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REVIEW ARTICLE
The neglected constituent of the basal forebrain corticopetal projection system: GABAergic projections

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Abstract

At least half of the basal forebrain neurons which project to the cortex are GABAergic. Whilst hypotheses about the attentional functions mediated by the cholinergic component of this corticopetal projection system have been substantiated in recent years, knowledge about the functional contributions of its GABAergic branch has remained extremely scarce. The possibility that basal forebrain GABAergic neurons that project to the cortex are selectively contacted by corticofugal projections suggests that the functions of the GABAergic branch can be conceptualized in terms of mediating executive aspects of cognitive performance, including the switching between multiple input sources and response rules. Such speculations gain preliminary support from the effects of excitotoxic lesions that preferentially, but not selectively, target the noncholinergic component of the basal forebrain corticopetal system, on performance in tasks involving demands on cognitive flexibility. Progress in understanding the cognitive functions of the basal forebrain system depends on evidence regarding its main noncholinergic components, and the generation of such evidence is contingent on the development of methods to manipulate and monitor selectively the activity of the GABAergic corticopetal projections.

Introduction

Research on the structure and function of basal forebrain (BF) corticopetal projections has mostly focused on the cholinergic component of this projection system. The availability of a selective immunotoxin, 192 IgG-saporin, to destroy cortical cholinergic inputs, as well as *in vivo* microdialysis techniques to assess changes in cortical acetylcholine (ACh) release in task-performing animals, have led to relatively specific hypotheses about the role of the cortical cholinergic input system in the mediation of attentional processes (for review see Voytko, 1996; Everitt & Robbins, 1997; Wenk, 1997; Sarter & Bruno, 2000; Sarter *et al*., 2001). For example, experiments demonstrated robust, lasting and specific attentional impairments following the loss of cortical cholinergic inputs, produced by intra-BF or intracortical infusions of 192 IgG-saporin (e.g. McGaughy *et al*., 1996; Turchi & Sarter, 1997; McGaughy & Sarter, 1998). Furthermore, higher levels of cortical ACh efflux in animals performing an operant task taxing attentional abilities, compared with ACh efflux in animals performing control procedures devoid of explicit demands on attention, were demonstrated (Himmelheber *et al*., 2000; Arnold *et al*., 2002). Likewise, prefrontal neuronal activity changes produced by increased demands on sustained attention performance were shown to depend on the integrity of the cholinergic inputs to the recording area (Gill *et al*., 2000). Collectively, these studies demonstrated that cortical cholinergic inputs mediate a wide range of attentional functions and capacities. As a result, it has been hypothesized that aberrations in the regulation of cortical ACh contribute to the symptoms of major neuropsychiatric disorders (Heimer *et al*., 1991; Sarter & Bruno, 1999).

By contrast, information about the behavioural/cognitive functions of the noncholinergic component of the BF corticopetal system has remained largely unavailable. The most prominent noncholinergic component of the BF corticopetal projection system are the γ-amino-butyric acid (GABA)ergic corticopetal projections. Below, the available information concerning the anatomy and function of the BF GABAergic corticopetal projection system will be reviewed. This review will be guided by the general hypothesis that the BF GABAergic projections to the cortex represent a component of the prefrontal cortex (PFC) efferent circuitry that mediates the cognitive flexibility required in tasks involving multiple sources of stimuli and multiple stimulus–response rules.

GABAergic neurons in the BF

Throughout the BF, GABAergic neurons are intermingled with cholinergic neurons. Although estimates about the number of GABAergic neurons vary across different studies and species, and appear to depend on the use of different markers for GABAergic neurons and different anatomical terminologies, GABAergic neurons generally have been demonstrated to outnumber cholinergic neurons in the BF by at least 2 : 1 (e.g. 9600 glutamic acid decarboxylase (GAD)-positive vs. 5100 choline acetyltransferase (ChAT)-positive cells per hemisphere; Gritti *et al*., 1993; Zaborszky, L., Buhl, D.L., Pobalashingham, S., Bjaale, J.G. & Nadasdy, Z., unpublished data). Most of these studies compared the number of ChAT-positive neurons with the number of neurons expressing the calcium-binding protein parvalbumin (PV) (Fig. 1). PV-positive cells are widely

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believed to be GABAergic in the BF (e.g. Brauer *et al*., 1990, 1993; Kiss *et al*., 1990). As illustrated in Fig. 1, in the rat the majority of the PV-positive cells are located in the lateral globus pallidus (GP), projecting mostly to di- and mesencephalic regions (Smith & Bolam, 1990; Von Krosigk *et al*., 1992). Conversely, the cholinergic neurons are mostly scattered along the medial wall of the GP [that is, the nucleus basalis of Meynert (nbM)] and ventral to the GP [that is, the substantia innominata (SI)].

Although results vary somewhat across different studies, species and cortical target region (e.g. Rye *et al*., 1984), it is now widely accepted that, compared with the number of cholinergic corticopetal projections, a roughly similar number of BF GABAergic neurons project to the cortex (Fisher *et al*., 1988; Walker *et al*., 1989; Gritti *et al*., 1997; Zaborszky *et al*., 1999).

The GABAergic corticopetal projection neurons appear to originate in most parts of the BF, including the magnocellular preoptic area (MCPA), SI and medial GP (Gritti *et al*., 1997). Gritti *et al*. (1993) suggested that the GAD-positive cells that are as large as the magnocellular ChAT cells represent the GABAergic component of the corticopetal projection system arising from the nbM, whilst the smaller GABAergic neurons are interneurons or may have descending projections (Gritti *et al*., 1994; Semba, 2000). With the exception of the GAD-positive projections to the PFC that appear to arise also from the more lateral GP (Gritti *et al*., 1997; their fig. 7), GABAergic corticopetal projections generally originate in areas in the BF that also contain ChAT-positive corticopetal projections.

Although there have been some suggestions that GABAergic and cholinergic neurons form discernable clusters in the BF (Zaborszky *et al*., 2002), the available anatomical evidence concerning corticopetally projecting neurons indicates that both types of neurons are codistributed in the BF, without forming clearly distinct subpopulations. In essence, cholinergic and GABAergic neurons of the BF project in parallel to the cortex (see also Jones & Mühlethaler, 1999).

BF GABAergic inputs to the cortex

Studies by Freund and colleagues, in cats and rats, demonstrated that, in the cortex, GABAergic inputs establish multiple contacts with GABAergic interneurons (Freund & Gulyás, 1991; Freund & Meskenaite, 1992). These cortical GABAergic interneurons are extensively collateralized, each contacting hundreds of pyramidal neurons (Freund *et al*., 1983). Thus, it has been widely suggested that stimulation of BF GABA corticopetal projections inhibits the excitability of these interneurons, thereby yielding widespread and potent cortical disinhibition. Additionally, if cortical GABAergic interneurons tonically suppress the activity of other cortical neurons, disinhibition as a result of increases in the activity of corticopetal GABAergic projections synapsing on cortical GABAergic interneurons would not just modulate, but in fact permit or gate, cortical information processing (Dykes, 1997).

However, the effects of increases in the activity of cortical GABAergic inputs are probably more complex. First, cortical cholinergic inputs stimulate GABAergic interneurons and thus may inhibit certain pyramidal neurons (e.g. Müller & Singer, 1989; Kondo & Kawaguchi, 2001). Therefore, GABAergic and cholinergic inputs exert opposite effects via cortical interneurons on the activity of cortical output cells (McCormick & Prince, 1985, 1986). Second, cholinergic inputs also make direct contact with pyramidal and spiny stellate cells (e.g. Houser *et al*., 1985; McCormick & Prince, 1986; Kawaguchi, 1997), thereby giving rise to a complex mixture of excitatory and inhibitory effects of ACh in the cortex. These effects of ACh may be modulated in complex ways by coactivation of GABAergic inputs. Third, the diversity of these interactions is enhanced by the possibilities that different populations of interneurons are targeted by cholinergic and GABAergic inputs (Freund & Gulyás, 1991), that the density of cholinergic and GABAergic inputs to GABAergic interneurons differ substantially across layers (Beaulieu & Somogyi, 1991), and by the observation that BF corticopetal cholinergic and GABAergic neurons exhibit local collaterals to other BF cells, thereby allowing local BF interactions between the two main components of the BF corticopetal projection system (Pang *et al*., 1998; Zaborszky & Duque, 2000; see also Jiménez-Capdeville *et al*., 1997). Clearly, the interactions between cortical cholinergic and GABAergic inputs, and their interrelated effects on cortical neuronal excitability, are immensely complex and remain poorly understood.

Afferent organization of BF GABAergic corticopetal projections

The inputs to BF cholinergic neurons originate in telencephalic, mesencephalic and brain stem regions, and their anatomical organization and modulation of the activity of BF cholinergic corticopetal projections in different states and behavioural/cognitive functions have been extensively reviewed (e.g. Gaykema *et al*., 1991; Zaborszky *et al*., 1999; Sarter & Bruno, 2000). Zaborszky *et al*. (1997) provided evidence for the intriguing possibility that, in rats, medial and lateral prefrontal and ventral orbitofrontal cortical projections to the BF, which are the only cortical inputs to the BF (see also Carnes *et al*., 1990), exclusively terminate on BF GABAergic neurons. The projections of these particular BF GABAergic target neurons remain to be demonstrated. However, the observation that the GABAergic neurons targeted by PFC projections include magnocellular neurons that therefore are part of the magnocellular cell complex, that is, the nbM (Gritti *et al*., 1997; Jones & Mühlethaler, 1999), supports the hypothesis that they project, at least in part, to the cortex (Fig. 2). In rhesus monkeys, orbitofrontal and medial, but not lateral, prefrontal areas also project to the basal forebrain, but the phenotype of the BF target neurons of this projection remains unsettled (Mesulam & Mufson, 1984; Ghashghaei & Barbas, 2001). As it has been suggested that rat medial (prelimbic and infralimbic) and lateral (insular) prefrontal regions are homologous to the primate orbitofrontal and medial PFC (Uylings & van Eden, 1990; Preuss, 1995), rats and primates appears to exhibit an analogous organization of prefrontal projections to the basal forebrain.

Summary of anatomical evidence

Although several authors have designed elaborate schemes that attempt to integrate the available anatomical information (see fig. 9 in Zaborszky & Duque, 2000; fig. 13 in Zaborszky *et al*., 1999), few pieces of information appear sufficiently substantiated to provide a reliable anatomical basis for attempts to interpret the functions of GABAergic corticopetal projections, in conjunction with their cholinergic counterparts. This is particularly true in light of accumulating evidence indicating that the function of BF circuits depends strictly on the state of activity of their afferent components (e.g. Sarter & Bruno, 1994; Fadel *et al*., 2001). Currently, the following facts appear to be well established. (i) A roughly equal number of BF GABAergic and cholinergic BF neurons project to

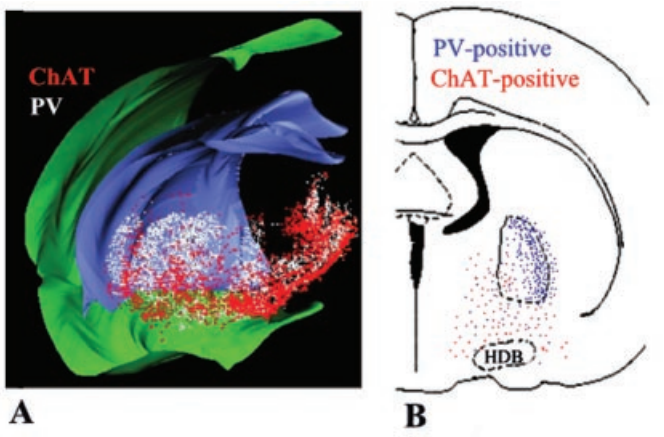

FIG. 1. Distribution of ChAT- and PV-positive neurons in the basal forebrain. As discussed in the text, it is largely agreed that PV-positive neurons are GABAergic. (A) A three-dimensional rendering of these neurons distributed throughout the entire basal forebrain of the left hemisphere of the rat. (B) The distribution of these neurons in the region of the globus pallidus, including the substantia innominata ventral to the globus pallidus, and in the horizontal nucleus of the diagonal band (HDB) as observed in a coronal section (taken from Zaborszky & Duque, 2000; reproduced with the permission of the author and Elsevier Science B.V.). As discussed in the text, roughly similar numbers of cholinergic and GABAergic neurons arise from mostly the medial globus pallidus (the nbM) and the SI to innervate the entire cortical mantle.

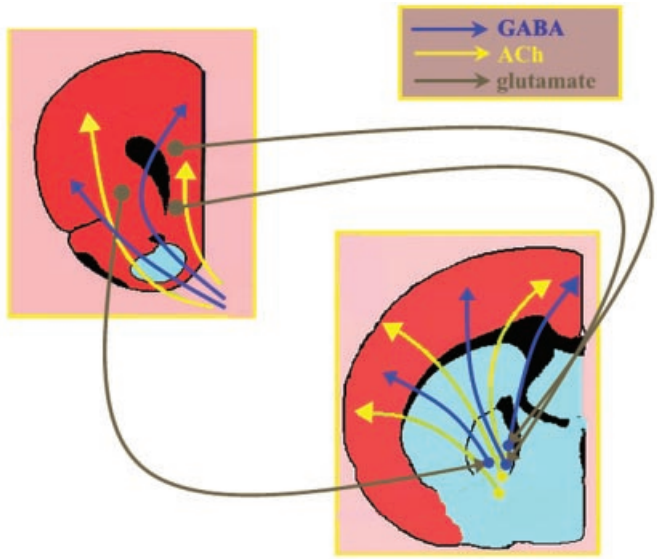

FIG. 2. Schematic depiction of the anatomical data that suggest that corticofugal projections to the BF (black) arise from prefrontal regions and exclusively contact BF GABAergic (blue), but not cholinergic (yellow), corticopetal projections. It is hypothesized that BF GABAergic projections represent a component of the prefrontal efferent circuitry that contributes to the processing of the subjects' ability to switch between the processing of stimuli and response rules (see text).

cortical areas. (ii) BF GABAergic corticopetal projections primarily contact cortical GABAergic interneurons. (iii) BF afferents originating in the PFC exclusively target GABAergic neurons.

Speculations about the functions of BF corticopetal GABAergic projections

Extensive evidence suggests that cortical cholinergic inputs facilitate sensory and associational cortical information processing. Such functions of cortical ACh are based mainly on two mechanisms. First, ACh directly facilitates the processing of other afferent (thalamic) input in all cortical areas. Second, cortical cholinergic inputs contribute to the top-down optimization of task- or modality-specific information processing in posterior associational regions (Sarter *et al*., 2001).

Speculations concerning the functions of the GABAergic component of the BF corticopetal projection system have focused largely on refining the role of ACh in stimulus processing and attention. These speculations can be organized roughly along one major dimension, that is, the postulated degree of anatomical segregation within the BF corticopetal projection system. It is important to note that the evidence supporting contrasting speculations about the organization and function of BF corticopetal projections originates in divergent levels of analysis, with anatomical studies suggesting a more segregated projection system and neurochemical studies supporting speculations about more global, cortex-wide actions of afferents originating in the BF. However, these currently contrasting perspectives about the degree to which BF corticopetal projections are organized topographically or in clusters may be unified in the future as more sensitive anatomical and neurochemical methods become available and allow a more precise mapping of these projections, and the monitoring of activity of BF corticopetal projections at higher spatial and temporal resolutions becomes possible.

Zaborszky and colleagues (e.g. Zaborszky *et al*., 1999) postulate anatomical segregations in the BF not just between noncholinergic and cholinergic neurons, but also between subpopulations of BF cholinergic neurons. They have suggested that these distinct populations of BF neurons give rise to nonoverlapping cortical columns that receive GABAergic or cholinergic inputs. Such an anatomical organization would support strong hypotheses about distinct information processing by BF corticopetal GABAergic and cholinergic projections, respectively. Furthermore, such anatomical segregation of BF corticopetal neurons would substantiate prior speculations about task- and modality-specific activation of selected cortical areas by the BF corticopetal system (see also Wenk, 1989).

These speculations contrast with the perspective suggesting that, given the limited topography in the organization of BF corticopetal projections and the limited cortical area- and layer-specificity of BF inputs and cholinergic and GABAergic receptor distributions, BF corticopetal projections act as a uniform system to gate cortical information processing (Sarter & Bruno, 1997). This perspective is supported by the results of studies which, using different methods, simultaneously assessed extracellular ACh levels in multiple cortical sites. Although some minor regional differences have been observed in some studies, collectively the available data do not indicate that the regulation of cortical cholinergic output differs substantially between cortical regions (Phillis & Chong, 1965; Rasmusson & Szerb, 1976; Jiménez-Capdeville & Dykes, 1996; Himmelheber *et al*., 1998).

Equivalent information concerning the cortical region-specific regulation of activity of cortical GABAergic inputs does not appear to be available and in fact may be difficult to generate for several methodological and conceptual reasons, including the complexities associated with attempts to differentiate between extracellular GABA concentrations originating from neurons vs. non-neurons, and from

cortical afferents vs. cortical interneurons. However, primarily because of the major differences in the afferent organization of BF cholinergic and noncholinergic neurons (above), the activity in cholinergic and GABAergic projections to the cortex is very unlikely to be regulated in parallel (see also Giovanni *et al*., 2001).

If PFC projections to the BF indeed exclusively stimulate BF GABAergic corticopetal projections, it would be hypothesized that the latter represents a component of the prefrontal efferent circuitry that mediates the executive aspects of cognitive task performance. Prefrontal circuits traditionally have been discussed in terms of mediating executive functions, specifically the management of processing resources and decisional mechanisms (e.g. Fuster, 2000; Robbins, 2000). In rats, such functions are reflected by the fundamental impairments in their abilities to perform attentional tasks that result from lesions of the PFC, including randomization of response selection (e.g. Miner *et al*., 1997; Passetti *et al*., 2000). Likewise, electrophysiological experiments demonstrated that PFC neuronal activity changes in attentional task-performing animals are triggered specifically by increases in the demands on attentional processing, as the animals' efforts to cope with such increases presumably require executive control (Gill *et al*., 2000; see also White & Wise, 1999). Therefore, in contrast to the cortical cholinergic input system, it would be speculated that the BF corticopetal GABAergic projections would be more closely associated with the executive components of attentional task performance, and conceptualized anatomically as a projection organized in parallel with the prefrontal cortico-cortical efferent system.

A recent experiment attempted to approach a test of such a hypothesis by comparing the effects of cholinospecific lesions of the BF, produced by intra-BF infusions of 192 IgG-saporin, with the effects of intra-BF infusions of ibotenic acid (IBO), on the performance of rats tested in a sustained attention task (Burk & Sarter, 2001). Intra-BF infusions of IBO have long been known to preferentially destroy noncholinergic BF neurons (Everitt *et al*., 1987; Evenden *et al*., 1989; Robbins *et al*., 1989; Dunnett *et al*., 1991; Page *et al*., 1991; Sarter & Dudchenko, 1991; Bednar *et al*., 1998).

In this experiment, infusions of IBO destroyed 60% of the BF PV-positive cells but decreased cortical acetylcholinesterase (AChE)-positive fibre density by $<25\%$. Conversely, and as expected, infusions of the cholinotoxin did not affect the number of PV-positive cells but decreased cholinergic fibre density in the cortex by $>80\%$. Such selective lesions of the BF cholinergic system were repeatedly demonstrated to result in a decrease in the animals' ability to detect a range of visual signals but not to affect their conditioned response to nonsignal trials (e.g. McGaughy *et al*., 1996; McGaughy & Sarter, 1999). In contrast to the effects of cortical cholinergic deafferentation, BF infusions of IBO selectively increased the number of 'claims' for signals in nonsignal trials. Analyses of the response latencies supported the hypothesis that this effect was due to an impairment in the animals' ability to switch from the processing of rules for signal trials to those governing nonsignal trials (for details see Burk & Sarter, 2001). Switching between task-governing rules represents a core aspect of cognitive flexibility and thus of the executive function traditionally attributed to PFC networks (e.g. Miller, 2000).

To the extent that this finding reflects the loss of GABAergic corticopetal projections, it would support the general idea that the GABAergic branch of the BF corticopetal projection system represents a component of the 'executive' circuitry of the PFC. This hypothesis also allows a re-conceptualization of the deficits resulting from excitotoxic BF lesions observed in numerous studies conducted prior to the advent of the selective cholinotoxin (e.g. Everitt *et al*., 1987; Roberts *et al*., 1990; see also the discussion in Détari, 2000). The behavioural nature of these deficits generally suggested the disruption of more fundamental cognitive functions when compared to the rather specific attentional impairments of cholinospecific lesions (above). For example, Evenden *et al*. (1989), using rats, observed that such lesions did not affect the learning or performance of a conditional discrimination, but they impaired reversal learning. This effect was, as would be expected based on this hypothesis, unrelated to the degree of loss of cortical ChAT-positive cells. Furthermore, reversal learning requires the manipulation, and in fact a complete switch, of the stimulus-response rules, and thus taxes executive functions as they have been typically attributed to PFC circuitry. Data from experiments on the cognitive consequences of excitotoxic BF lesions in marmosets yielded corresponding conclusions, particularly in terms of a lesion-induced 'cognitive rigidity' indicated by, for example, severe impairments in the learning of serial reversals of visual discriminations in the studies by Roberts *et al*. (1990, 1992). Importantly, this lesion did not disrupt the animals' ability to acquire a new discrimination that involved a shift of attention towards a previously non-discriminated aspect of the compound stimuli (Roberts *et al*., 1992). Whilst the cognitive processes underlying such a shift are complex, these data suggest that the cognitive inflexibility produced by such lesions are restricted to the processing of stimulus–response–reward relationships.

Collectively, these data support the general idea that BF IBO lesions, as opposed to the effects of BF cholinergic lesions, impair functions traditionally attributed to PFC circuitry, possibly by disrupting the PFC efferent regulation of BF GABAergic corticopetal projections. However, it is obvious that studying the effects of such lesions represents an extremely crude and preliminary approach, as they destroy corticopetal as well as other noncholinergic and cholinergic projections and BF interneurons. Future, more informative research approaches will depend on the availability of a GABA-selective toxin and other methods (below).

Clinical significance

Efforts to integrate the BF corticopetal circuits into theory and models of neuropsychiatric disorders, particularly schizophrenia and dementia, have focused on the role of the attentional dysfunctions mediated via abnormal regulation of the reactivity of cortical cholinergic inputs, and the decreases in the integrity of this neuronal system, respectively, in the manifestation of the cognitive symptoms of these disorders (Mesulam, 1990; Sarter, 1994; Sarter & Bruno, 1999; Heimer, 2000). The hypothesis that the GABAergic corticopetal component of the BF system mediates 'executive' aspects of performance suggests that the role of the BF corticopetal projection system in these disorders is even more profound. Specifically, abnormal regulation of PFC circuitry, as a result of either pathology within the PFC (e.g. Lewis, 2000; Selemon *et al*., 1998) and/or as part of a multisynaptic mesolimbic network through which the functional consequences of telencephalic pathology are manifested (e.g. Deutch, 1993; Grace, 2000), would be expected to also yield dysregulation in BF GABAergic efferents (Fig. 2). Thus, the BF corticopetal system is subject to at least two sources for afferent dysregulation in schizophrenia, namely the PFC glutamatergic innervation of BF GABAergic neurons (above) and the nucleus accumbens (NAC) GABAergic innervation of BF cholinergic neurons (e.g. Moore *et al*., 1999; Sarter & Bruno, 1999). Collectively, such afferent dysregulation of the BF corticopetal system would be expected to affect all cortical information processing, thereby contributing to the mediation

of the attentional as well as the mnemonic and planning deficits of schizophrenics (e.g. Pantelis *et al*., 1997).

The central role of the loss of BF cholinergic corticopetal projections in the development of age- and dementia-related cognitive impairments, despite some popular criticism (see the discussion in Sarter & Turchi, 2002), represents an impressively substantiated hypothesis (e.g. Geula, 1998; Minger *et al*., 2000; Mufson *et al*., 2000). The question of whether the vulnerability of BF neurons extends to noncholinergic neurons remains unsettled (e.g. Rasool *et al*., 1986; Lehéricy *et al*., 1993). However, even if BF neuronal degeneration does not include GABAergic corticopetal projections (see also Palmer, 1996), the loss of cholinergic neurons limits the proper 'recruitment' of the PFC in attention-demanding situations and therefore the PFC corticofugal projection to the BF can also be expected to remain inadequately activated (Sarter *et al*., 2001). The subsequent corticofugal dysregulation of BF GABAergic neurons may also contribute to the mediation of the escalating cognitive decline in dementia.

Summary and conclusions

About half of all BF neurons which project to the cortex are GABAergic. The present speculations about their contributions to the functions of the BF projection system rely mostly on evidence suggesting the corticofugal projections target BF GABAergic, but not cholinergic, corticopetal projections. The conceptualization of the role of BF GABAergic corticopetal projections in terms of representing a component of the PFC efferent circuitry, contributing to the mediation of executive functions, is supported by the effects of excitotoxic lesions of the BF that preferentially, but not selectively, destroy GABAergic neurons. It is specifically hypothesized that BF GABAergic corticopetal projections mediate the cognitive flexibility required, for example, to switch between multiple sources of information and response rules. Furthermore, if future anatomical studies confirm that the BF GABAergic corticopetal neurons are the exclusive target of the corticofugal projections to the BF, it would be speculated that BF GABAergic corticopetal projections more generally contribute to the mediation of the top-down regulation of sensory input processing, and the associational processing of sensory information in posterior cortical areas (Sarter *et al*., 2001). Collectively, it would be concluded that the BF corticopetal system consists mainly of a cholinergic component that serves to amplify sensory input and fundamental attentional processing, and the activation of the anterior attention system (Sarter *et al*., 2001), and a GABAergic component that represents a branch of the prefrontal system mediating executive functions critical for performance in situations demanding switching between stimuli and response rules.

Future research on the function of these neurons depends on the development of methods to selectively manipulate or monitor BF GABAergic corticopetal neurons. Such methods may include the development of immunotoxins using receptors specifically expressed by these neurons to import neuronal toxins (D. A. Lappi and M. Sarter, unpublished project) and the development of methods to differentiate between cortical extracellular GABA levels that originate from cortical interneurons vs. BF GABAergic inputs. These approaches entail formidable methodological problems; however, our understanding of the functions of the BF cortical projection system will remain premature in the absence of evidence concerning the role of its GABAergic and other noncholinergic (Manns *et al*., 2001) components.

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Abbreviations

ACh, acetylcholine; AChE, acetylcholine esterase; BF, basal forebrain; ChAT, choline acetyltransferase; GABA, γ-amino butyric acid; GAD, glutamic acid decarboxylase; GP, globus pallidus; IBO, ibotenic acid; MCPA, magnocellular preoptic area; NAC, nucleus accumbens; nbM, nucleus basalis of Meynert; PFC, prefrontal cortex; PV, parvalbumin; SI, substantia innominata.

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