BRAIN RESEARCH 1450 (2012) 174–193

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BRAIN RESEARCH

Review

Neuroinformatics analysis of molecular expression patterns and neuron populations in gray matter regions: The rat BST as a rich exemplar

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ARTICLE INFO

Article history:
Accepted 14 February 2012
Available online 22 February 2012

Keywords:
Bed nuclei of stria terminalis
BST
Neurons types
Gene expression
Neuroinformatics
Database
BAMS

ABSTRACT

The rat bed nuclei of the stria terminalis (BST) is an important part of the cerebral nuclei, both structurally and functionally. However, the literature is rather scarce and more importantly, often contradictory. In this paper we review the literature related to neuron populations reported in different rat BST parts, and to a set of more than 50 expressed molecules. The information related to neuron populations and molecules detected in the BST was expertly collated manually in a publicly available neuroinformatics system, the Brain Architecture Knowledge Management System (BAMS; http://brancusi.usc.edu/bkms). Using the tools implemented in BAMS, we organized the collated information, and further analyzed it statistically. The result of our analysis over the set of >50 expressed molecules confirms the BST parcellation scheme proposed by Swanson in 2004, with two exceptions. We present and discuss these results, and propose refined parcellation ventrally in the BST. We also review and discuss the presence of cholinergic neurons in the BST, and of neuron populations that express serotonin receptors. This review is one of the most comprehensive for the rat BST published in the literature, and it was possible only by using neuroinformatics tools.

Contents

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doi:10.1016/j.brainres.2012.02.034

1. Introduction

The bed nuclei of the stria terminalis (BST) is a part of the cerebral nuclei (basal ganglia; Bota and Swanson, 2010; for a standard nomenclature see Swanson and Bota, 2010) that was first named as such in the rat forebrain by Johnston (1923) and Gurdjian (1925). The first parcellation of the BST as a standalone gray matter region was provided by de Groot (1959). Since then, the BST has been frequently subdivided in different subparts, divisions, or nuclei by different authors (for a review on nomenclatures of the rat BST, see Bota and Swanson, 2010). However, there are currently only two main topographically distinct classification schemas: medial–lateral and anterior–posterior. The classical medial–lateral parcellation schema is based on cytoarchitecture, chemoarchitecture, and input connections from the amygdalar region (de Olmos and Heimer, 1999; de Olmos et al., 1985; de Olmos et al., 2010; Geeraedts et al., 1990; Paxinos and Watson, 1986, Paxinos and Watson, 1998). This schema usually includes BST as part of the "extended amygdala" (de Olmos et al., 2010) and the number of component nuclei is variable. The modern anterior–posterior classification schema is based on a) ontogeny of neuron populations in gray matter regions (Bayer, 1987), as a criterion for demarcation from the preoptic region of the hypothalamus and for distinguishing internal divisions; b) cytoarchitecture and gene expression patterns (Ju and Swanson, 1989; Ju et al., 1989); and most importantly c) complex input connection patterns from the amygdalar region (Dong et al., 2001) and output connection patterns from component nuclei to many parts of the brain (Dong and Swanson, 2003, 2004, 2006; Swanson, 2004). Even though these two dominant parcellation schemes may appear as topographically orthogonal, they also include common nuclei, such as the juxtacapsular nucleus (BSTju; Moga et al., 1989). However the most common results of qualitative (topological) comparison performed by us (Bota and Swanson, 2010) lead to the relation of "partial correspondence" (Swanson and Bota, 2010) between the BST nuclei of these two parcellations.

The set of molecules known to be expressed in the rat BST nuclei increased with each relevant study there or in neighboring regions (de Olmos et al., 2010; Gray and Magnuson, 1987; Hammack et al., 2007; Ju et al, 1989; Moga et al., 1989; Poulin et al., 2006; Puente et al., 2010; Rainnie, 1999; Swanson et al., 1983; Zaborszky et al., 2005). Moreover, some molecular expression patterns are sex-specific (Polston and Simerly, 2003). However, there are very few reviews or surveys of the molecular architecture of rat BST nuclei (de Olmos et al., 2010)—and the same is true for neuron populations, classes, and types in the BST. Although the literature concerning BST neuron classification is more than 30 years old, few studies have used multiple classification schemas, the polythetic approach (see Bota and Swanson, 2010 for a review). Most studies reviewed here classify BST neurons according to one criterion, usually cytoarchitecture (unithetic approach), or several criteria at most. Moreover, the lack of agreement across neuroanatomical nomenclatures, accompanied by equivocal relations between gray matter regions, makes the results of experimental connection analyses difficult to interpret, compare, and integrate.

Proposed functions of the rat BST range from modulation of basic autonomic responses (Moga et al., 1989; Swanson and Sharpe, 1973), large sets of motor behaviors (Dong and Swanson 2003, 2006), and circadian rhythmicity (Amir et al., 2004), to stress- and anxiety-related behaviors (Choi et al., 2009; Levita et al., 2004; Walker et al., 2003), and behaviors related to drugs of abuse (Aston-Jones and Harris, 2004). This large set of functions can be explained only by complex patterns of connections, and a large set of expressed molecules. This in turn implies multiple neuron populations in the rat BST that can be distinguished using the multiple criteria (polythetic) approach for their classification (Bota and Swanson, 2010). Hence, a survey of molecules differentially expressed in the rat BST nuclei, and of identified neuron types, is not only valuable for a comprehensive description of this cerebral nuclei region, but is also necessary for establishing the structure–function relationships of each of the BST nuclei.

In this paper we survey comprehensively the published literature on molecular expression patterns and neuron populations, classes, and types identified in the rat BST. It can be viewed as a companion to an earlier paper (Bota and Swanson, 2010) where we proposed a methodology for collating and curating neuroanatomical nomenclatures in online neuroinformatic systems, and reviewed the literature on rat BST parcellation schemes. Because large scale efforts are greatly facilitated by neuroinformatics systems, we collated the molecular expression pattern and neuron population information in the Brain Architecture Knowledge Management System (BAMS). This allowed us to manage the inserted data in tabular formats and to analyze it statistically. Moreover, all the collated data and metadata is publicly available to the neuroscience community.

First, we briefly describe BAMS and its new interfaces and inference engine, created to integrate the results of different experiments and data types. This is accompanied by a description of the methodology used to map and collate data from the published literature. Second, we present the results of our survey of molecular expression data collated in BAMS, and the results of relevant statistical analyses. We then review the published literature on neuron populations identified in the BST, and on relations between them. Finally, we discuss the results of our survey and analysis, and propose