Available online at www.sciencedirect.com
SCIENCE DIRECT
Neuroscience and Biobehavioral Reviews 30 (2006) 148–172
NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS
www.elsevier.com/locate/neubiorev

Review

The evolving theory of basal forebrain functional—anatomical 'macrosystems'

Daniel S. Zahm*

Department of Pharmacological and Physiological Science, St Louis University School of Medicine, 1402 S. Grand Boulevard, St Louis, MO 63104, USA

Received 16 January 2005; revised 3 June 2005; accepted 10 June 2005

Abstract

The conceptual basis and continuing development of Alheid and Heimer's [Alheid, G.F., Heimer, L., 1988. New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid and corticopetal components of substantia innominata. Neuroscience 27, 1–39] theory of basal forebrain organization based on the description of basal forebrain functional-anatomical 'macrosytems' is reviewed. It is posed that the macrosystem theory leads to a hypothesis that different macrosystems cooperate and compete to exert distinct influences on motor and cognitive function. Emergent corollaries include, e.g. that the organization of the outputs of different macrosystems should differ. Consistent with these considerations, extant literature and some unpublished data indicate that the input nuclei of macrosystems are not abundantly interconnected and macrosystems systems have distinct neuroanatomical relationships with basal forebrain and brainstem cholinergic and dopaminergic ascending modulatory systems. Furthermore, macrosystem outputs appear to be directed almost exclusively at the reticular formation or structures intimately associated with it. The relative merits of the theory of functional-anatomical macrosystems are discussed in relation to Swanson's model of cerebral hemisphere control of motivated behavior.

Keywords: Reticular formation; Dopamine; Acetylcholine; Dopaminergic; Cholinergic; Adaptive response; Behavior

Contents

* Tel.: +1 314 977 8003; fax: +1 314 977 6411.
E-mail address: zahmds@slu.edu

0149-7634/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2005.06.003

1. Introduction

Basal forebrain consists of some rather well differentiated structures, such as the nucleus accumbens, ventral pallidum, septum-diagonal band complex, bed nucleus of the stria terminalis, and amygdaloid complex, but also less clearly differentiated neural tissue in the preoptic area, hypothalamus and regions beneath the anterior commissure and globus pallidus, i.e. the so-called subcommissural and sublenticular regions, respectively, frequently referred to as substantia innominata (Heimer et al., 1997a,b). In addition, distinct collections of neurochemically- and connectionally-specified neurons are interspersed within and among a number of the basal forebrain structures.

Basal forebrain in concert with the cerebral cortex, diencephalon and brainstem is thought to generate neural correlates of biological states involving, e.g. hunger, thirst, fear, reward, aversion, and reproductive and affiliative drives, and from competing demands orchestrate the synthesis of flexible, biologically adaptive actions. To accomplish this requires a spectrum of neural mechanisms reflected in fundamental adaptive activities, some of which include anticipating, appreciating, arousing, associating, attending, detecting, freezing, moving, and (behavioral) switching (see, e.g. Cardinal et al., 2002; Dayan and Balleine, 2002; Everitt et al., 1989, 1991; Gallagher and Holland, 1994; Kalivas and Nakamura, 1999; Kelley, 1999; Parkinson et al., 2000; Robbins and Everitt, 1996; Sarter and Bruno, 2000; Sarter et al., 1999). Together, these contribute to the genesis of motivation and its transformation to action (Mogenson et al., 1980).

How basal forebrain contributes to the melding of multiple behavioral components into integrated, flexible patterns of behavior constitutes one of the big extant questions in the field of neurobiology. The mechanisms that underlie this capacity must depend upon the functional-anatomical organization of basal forebrain, which at this time remains very much at issue among neuroscientists concerned with the problem. This paper works forward from the conceptualization of basal forebrain functional-anatomical systems by Heimer, de Olmos, Alheid and colleagues to state a hypothesis: that different macrosystems cooperate and compete to exert distinct influences on motor and cognitive function. Subsidiary hypotheses that emerge as corollaries are then considered, e.g. that different basal forebrain macrosystems act largely in segregation and that the outputs from different macrosystems to re-entrant trans-thalamic corticopetal pathways, to diencephalic and brainstem effector systems and, particularly, to ascending modulatory projections, e.g., those utilizing dopamine and acetylcholine, should differ.

2. Methods

Some illustrations in this review show preparations containing anterogradely labeled axons and immunohistochemical detection of enzymes and peptides. This material reflects cases that were evaluated but not illustrated in previous papers from this laboratory. Relevant experimental procedures are described in detail in Zahm et al. (1999, 2003) and Gastard et al. (2002).

3. Basal forebrain functional-anatomical macrosystems

An appreciation of the neuroanatomical composition of basal forebrain is fundamental to understanding basal forebrain function. A tangible result of progress made toward this end during the past 25 years was the description of several basal forebrain 'functional-anatomical macrosystems' by Alheid and Heimer (1988). They proposed that the ventral striatopallidum, extended amygdala, septum (with associated structures) and magnocellular corticopetal system represent separate processing units that receive specific information derived largely from the cortex and provide 'either local… or distal feedback to cortex' and output to brainstem motor effectors. (*Note:* The descriptor 'functional-anatomical system,' and synonymous term 'macrosystem' emerged in subsequent papers (Heimer and Alheid, 1991; Heimer et al., 1991a).[1]

The paper by Alheid and Heimer (1988) treated a broad variety of specific neurochemical, connectional

[1] Heimer and colleagues described medial and central divisions of the extended amygdala. The medial division comprises medial parts of the amygdala and bed nucleus complex and associated neurons in intervening parts of the basal forebrain and stria terminalis. It is related primarily to the accessory olfactory system and medial preoptic–hypothalamus continuum and will not be considered further in this paper. The central division of the extended amygdala includes the central nucleus of the amygdala, lateral parts of the bed nucleus of the stria terminalis complex and associated neurons that extend between these structures in the sublenticular region and within the stria terminalis. It projects to the lateral hypothalamus and brainstem and, via midline-intralaminar thalamus, to the cortex. Purely in order to simplify the presentation, reference to extended amygdala in this paper implies exclusively the central division.