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DISSOCIATION BETWEEN THE ATTENTIONAL FUNCTIONS MEDIATED VIA BASAL FOREBRAIN CHOLINERGIC AND GABAERGIC NEURONS

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Abstract—The role of basal forebrain corticopetal cholinergic projections in attentional functions has been extensively investigated. For example, 192 IgG-saporin-induced loss of cortical cholinergic inputs was repeatedly demonstrated to result in a selective impairment in the ability of rats to detect signals in a task designed to assess sustained attention performance. The loss of cortical cholinergic inputs correlated highly with the decrease in the hit rate. Little is known about the functions of basal forebrain non-cholinergic neurons, particularly corticopetal GABAergic neurons, largely because of the absence of specific research tools to manipulate selectively this projection. As basal forebrain lesions produced with ibotenic acid were previously observed to potently destroy non-cholinergic, particularly GABAergic neurons while producing only moderate decreases in the density of cortical cholinergic inputs, the present experiment examined the effects of such lesions on sustained attention performance and then compared these effects with the immunohistochemical and attentional consequences of selective cholinotoxic lesions produced by intra-basal forebrain infusions of 192 IgG-saporin. In contrast to the selective decrease in hits previously observed in 192 IgG-saporin-lesioned animals, the attentional performance of ibotenic acid-lesioned animals was characterized by a selective increase in the relative number of false alarms, that is 'claims' for signals in non-signal trials. Analyses of the response latencies suggested that this effect of ibotenic acid was due to impairments in the animals' ability to switch from the processing of the response rules for signal trials to those for non-signal trials. As expected, 192 IgG-saporin did not affect the number of basal forebrain parvalbumin-positive neurons, that are presumably GABAergic, but decreased cortical acetylcholinesterase-positive fiber density by over 80%. Conversely, in ibotenic acid-lesioned animals, basal forebrain parvalbumin-positive cells were decreased by 60% but cortical acetylcholinesterase-positive fiber density was only moderately reduced (less than 25%).

These data form the basis for the development of the hypothesis that basal forebrain GABAergic neurons mediate executive aspects of attentional task performance. Such a function may be mediated in parallel via basal forebrain GABAergic projections to the cortex and the subthalamic nucleus.

Key words: basal forebrain, acetylcholine, GABA, attention, 192 IgG-saporin, ibotenic acid, rat.

Studies using diverse experimental approaches, including immunotoxic lesions, extracellular recording, and *in vivo* microdialysis to monitor cortical acetylcholine (ACh) release in task-performing animals, have generated substantial evidence in support of hypotheses about the role of basal forebrain (BF) cholinergic corticopetal neurons in attentional processing (Everitt and Robbins, 1997; Sarter and Bruno, 1997; Sarter et al., 2001). Using an operant task designed to assess sustained attention performance (McGaughy and Sarter, 1995), intra-BF as well as intracortical infusions of the selective cholinotoxin 192 IgG-saporin (192-SAP) were demonstrated to result in a decrease in the detection of visual signals (or hits) (McGaughy et al., 1996, 2000; McGaughy and Sarter, 1998, 1999). Furthermore, such lesions were also demonstrated to limit the availability of processing resources, or divided attention performance (Turchi and Sarter, 1997, 2000). These data, in conjunction with studies demonstrating that cortical ACh efflux (Himmelheber et al., 2000) and ACh-mediated medial prefrontal cortex (mPFC) neuronal activity reflect demands on sustained attention (Gill et al., 2000), strongly supported the hypothesis that the detection of signals is mediated via this component of the BF neuronal system. The role of cortical cholinergic inputs in attention is not limited to the facilitation of the detection and discrimination of inputs at the level of sensory information processing, but likely includes the activation of top-down processes that optimize the cognitive and sensory components of attentional performance (Sarter et al., 2001).

In contrast to research on the cortical cholinergic input system, little is known about how other BF neuronal populations, including the GABAergic corticopetal projections, affect attention. GABAergic neurons outnumber cholinergic neurons in the globus pallidus/sub-

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Abbreviations: ACh, acetylcholine; AChE, acetylcholinesterase; ANOVA, analysis of variance; BF, basal forebrain; ChAT, choline acetyltransferase; DAB, 3,3′-diaminobenzidine; GP, globus pallidus; IBO, ibotenic acid; ITI, intertrial interval; mPFC, medial prefrontal cortex; nbM, nucleus basalis of Meynert; PBS, phosphate-buffered saline; PV, parvalbumin; 192-SAP, 192 IgG-saporin; SI, substantia innominata; STN, subthalamic nucleus; TBS, Tris-buffered saline.

stantia innominata (GP/SI) region of the BF (9,600 vs. 5,100 cells/hemisphere; Gritti et al., 1993). These GABAergic neurons are immunopositive for a number of calcium-binding proteins including parvalbumin (PV), calbindin, and calretinin (Brauer et al., 1993; Zaborszky and Duque, 2000). In the BF, neurons that stain for PV are widely believed to be GABAergic (Brauer et al., 1991, 1993; Freund, 1989; Kiss et al., 1990). The majority of the PV-positive cells are located in the lateral GP, either projecting mostly to di- and mesencephalic regions or are interneurons, while the cholinergic neurons are scattered along the medial wall of the GP (the nucleus basalis of Meynert; nbM) and ventrally from the GP (the SI). GABAergic neurons projecting to the cortex are assumed to be situated mostly in the region of the nbM and the SI (references above) while lateral GP GABAergic neurons primarily project to the subthalamic nucleus (STN) and substantia nigra (Smith et al., 1998).

GABAergic and cholinergic neurons are not completely segregated in the BF and overlap in the medial GP and SI (L. Zaborszky, D.L. Buhl, S. Pobalashingham, S.G. Bjaalie and Nadasdy, unpublished manuscript). Most studies suggested that corticopetal cholinergic and GABAergic neurons are co-distributed in medial GP and SI (Fisher et al., 1988; Gritti et al., 1997). Estimates about the relative proportion of GABAergic corticopetal to cholinergic corticopetal neurons range from 20 to 50% (Gritti et al., 1997; Rye et al., 1984), supporting the possibility that both populations arise mainly from the medial GP and the SI. In the cortex, GABAergic projections appear to terminate mostly onto GABAergic inhibitory interneurons (Freund and Gulyas, 1991; Freund and Maskenate, 1992), therefore yielding disinhibition and acting in parallel with ACh to activate the cortex (Dykes, 1997; Semba, 2000). This view is supported by the findings that, in the BF, extensively collateralized cholinergic neurons locally make contact with GABAergic cells (Zaborszky and Duque, 2000), and that the firing rate of both BF PV and choline acetyltransferase (ChAT)-positive cells are correlated with cortical electroencephalographic activation (Duque et al., 2000). However, cholinergic inputs to the cortex in part also terminate on cortical GABAergic neurons (Beaulieu and Somogy, 1991), exerting fast muscarinic excitation of these neurons (Kawaguchi, 1997; McCormick and Prince, 1985; Muller and Singer, 1989). These findings indicate that the combined effects of GABAergic and cholinergic inputs on cortical neuronal excitability are extremely complex because they also interact with the status of other converging inputs (McCormick, 1990).

The absence of methods to lesion or manipulate selectively the BF GABAergic neurons has limited research on their role in attention. The present study represents an initial effort to compare the attentional effects of loss of primarily BF PV-positive cells, produced by infusions of ibotenic acid (IBO), with the well established effects of the 192-SAP-induced loss of BF corticopetal cholinergic neurons. Intra-BF infusions of IBO were previously demonstrated to produce substantial damage to non-cholinergic BF neurons while resulting in an only limited loss of cortical cholinergic input, as measured either by cortical ChAT activity or by counting cortical acetylcholinesterase (AChE)-positive fibers (Bednar et al., 1998; Dunnett et al., 1991; Evenden et al., 1989; Everitt et al., 1987; Page et al., 1991; Robbins et al., 1989; Robinson et al., 1996; Sarter and Dudchenko, 1991). Furthermore, surviving BF cholinergic neurons were observed repeatedly in IBO-lesioned animals, although the discrepancy between the residual number of BF cholinergic neurons and the rather moderate decreases in cortical ChAT activity of AChE-positive fiber density (on average between 20 and 30%) has remained unexplained (see the discussion in Sarter and Dudchenko, 1991; Shaughnessy et al., 1994). The moderate toxic effects of IBO on cortical cholinergic inputs were also reflected by a lack of effect on cortical ACh efflux, despite reporting extensive gliosis in the BF (Ammassari-Teule et al., 1993). IBO-induced lesions were also observed to potently destroy GABAergic neurons in the entire GP (Shaughnessy et al., 1994).

Although representing an imperfect approach, the effects of IBO lesions, when compared with the effects of the selective cholinotoxic effects of 192-SAP, may form the basis for the initial development of hypotheses about the attentional functions mediated by predominantly BF non-cholinergic and thus largely GABAergic neurons. In the present study, the cholinotoxic effects of IBO and 192-SAP were assessed primarily by estimating the residual density of cortical AChE-positive axons (for a discussion of the validity of this measure see Lysakowski et al., 1989), because this measure correlates with decreases in hits in 192-SAP-lesioned animals (references above). The loss of GABAergic neurons was estimated by counting BF PV-positive cells. The overall aim of this study was to determine the effects of IBO-induced lesions of the BF on sustained attention performance, and to attribute these effects to the loss of primarily GABAergic neurons in the medial and ventral regions of the GP. For this purpose, comparative data on the effects of 192-SAP-induced lesions on cortical AChE-positive fiber density and the number of BF PV-positive neurons were also generated.

EXPERIMENTAL PROCEDURES

Subjects

Subjects were 24 male Fischer/Brown Norway rats (Harlan Sprague–Dawley, Indianapolis, IN, USA) that were 3 months old at the beginning of the experiment. Animals were housed individually in a temperature- and humidity-controlled vivarium with a 12-h light/dark cycle (lights on 0630). Rats received access to food *ad libitum*. Water was available as reward during behavioral training (below) and for 8 min at the end of each session. Sixteen of the animals were used for behavioral training and eight rats were used strictly for histochemical and immunohistochemical analyses (see below). Subjects were treated in accordance with the guidelines of the Institutional Laboratory Animal Care and Use Committee at The Ohio State University in facilities accredited by the American Association of Accreditation of Laboratory Animal Care (AAALAC).

Apparatus

Training occurred in eight operant chambers (Med Associates, East Fairfield, VT, USA). Each chamber was equipped with two retractable levers, three panel lights, and a houselight above the central panel light in the front of the chamber. The luminance values for the houselight and the panel lights were previously reported (McGaughy et al., 1996; see also Holley et al., 1995 for an analysis of stimulus properties derived by these filament bulbs). A water port and a 2900-Hz tone generator were located in the back of the chamber. Each operant chamber was enclosed within a sound-attenuating box that was equipped with a fan that provided ventilation and white noise. An IBM 486-PC clone controlled data collection and execution of programs. Signal presentation, lever operation and water dispension were controlled by an IBM clone computer using MED-PC software (V1.10; Med Associates).

Presurgical operant training

Training occurred between 1:30 p.m. and 4:30 p.m. for 6 days/week. After being trained to lever press for reinforcement (40 µl of water), animals were shaped to perform the sustained attention task. In the initial stage of training, a trial began with a signal (1 s illumination of the central panel light) or a non-signal (no illumination of the central panel light) event followed 2 s later by extension of the levers into the chamber. After a signal, a press on the left lever was rewarded, and scored as a hit and a press on the right lever was not rewarded and scored as a miss. After a non-signal, a press on the right lever was rewarded and recorded as a correct rejection, and a press on the left lever was not rewarded and recorded as a false alarm. All incorrect responses were followed by a correction trial that was identical to the previous trial. If animals committed three consecutive errors on correction trials, a forced trial was introduced. During a forced trial, after illumination of the central panel light (if the error was committed during a signal trial) or no illumination (if the error was committed during a non-signal trial), only the correct lever was extended into the chamber until it was pressed or 90 s elapsed. The intertrial interval (ITI) was 12 ± 3 s and the houselight was not illuminated during this stage of training. Criterion performance was five consecutive days of 70% accuracy during signal and non-signal trials.

After reaching criterion, the task parameters were changed in two ways. First, shorter signals (500, 50, or 25 ms) were presented semi-randomly within a session. Second, correction trials and forced trials were eliminated. Rats were required to reach a criterion of 70% accuracy during the 500-ms signal and non-signal trials and of fewer than 25% of the trials being omissions for seven consecutive days before training on the final task. The final task was the same as the previous stage except that the ITI was decreased to 9 ± 3 s and the houselight was illuminated throughout the session. Criterion performance during this stage of training was seven consecutive days of 70% accuracy during the 500-ms signal and non-signal trials and fewer than 25% of trials omitted during each session. Similar to previous studies using this task, animals reached criterion performance after approximately 4 months of training. Rats were assigned to lesion or sham conditions ($n = 8$/group) using block randomization to ensure that groups were matched for performance in the sustained attention task.

Postsurgical operant training

Postsurgical training began 7 days after surgery. Rats were trained in the sustained attention task until reaching stable, asymptotic performance (defined as three consecutive sessions with accuracy varying to the longest signal by less than 15%, to non-signal trials by less than 10%, and with omissions varying by less than 15). After reaching stable performance, rats were trained for 60 additional sessions to test whether any lesion effects were attenuated with continued practice of the task.

Behavioral measures

The total number of hits, misses, correct rejections, false alarms, and omissions was collected during each session. Based on these data, the relative number of hits [h; h = hits/(hits+misses)] and correct rejections [cr; cr = correct rejections/(correct rejections+false alarms)] were calculated. Analyses of omissions were conducted separately from those of hits and correct rejections in order to avoid confounding the interpretation of hits and correct rejections with omissions. Each of these measures was calculated for both the entire session and per block of 54 trials. In addition, the response latencies were recorded; latencies were defined as the time between extension of the levers and lever operation. Response latencies were analyzed in accordance to trial type (signal trial or non-signal trial) and trial outcome (hit/miss or correct rejection/false alarm).

Surgical procedures

Rats were anesthetized with ketamine (90.0 mg/kg, i.p.) and xylazine (6.0 mg/kg, i.p.) and placed in a stereotaxic instrument (Kopf, Tujunga, CA, USA). All surgical procedures were conducted under aseptic conditions. Bilateral infusions into the BF were made at the following coordinates (anterioposterior and mediolateral relative to bregma and dorsoventral relative to the interaural line): anterioposterior −0.5 mm, mediolateral ± 2.9 mm, and dorsoventral +2.5 mm (Paxinos and Watson, 1986). Animals received infusions of 0.5 µl/site of 0.06 M IBO (Sigma, St. Louis, MO, USA) in 0.1 M phosphate buffer (pH 7.4) or of vehicle. For histochemical and immunohistochemical comparisons, eight rats were given bilateral infusions of the selective cholinergic immunotoxin 192-SAP in Dulbecco's saline (Advanced Targeting Systems, San Diego, CA; 0.1 µg/0.5 µl/hemisphere; lot # 4-1). Infusions were made in a bolus using a 1.0-µl Hamilton syringe at a rate of 0.5 µl/min with the syringe remaining in place for 2 min after the infusion. Animals were allowed 7 days *ad libitum* access to food and water prior to postsurgical training.

Histological and immunohistological procedures

Rats were perfused transcardially with cold saline followed by 4.0% cold paraformaldehyde. Brains were removed, stored in 4.0% paraformaldehyde overnight, placed in 30.0% sucrose in phosphate buffer until they sank, and then sectioned at 30 µM in a cryostat. Parallel sections were processed for the histochemical visualization of cortical AChE-positive fibers, the immunohistochemical visualization of BF ChAT and PV-positive neurons, and for Cresyl Violet staining.

A modified protocol by Tago et al. (1986) was used for AChE staining. After rinsing in 0.1 M phosphate buffer (pH 7.4), sections were incubated in 0.1% H_2O_2 for 30 min. Sections were rinsed in 0.1 M maleate buffer (pH 6.0) and then immersed in a solution containing: 0.0147 g sodium citrate, 0.00165 g potassium ferricyanide, 0.00749 g copper sulfate, and 5.0 mg of acetylthiocholine iodide in 200.0 ml of 0.1 M maleate buffer (pH 6.0). After rinsing with 50.0 mM Tris buffer (pH 7.6), sections were incubated in a solution of 50.0 mg of 3,3′-diaminobenzidine (DAB) and 0.375 g nickel ammonium sulfate in 125.0 ml of 50.0 mM Tris buffer (pH 6.2). After 10 min, eight drops of 0.1% H_2O_2 were added and sections continued to incubate until cortical layering could be detected.

For the demonstration of PV/ChAT immunoreactivity, sections were rinsed with phosphate-buffered saline (PBS) and placed for 10 min in a solution of 0.5% H_2O_2 and 0.3% Triton X-100 in PBS. Following a rinse in PBS, sections were incubated in 2.0% bovine serum albumin (Sigma, St. Louis, MO, USA), 5.0% normal donkey serum, and 0.3% Triton X-100 in PBS. Sections were then incubated overnight in a monoclonal mouse anti-PV antibody (Sigma; 1:2000) at room temperature on an orbital shaker. After rinsing in PBS, sections were incubated in a donkey anti-mouse secondary antibody (Chemicon, Temecula, CA, USA; 1:50) for 90 min, rinsed in PBS, and then exposed to mouse peroxidase anti-peroxidase complexes for

90 min. DAB with nickel ammonium sulfate enhancement in Tris-buffered saline (TBS) was used as a chromogen. Staining then began immediately for ChAT with similar rinsing procedures as for PV staining. Sections were incubated overnight at room temperature in goat anti-ChAT (Chemicon; 1:200), and then in a biotinylated donkey anti-goat secondary antibody (Chemicon; 1:500). After incubation in solutions from an avidin–biotin–peroxidase complex (ABC) Elite kit (Vector laboratories, Burlingame, CA, USA), ChAT was visualized with DAB.

Quantification of cortical AChE-positive fibers and BF PV-positive cells

A quantitative estimate of AChE-positive fiber density was used to indicate the degree of loss of cortical cholinergic fibers following lesions. This method was identical to that used in previous studies on the behavioral and histochemical effects of intra-basalis infusions of IBO (Sarter and Dudchenko, 1991) or 192-SAP (McGaughy et al., 1996). Cortical areas were delineated in accordance to the atlas by Lysakowski et al. (1989). A modified grid counting method, initially described by Stichel and Singer (1987) was used to quantify AChE-positive fibers (Holley et al., 1994; McGaughy et al., 1996). At a magnification of 25×, the focusing magnifier of a VANOX Olympus Research Microscope (Olympus America, Melville, NY, USA) was inserted such that four orthogonal double cross lines were superimposed over the cortical region of interest. Each fiber that crossed the double lines was counted. The cortical areas in which AChE-positive fiber densities were counted are listed in Table 1. For each cortical area, counts were made in each hemisphere for three different sections.

PV-positive cells were counted using the microscope specified above. The number of cells in a triangular region of the BF was counted. On coronal sections taken at about −1.3 mm from bregma, the corners of this region were placed at the dorsal tip of the GP that borders the internal capsula, the most ventro-lateral extension of the SI, and the medio-dorsal edge of the magnocellular medial preoptic area. PV-positive cells were counted in each hemisphere in two different sections. It is important to note that such uncorrected counts of PV-positive cells, similar to the counts of cortical AChE-positive fibers, were used solely to provide estimates of the efficacy of the lesions.

Statistical analyses

Percentage data were angularly transformed (McGaughy et al., 1996; Zar, 1974) and then tested with mixed factor analyses of variances (ANOVAs) that included lesion (sham- and IBO-induced lesions), signal length (where appropriate), block (three blocks of 54 trials within each session), and time (immediate stable performance and performance after 60 sessions). The *P*-values reported for within-subject main effects and interactions were corrected with the Huynh–Feldt procedure (Maxwell and Delaney, 1990). Multiple comparisons used to further analyze significant interactions were corrected with the Bonferroni procedure (Keppel, 1991). In order to assess statistically the effects of lesions on response latencies, the median response latency was calculated for each animal, trial outcome, and session, as means may be more susceptible to outliers, specifically in cases when the overall number of data points is relatively small. For histological analyses, the non-parametric Kruskal–Wallis statistic was used to test for differences between the lesion groups. An α level of 0.05 was adopted. Data analyses were conducted with SPSS 10.0 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Presurgical performance

The attentional performance of the two groups of animals did not differ prior to surgery. One lesioned animal did not regain stable performance postsurgically and was subsequently excluded from statistical analyses. Data collapsed over the last five sessions prior to surgery indicated that the relative number of hits was similar in both groups (sham/lesioned): 500 ms: 91.2%/92.5%; 50 ms: 68.7%/72.3%; 25 ms: 47.0%/49.9%; $F(1,13) = 1.06$, $P = 0.32$). Likewise, both groups of animals performed identically in non-signal trials (relative number of correct rejections: 78.6%/81.4%; $F(1,13) = 0.38$, $P = 0.55$).

Immediate postsurgical performance

Immediate postsurgical performance was assessed by collapsing the data from the first three sessions following postsurgical asymptotic performance. To achieve stable postsurgical performance (see Experimental procedures for the definition of the performance criteria), sham-lesioned animals required 29.9 ± 3.0 sessions and lesioned animals needed 45.6 ± 9.5 sessions. BF infusions of IBO did not result in changes in the animals' ability to detect signals (Fig. 1). A three-way lesion × block × signal length ANOVA (see Experimental procedures for details regarding each of these factors) indicated that sham-lesioned and IBO-lesioned groups did not differ on the relative number of hits ($F(1,13) = 2.01$, $P = 0.18$). As expected, signal length affected the hit rate ($F(2,26) = 46.8$, $P < 0.001$), reflecting a decrease in hits in both groups to shorter signals (Fig. 1). Furthermore, there were no interactions between any combination of the three factors (lesion × block: $F(2,26) = 0.13$, $P = 0.88$; lesion × signal length: $F(2,26) = 1.94$, $P = 0.16$; block × signal length: $F(4,52) = 0.70$, $P = 0.60$; lesion × block × signal length: $F(4,52) = 0.49$, $P = 0.74$).

Compared with sham-lesioned animals, IBO-induced

Table 1. Cortical AChE-positive fiber density: group data (mean ± S.D.)

Brain area	4	3b		41	
Layer	V	II/III	V	II/III	V
Sham-lesioned ($n = 8$):	28.9 ± 1.0	31.2 ± 0.7	29.5 ± 0.9	28.5 ± 0.7	28.6 ± 1.0
IBO-lesioned ($n = 7$):	20.5 ± 2.8[a]	25.3 ± 2.1[a]	23.1 ± 2.2[a]	21.9 ± 1.7[a]	21.3 ± 1.9[a]
Δ (%)	−29.1	−18.9	−21.7	−23.2	−25.5
192-SAP-lesioned[b]; Δ (%)	−85.8	−85.6	−82.7	−66.4	−53.8

[a]Significantly different from the sham-lesioned group (all $P < 0.03$; see main text).
[b]Data taken from McGaughy et al., 1996. Note that these data from 192-SAP-lesioned animals ($n = 6$) were used for this comparison because they were from animals with defined sustained attentional impairments (see main text).

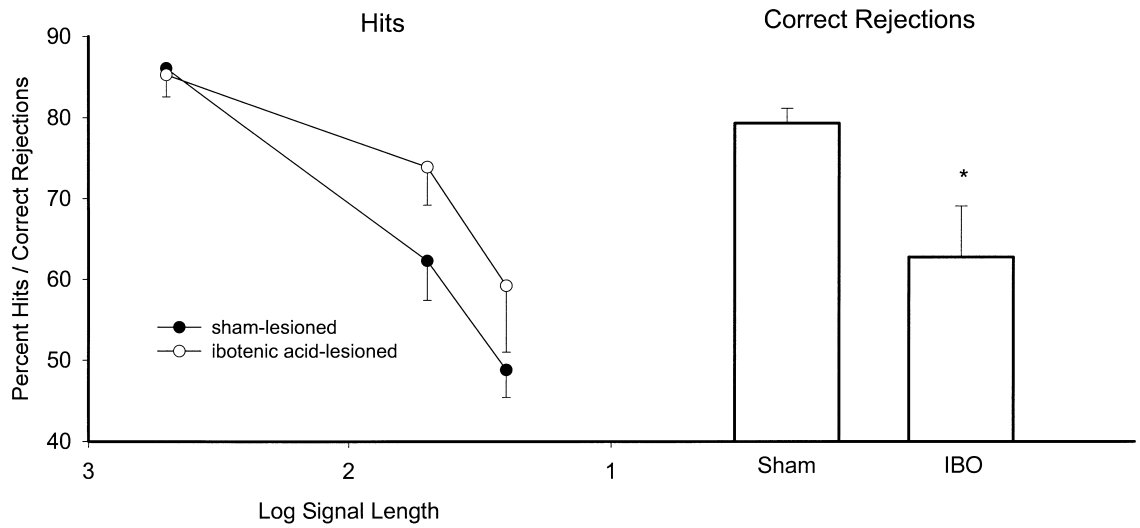


Fig. 1. Effects of lesions on the relative number of hits (left part) and correct rejections (right part). The lesions did not significantly affect the animals' ability to detect signals. However, IBO-lesioned animals ($n=7$) exhibited a decrease in the number of correct rejections of non-signals compared with sham-lesioned animals ($n=8$; indicated by the asterisk). In other words, lesioned animals more frequently 'reported' a signal while none was presented.

lesions resulted in a significant impairment in the ability to reject non-signals ($F(1,13)=7.04$, $P=0.02$; Fig. 1). The lack of effect for block ($F(2,26)=1.29$, $P=0.29$) or for lesion and block ($F(2,26)=0.11$, $P=0.88$) indicated that the effects of the lesion on correct rejections did not interact with number of trials completed within a session.

Lesioned animals omitted more trials than sham-lesioned rats ($F(1,13)=13.1$, $P=0.003$). This effect of the lesion did not interact with block (block: $F(2,26)=2.74$, $P=0.10$; lesion × block: $F(2,26)=0.40$, $P=0.61$). Lesioned animals had 37.5 ± 4.8 omissions/session, compared with 19.9 ± 1.8 omissions/session in sham-lesioned animals. The percent omitted trials per trial type did not indicate a systematic difference in the pattern of omissions between sham and lesioned animals (sham/lesioned): 55.3%/57.5% non-signal trials omitted; 13.9%/11.9% 500 ms signal trials omitted; 16.7%/14.0% 50 ms signal trials omitted; 14.1%/16.6% 25-ms signal trials omitted). A lesion × trial type ANOVA did not yield a significant interaction ($F(3,39)=1.94$, $P=0.15$) indicating that the pattern of omissions for the sham and lesion groups did not systematically vary across trial type (i.e., signal vs. non-signal trial).

Analyses of the response latencies to the different trial outcomes (hit, miss, correct rejection, false alarm; see Experimental procedures) indicated that the lesioned animals' response latencies were higher for correct rejections and misses than for hits and false alarms (Fig. 2). In contrast, the response latencies of sham-lesioned animals did not differ between trial outcomes (Fig. 2). Median response latencies were averaged for each animal over the three sessions used for this analysis and subjected to a two-way ANOVA (lesion × trial outcome). While there was no main effect of the lesion on response latencies ($F(1,13)=0.02$, $P=0.91$), response latencies varied by trial outcome ($F(3,39)=9.04$, $P=0.001$), and this effect interacted with lesion ($F(3,39)=7.85$, $P=0.002$). Multiple comparisons indicated that the main effect of trial outcome was due to all animals exhibiting shortest latencies for hits when compared to misses ($F(1,13)=15.4$, $P=0.002$) and false alarms ($F(1,13)=9.86$, $P=0.007$). One-way ANOVAs testing the effects of trial outcome on the latencies were conducted separately for the sham-lesioned and IBO-lesioned groups to determine the basis for the lesion × trial outcome interaction. Response latencies varied by trial type in lesioned ($F(3,18)=20.69$, $P=0.001$) but not sham-lesioned animals ($F(3,21)=2.36$, $P=0.13$). Multiple comparisons indicated that in lesioned animals the latencies for misses and correct rejections were longer than for hits and false alarms (misses vs. hits: $t(6)=5.48$, $P=0.002$); misses vs. false alarms: $t(6)=6.88$, $P=0.001$; correct rejections vs. hits: $t(6)=4.04$, $P=0.007$; correct rejections vs. false alarms: $t(6)=4.24$, $P=0.005$).

Comparison between immediate and long-term postsurgical performance

In order to test for the possibility that the lesion-induced decrease in the relative number of correct rejections (or its inverse, an increase in false alarms) reflected a transient consequence of the lesion, additional analyses were conducted in which the data from the sessions analyzed above were compared with data taken from three test sessions conducted 60, 61, and 62 sessions following the 3rd session used in the primary analysis (effects of time). These analyses indicated that the immediate effects of the lesion on attention performance remained stable over time.

The relative number of hits did not significantly differ with over 60 sessions of additional training. Time did not affect the relative number of hits ($F(1,13)=3.22$, $P=0.10$), nor did the effects of lesion and time interact ($F(1,13)=3.68$, $P=0.08$). The previously observed effect of the lesion on the relative number of correct rejections remained stable as indicated by a significant effect of

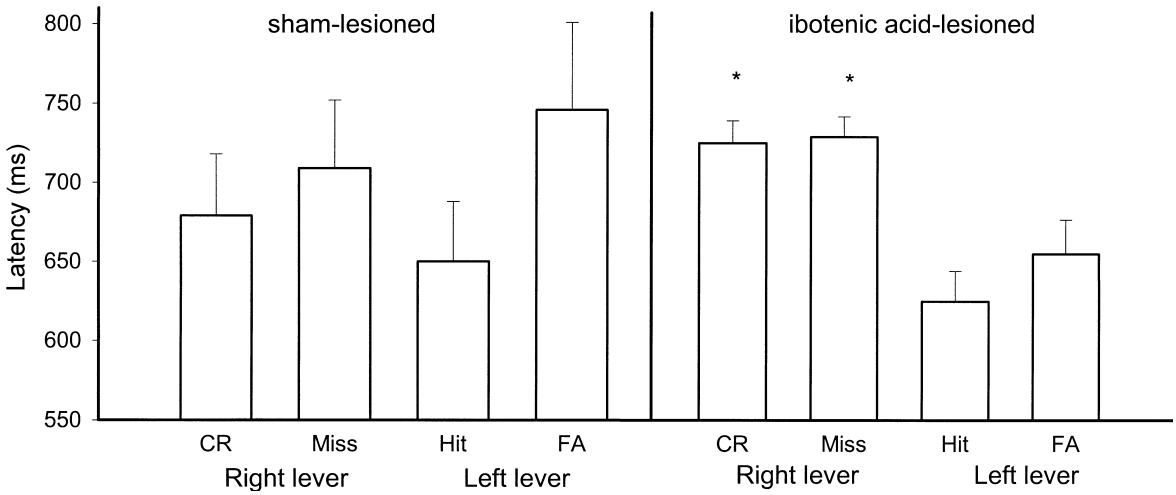


Fig. 2. Effects of lesions on response latencies. Hits were associated with shortest response latencies in all animals (sham-lesioned $n=8$; IBO-induced lesioned $n=7$). However, in lesioned animals, the latencies for both hits and false alarms (FA) were shorter than for correct rejections (CR) and misses (indicated by the asterisks). These data support the speculation that IBO lesions impaired the animals' cognitive switching from the predominating processing of the rules for the detection of hits to the processing for the rules governing non-signal trials (see main text).

lesion on this measure ($F(1,13)=4.84$, $P=0.046$; percent correct rejections in the late set of data; sham-lesioned: $80.9\pm1.8\%$; lesioned: $74.8\pm4.3\%$). However, the effects of lesion and time on correct rejections interacted significantly ($F(1,13)=8.75$, $P=0.011$) reflecting a partial attenuation of the lesioned animals' reduced correct rejection rate over time. A comparison of correct rejections for each group at the two time points demonstrated that the relative number of correct rejections in lesioned animals increased with additional training ($F(1,6)=16.2$, $P=0.007$) while that of the sham group did not ($F(1,7)=3.61$, $P=0.10$). Importantly, however, as indicated above, the main effect of the lesion on the performance in non-signal trials persisted over time.

Finally, the lesion-induced increase in omissions remained unaffected by time (lesion: $F(1,13)=15.8$, $P=0.001$; time ($F(1,13)=3.02$, $P=0.11$; lesion$\times$time: $F(1,13)=0.05$, $P=0.82$). Likewise, time did not affect response latencies ($F(1,13)=3.62$, $P=0.08$) and the interactions between lesion and trial outcome on latencies observed in the initial analysis remained significant ($F(3,39)=7.15$, $P=0.005$).

Histological analyses

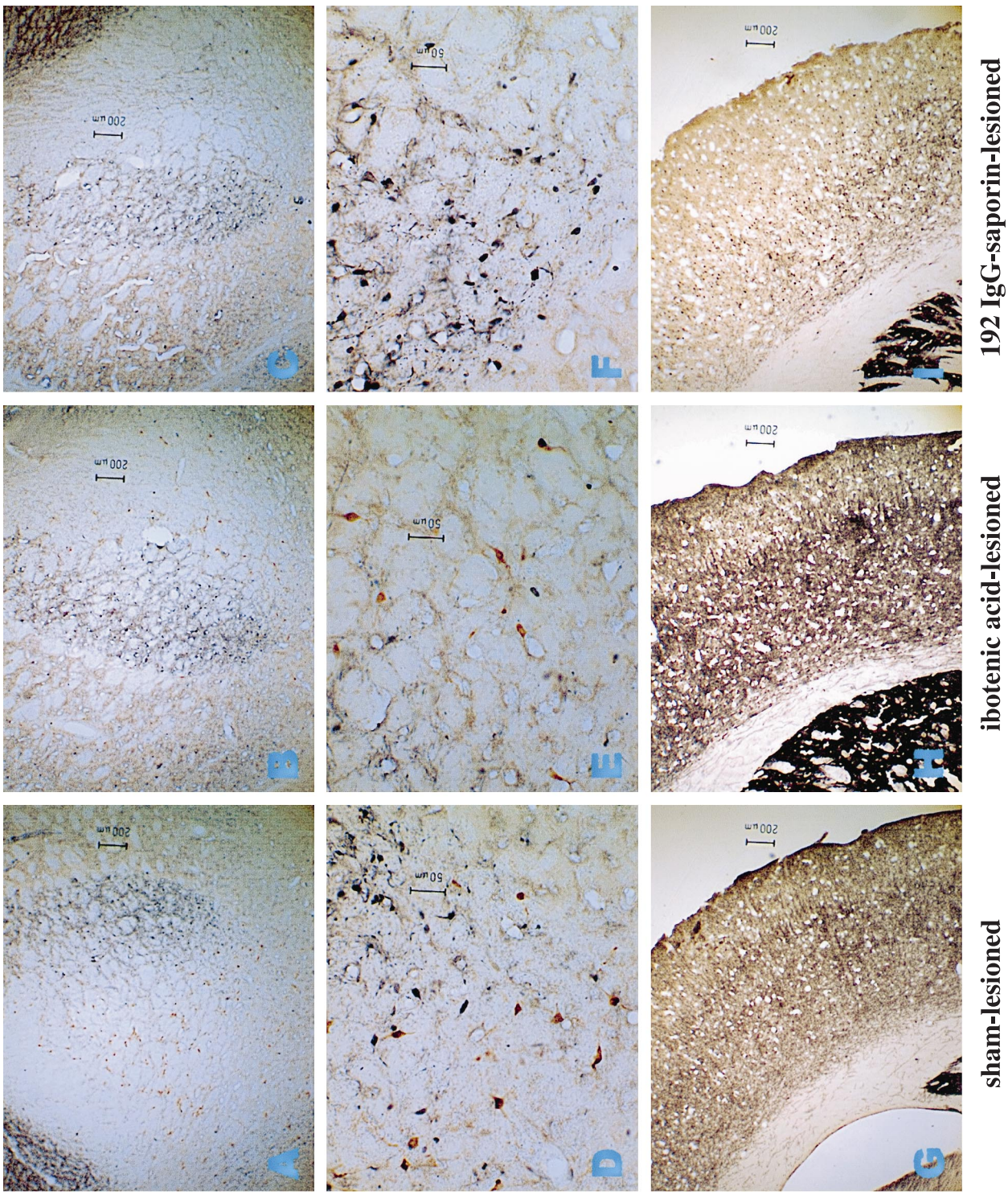
Cortical AChE-positive fiber density. Across the cortical regions examined, infusions of IBO produced an 18.9–29.1% decrease in the number of AChE-positive fibers (Table 1). The IBO-induced decreases in AChE-positive fiber densities were statistically significant for all cortical regions (all P's <0.03). As was expected based on the use of concentrations of 192-SAP that were equivalent to those used by McGaughy et al. (1996), the loss of cortical AChE-positive fibers in the brains of 192-SAP-lesioned animals matched the 53–85% decrease in cortical AChE-positive fiber density in the lesioned animals whose attentional performance was characterized by decreases in hits (see Fig. 3I and Table 1; McGaughy et al., 1996).

Thus, BF infusions of IBO, similar to previous studies (references in Introduction), resulted in moderate decreases in cortical AChE-positive fiber density. Conversely, lesions with 192-SAP resulted in an extensive loss of cortical AChE-positive fibers (Table 1).

BF PV/ChAT-positive neurons. Infusions of IBO into the BF resulted in loss of PV- and ChAT-positive neurons in the GP, mostly in the medial and ventral aspects including the nucleus basalis regions and the SI. As shown in Fig. 3E, ChAT-positive cells were visible, primarily in the ventral GP where PV-positive cells were largely absent (see also Fig. 4). Generally, IBO lesions were characterized by gliosis and calcifications in the center region of the injections (Saura et al., 1995) and, similar to previous studies (Everitt and Robbins, 1997; Robbins et al., 1989; Sarter and Dudchenko, 1991), there was a fair degree of variability in the extent of damage to the dorsal GP.

IBO-lesions resulted in a $\sim$60% decrease in PV-positive cells in the BF (from an average of 75.9 ± 2.5 PV-positive neurons in sham-lesioned brains to 43.3 ± 4.10 in IBO-lesioned animals; see Experimental procedures for counting procedures). The IBO-induced loss of PV-positive cells was large and statistically significant ($\chi^2(1)=9.89$, $P=0.002$). As expected, 192-SAP lesions, despite producing massive decreases in cortical AChE-positive fiber densities and virtually a complete loss of ChAT-positive neurons in the BF (see Fig. 3F), did not result – as expected based on the selectivity of 192-SAP – in changes in the PV-positive cell counts (71.2 ± 3.2 neurons; $\chi^2(1)=0.93$, $P=0.336$; Fig. 3F; see also Roßner et al., 1995).

Thus, the effects of IBO and 192-SAP on cortical AChE-positive fiber density and BF PV-positive cells


192 IgG-saporin-lesioned
ibotenic acid-lesioned
sham-lesioned

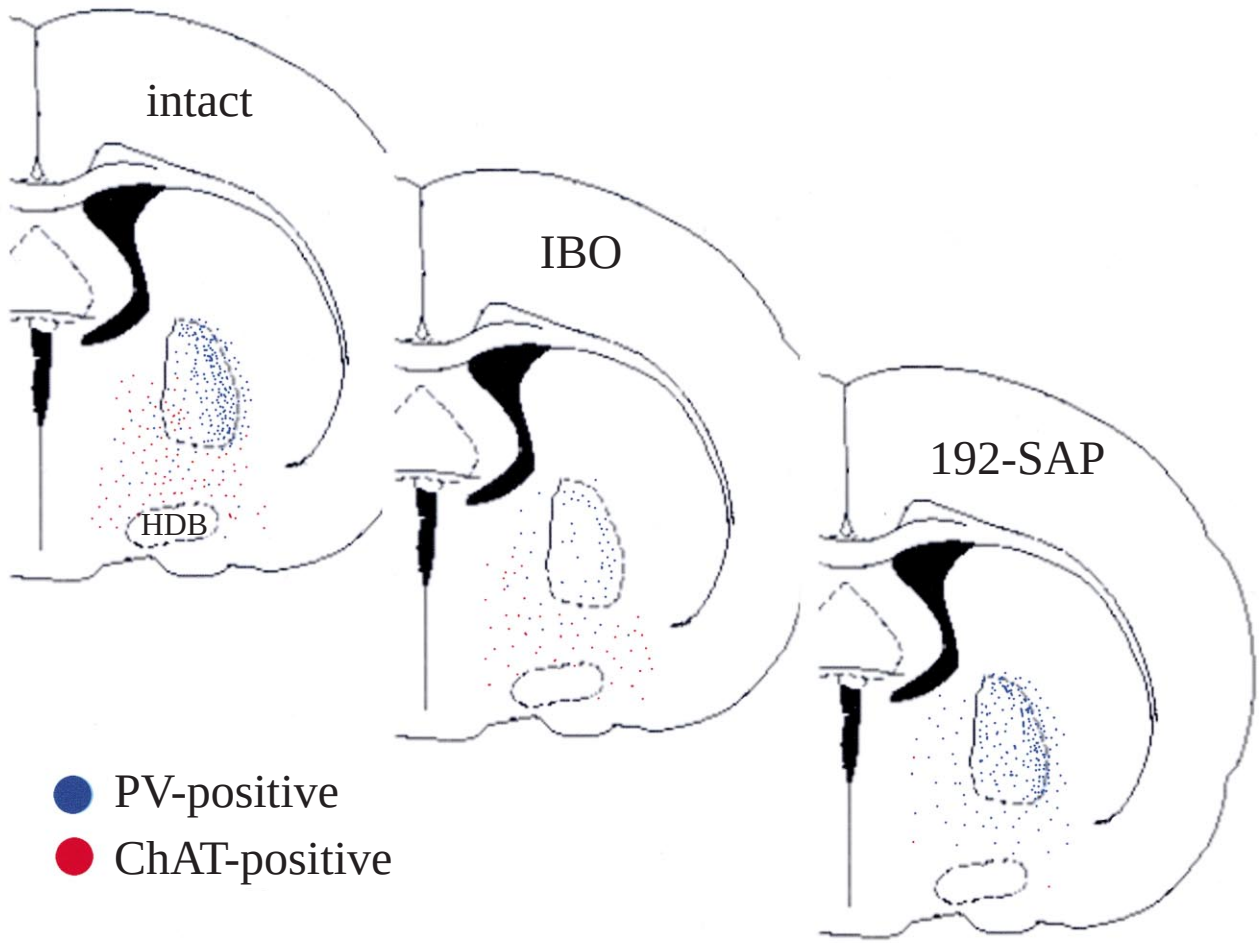


Fig. 4. Schematic illustration of the distribution of PV- (blue dots) and ChAT-positive (red dots) neurons on representative sections of the BF of intact, 192-SAP-lesioned, or IBO-lesioned animals. Note that this figure does not depict the distribution of immunoreactive neurons in neighboring areas, particularly the caudate-putamen and the horizontal nucleus of the diagonal band (HDB). Intra-basalis infusions of 192-SAP selectively destroyed ChAT-positive neurons and did not affect the number of PV-positive neurons. Conversely, infusions of IBO resulted in a ~60% decrease in the number of PV-positive cells, with more modest effects on BF cholinergic neurons and the integrity of cortical cholinergic inputs (see Table 1).

can be effectively dissociated, with IBO yielding moderate effects on cortical cholinergic fibers but a substantial loss of BF PV-positive cells, and 192-SAP yielding extensive loss of cortical cholinergic inputs but no loss in PV-positive cells (Roßner et al., 1995). This dissociation is the basis for the discussion of the potential role of BF GABAergic neurons in attentional performance.

DISCUSSION

BF lesions with IBO resulted in a decrease in the relative number of correct rejections, or its inverse, an increase in false alarms. The animals' ability to detect signals was not affected. Similar to the results described in previous reports, IBO potently decreased the number

Fig. 3. BF PV- and ChAT-positive neurons and cortical AChE-positive fiber density in sham-lesioned (left column), IBO-lesioned (middle), and 192-SAP-lesioned (right) animals. The top row (A,B,C) shows low magnification photomicrographs of the GP area (200-μm scale inserted). ChAT-immunoreactive cells appear reddish-brown and PV-immunoreactive cells are labeled black (A shows a right hemisphere and (B) and (C) are microphotographs from left hemispheres). In intact animals (A), the cholinergic cells are concentrated along the medial wall of the GP (that is the nbM), and latero-ventrally to the GP, that is the SI. The microphotographs shown in the middle row (D,E,F) are higher magnifications of the SI area of the sections shown in the top row (50-μm scale inserted). In (D), the normal co-distribution of PV- and ChAT-positive neurons in the SI is clearly visible. As shown in (B) and (E), infusions of IBO substantially decreased the number of both types of neurons but also spared ChAT-positive cells. In contrast, infusions of 192-SAP destroyed all ChAT-positive cells (C,E) but did not affect PV-positive cell counts (see Results). Cortical AChE-positive fiber density was extensively decreased in 192-SAP lesioned animals (I), while the decreases in IBO-lesioned animals (H) remained more moderate (see also Table 1). Thus, the effects of IBO and 192-SAP on cortical AChE-positive fiber density and BF PV-positive cells can be dissociated. This dissociation and the opposed effects of IBO and 192-SAP lesions on sustained attention performance form the basis for a hypothesis about the role of BF GABAergic neurons in attention (see main text).

of GABAergic neurons in the GP, while only moderately decreasing cortical AChE-positive fiber density. Furthermore, the potent and selective cholinotoxic effects of 192-SAP were confirmed. Animals with such lesions have been repeatedly demonstrated to exhibit attentional impairments opposite of the effects of IBO, that is decreases in hits and no effect on false alarms.

The effects of IBO on sustained attention performance were characterized by an impaired ability to reject non-signal events. In other words, IBO-lesioned animals exhibited an increased frequency in 'reporting' signals when none were presented. Because of the operant rules governing this task, and in the absence of associated effects on the ability to detect signals, this effect cannot be explained by any more trivial behavioral mechanisms such as increases in lever- or side-biases, or switching behavior. Any such effect would have produced more global performance changes (i.e., changes in both the percentage of hits and correct rejections) that clearly would have signified the role of non-cognitive mechanisms. Increases in the relative number of false alarms were previously observed following three pharmacological manipulations: repeated systemic administration of amphetamine (Deller and Sarter, 1998), BF infusions of a negative GABA modulator (Holley et al., 1995) or intra-BF infusions of NMDA (Turchi and Sarter, 2001). In these cases, the increases in the number of false alarms were thought to reflect an abnormally low threshold for the detection of signals, and/or a shift toward a 'riskier' criterion for the detection of signals. The present analysis of the response latencies suggests a more cognitive explanation. The general observation that, in all animals, the response latencies for hits were shorter than for other responses may indicate that they predominantly processed the rules for signal trials and, upon the presentation of a non-signal trial, disengaged from the processing of these rules, and switched to those governing the responses in non-signal trials. In IBO-lesioned animals, response latencies were longest for correct rejections and 'incorrect' rejections, that is misses (see Fig. 2), supporting this speculation. Interestingly, however, the lesioned animals' response latencies for false alarms were almost as short as for hits, allowing the speculation that the increases in false alarms were associated with an 'impulsively' fast response. Such a speculation corresponds with the hypothesis that lesioned animals were impaired in their ability to disengage cognitively from the dominant processing of hit rules and thus, with a higher probability than in intact animals, responded to non-signals by reporting a signal. It should be reiterated that the findings that the hit rate remained unchanged and signal length-dependent, and that lesioned animals remained able to reject about 62% of the non-signal trials, indicate that the effect was not due to impulsive responding to a particular lever (the false alarm/hit lever). Rather, lesioned animals were specifically impaired in switching to the processing of the response rules for non-signal trials. Thus, the attentional effects of IBO, in contrast to the decreases in the detection of signals consistently observed following 192-SAP lesions, may reflect a more cognitive impairment of an executive function governing the switching between trial type-specific response rules.

The attribution of the attentional effects of IBO to the loss of GABAergic neurons requires caution. Because of the moderate effects of IBO on cortical AChE-positive fiber density, and because of the close relationship between the animals' ability to detect signals and cortical cholinergic transmission (references in Introduction), the increase in the number of false alarms in IBO-lesioned animals was possibly unrelated to the loss of cortical cholinergic inputs. However, the assumption that the effects of IBO were due to a loss of BF GABAergic neurons in general, or a loss of BF corticopetal GABAergic neurons in particular, requires a restrained discussion. Obviously, IBO is not a specific toxin for GABAergic neurons, and other non-GABAergic neurons in the GP may have been destroyed by IBO. Furthermore, while PV-positive cells are assumed to be GABAergic (Brauer et al., 1991, 1993; Kiss et al., 1990), this assumption may still be premature (see Introduction). Finally, although the IBO lesions targeted the more medial and ventral GP neurons that presumably contain mostly the GABAergic neurons projecting to the cortex, it is also obvious that the loss of PV-positive cells was not restricted to corticopetal neurons. Thus, the present data may support the hypothesis that the attentional effects of IBO were due to the loss of primarily GABAergic neurons, but the attribution of these effects to the loss of corticopetal GABAergic neurons remains speculative.

As the IBO-induced loss of BF PV-positive cells clearly included neurons projecting to subcortical regions, it is noteworthy that premature responding observed following lesions of the STN was observed in rats performing the 5-choice serial reaction time task (Baunez et al., 1995; Baunez and Robbins, 1997, 1999; Phillips and Brown, 2000). These findings may be considered evidence in support of the possibility that the present IBO lesions disinhibited thalamo-cortical functions via the STN. The loss of GABAergic corticopetal and subthalamic projections may act in parallel to over-activate cortical information processing, the former acting via disinhibition of cortical GABAergic interneurons (references in the Introduction).

The speculation that the IBO-induced false alarm rate was due to an over-activation of cortical functions corresponds with the neuronal effects of the other manipulations observed to increase the false alarm rate (listed above). All these manipulations are known to produce abnormally high levels of cortical ACh release (Fadel et al., 2001; Moore et al., 1995; Nelson et al., 2000). Therefore, the increase in the false alarm rate generally may be discussed in terms of hyperattentional impairments mediated via an uncommonly high reactivity of cortical afferents to stimulation. Such hyperattentional impairments would be predicted to consume processing resources and therefore be associated with impairments in the resource-demanding switching between trial type-specific response rules (see above).

The functions of the BF corticopetal projection system were recently re-conceptualized as a component of the

brain's anterior attention system that, via direct effects on the processing of sensory inputs and top-down mechanisms, acts to bias the subject toward the processing of relevant stimuli (Sarter et al., 2001). In this framework, the GABAergic projections of the GP to the STN and directly to the cortex are speculated to mediate executive components of attentional task performance. Such a speculation is anatomically supported by the finding that projections from the prefrontal cortex back to the BF terminate primarily on non-cholinergic and thus possibly GABAergic BF neurons (Zaborszky and Duque, 2000). Thus, BF GABAergic neurons may be considered a primary component of the prefrontal efferent circuits mediating the executive processes crucial for normal attentional performance. This hypothesis predicts that IBO-induced loss of BF PV-positive neurons disrupts the recruitment of this component of the prefrontal efferent circuits and thus a component of the circuits mediating executive variables of task performance.

In conclusion, it needs to be reiterated that this experiment represents an initial approach to determine the contribution of BF GABAergic neurons to attentional functions. The present data form the basis for a hypothesis about the role BF GABAergic neurons that involves clear predictions. For example, systematic manipulation of the demands on the cognitive switching between response rules would be expected to interact with loss of BF GABAergic corticopetal and subthalamic projection. Such studies, combined with ongoing efforts to develop a specific toxin for BF GABAergic neurons eventually will demonstrate that BF GABAergic efferent projections represent an integral component of the forebrain circuitry mediating attentional functions.

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