and/or deactivation may be useful for early drug development and may be an efficient and cost-effective method of screening potential nicotinic agents. Further studies will have to be done to clarify whether such activity changes correlate with cognitive or affective outcomes that are clinically relevant. The use of functional brain imaging will be a key tool for probing pathologic changes related to brain illness and for nicotinic drug development.

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1. Introduction

Investigation of nicotinic cholinergic receptor function in the brain has traditionally relied on well-tested methods of behavioral pharmacology in animals and more recently in humans [1–5].

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doi:10.1016/j.bcp.2011.06.008

These methods, especially with more recent technical improvements have been extraordinarily productive and have led to major advances in understanding of the role of nicotinic receptor systems on basic cognitive and behavioral systems [6]. However, the nature of nicotinic signaling systems and the limitations of the currently available pharmacologic agents (especially in humans) and models place constraints on the ability to discern how nicotinic modulation affects simple and more complex cognitive processes. Difficulties with acute vs. chronic dosing in both animal and human models, especially with regard to studies of cognitive performance, along with the well-known constraints of studying smokers have led to uncertainties regarding to what extent nicotinic modulation is active in a variety of behavioral and cognitive domains. In addition, such limitations have presented significant obstacles to targeted drug development of nicotinic agents for the amelioration of cognitive and behavioral disorders. For example, it is difficult to model certain aspects of cognitive processes in rodents, especially in the area of episodic memory, executive, or emotional processing. It is likely that the underlying task-related neural circuitry is significantly different between rodent and human models due to differences in neuroanatomy. This has led to challenges in utilizing animal models to predict the effects of human administration of nicotine or related compounds [7]. These challenges have contributed to problems translating basic and human-based findings into the development of strategies to preserve or enhance nicotinic functioning through drug development. Advances in human functional brain imaging offer new opportunities for direct observation of the neurobiological effects of nicotine, nicotinic antagonists, and novel nicotinic agonists on cognitive and behavioral performance.

Careful research over the last decade has enabled investigators to begin to explore the functional neuroanatomy and neural circuitry of numerous tasks in domains such as selective attention, working memory, episodic memory, behavioral inhibition and control, and emotional processing. As the cortical networks underlying cognitive operations are beginning to be understood, the opportunity to both acutely and chronically investigate how nicotinic modulation affects these cortical networks and their activity patterns becomes possible. Correlating the activity of these regions and networks with cognitive performance and accounting for variables such as age, gender, and baseline performance will allow a much clearer understanding of both how important nicotinic modulation is to a particular cognitive task or domain as well as the potential for utilizing nicotinic agents to either stabilize or improve cognitive performance. It is now possible to see how utilizing drugs during functional brain imaging or so-called pharmacologic fMRI or PET may become an important tool in not only understanding how nicotinic systems modulate task-related cortical activity but such approaches may also be useful for initial drug development, examining whether a putative agent has significant activity on cognitive or behavioral domains relevant to potential target indications. The majority of such studies use an acute drug challenge before volunteers undergo a cognitive task in a magnetic resonance imaging (MRI) scanner. Functional MRI measurements basically capture blood oxygenation within brain regions via the so called BOLD (blood oxygen level dependent) contrast which has been shown to be related to input and processing of neuronal activity within brain regions [8]. A comparison between drug and placebo then reveals the drug's action on task-related brain activity. Note that the findings of such studies identify neurochemical modulation of brain activity that is induced by a specific task rather than excitation or inhibition of brain regions per se. In principle, designs of so called "pharmacological fMRI" studies do not differ from conventional fMRI experiments. The essential point in the data analysis is the group by condition interaction showing areas with significant differences in task-related activity between the drug and placebo. Plotting activity changes in these areas will provide further information on the modulatory action of the drug on a given cognitive process. This is illustrated for a nicotinic study of cognitive performance in Fig. 1.

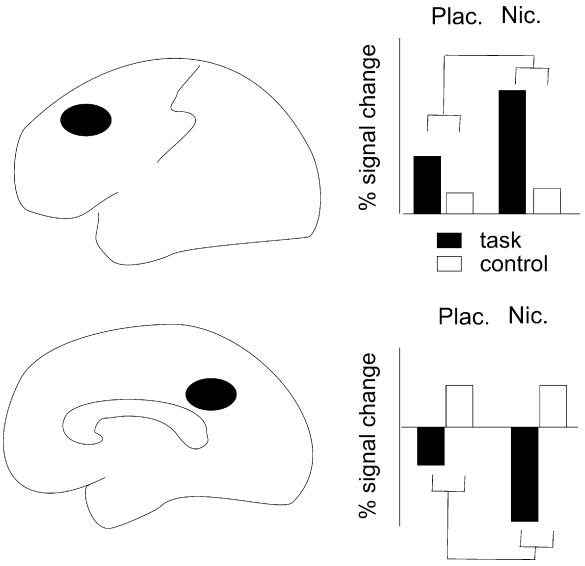

Fig. 1. Schematic illustration of two different groups (placebo vs. nicotine) by condition (task vs. control) interactions in a pharmacological fMRI study. The upper part illustrates a nicotine-induced task related increase in neural activity in frontal cortex, as for example found in working memory or sustained attention paradigms. The lower part illustrates a nicotine-induced increase in deactivation in the posterior cingulate cortex. Such deactivations are usually found during task performance and are increased under nicotine.

In addition, recent progress in understanding functional and effective connectivity between brain regions utilized during cognitive and emotional processes offers new opportunities for examining drug effects on network-related activity. As activity patterns in cortical networks become better characterized, especially with regard to optimized cognitive or behavioral functioning, these patterns of activity may come to represent biomarkers that may be usable for investigating nicotinic function and/or predicting nicotinic drug effects on performance and behavior.

This review will evaluate available nicotinic functional brain imaging studies focusing on the specific cognitive domains of attention, memory, cognitive control, and emotional processing. While information on how nicotinic modulation affects some of these domains is limited or is just beginning to be studied in depth, the available literature allows preliminary conclusions and hypotheses to be developed on how nicotinic stimulation or blockade alters the cortical activity associated with certain cognitive operations. In addition, considerations of agonists and antagonists in terms of their use in functional imaging will be considered.

2. Attention

2.1. Visuospatial selective attention and sustained attention

Several attentional functions are modulated by the cholinergic agonist nicotine (for review see [1]). The neuroimaging literature has focused to a large extent on visuospatial selective attention and sustained attention. The first pharmacological fMRI study investigated the effects of 21 mg transdermal nicotine in a within-subject design in smokers using a rapid visual information processing task [9]. Behaviorally, an increased number of hits was observed under