

Unmasking of silent ‘task-related’ neuronal activity in the monkey prefrontal cortex by a GABA_A antagonist

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Abstract

To examine the role of GABA on prefrontal neuronal activity in the control of behavior, a GABA_A receptor antagonist, bicuculline methiodite (BMI), was iontophoretically applied to prefrontal neurons while monkeys performed a visual reaction time task. Iontophoretic application of BMI uncovered ‘task-related’ activity of silent neurons ($n = 40$), which did not show any activity during performance of the task. The distribution, by type, of these silent ‘task-related’ neurons differed from that of standard (i.e. active) task-related neurons ($N = 95$), and a particular type of silent ‘task-related’ neuron was found most frequently. These findings suggest that GABA continuously and preferentially suppresses neuronal activity via GABA_A receptors to limit the population of prefrontal neurons related to behavior, thereby organizing neuronal activities for behavior mediated by the prefrontal cortex. © 2001 Elsevier Science Ireland Ltd and Japan Neuroscience Society. All rights reserved.

Keywords: Prefrontal cortex; GABA; GABA_A receptor; Iontophoresis; Visual reaction time task; Monkey

1. Introduction

The prefrontal cortex (PFC) of primates is responsible for various behaviors that require cognitive functions such as working memory and the association of sensory information with motor performance (for reviews, see Goldman-Rakic, 1995; Fuster, 1997). Whereas neuronal activity in the PFC has been studied extensively in a variety of behavioral tasks (e.g. delayed-response, delayed-alternation, visual discrimination go/no-go, and visual reaction time tasks; see Fuster, 1997), its neurochemical basis remains to be revealed. In the PFC of primates, there are numerous neurons that contain an inhibitory neurotransmitter, gamma-aminobutyric acid (GABA) (Schwartz et al., 1988), and the primate cerebral cortex contains a high level of GABA_A receptors (Jones, 1993). Previous studies in monkeys have demonstrated that local injection of a GABA_A antagonist, bicuculline methiodite (BMI),

into the dorsolateral PFC induces abnormal bursting activity at the injection site and induces deficits in behavioral tasks, such as a delayed-response task (Sawaguchi et al., 1988, 1989a) and a go/no-go visual-discrimination task (Oishi and Kubota, 1990). Therefore, it is likely that GABA might continuously inhibit prefrontal neuronal activity via GABA_A receptors to organize it for controlling various behaviors mediated by the PFC.

To address this hypothesis, we examined the effects of BMI on neuronal activity in the PFC in monkeys that performed a visual reaction time task, using iontophoretic techniques. A subset of neurons in the monkey PFC are involved in this task and show different types of activities related to its different phases (Sawaguchi, 1987a; Sawaguchi et al., 1989b). We report here that iontophoretic application of BMI uncovered the ‘task-related’ activity of neurons that are normally silent during task performance and that a particular type of silent ‘task-related’ neuron was found most frequently. Our findings suggest that the continuous and preferential suppression by GABA via GABA_A receptors plays a role in organizing prefrontal neuronal activity during behaviors mediated by the PFC.

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2. Materials and methods

2.1. Subjects and behavioral task

The details of the various techniques, the behavioral task, and the instrumentation have been described previously (Sawaguchi, 1987a,b; Matsumura et al., 1992). The experiment was carried out in accordance with the Guide for Care and Use of Laboratory Animals (National Institutes of Health) and the Guide for Care and Use of Laboratory Primates (Primate Research Institute, Kyoto University). Two male rhesus monkeys (*Macaca mulatta*, weighing 3.5–4.5 kg) were trained to perform a visual reaction time task (Fig. 1A). The monkeys faced a panel on which a (two-color light-emitting-diode (LED) was located at eye level, and a lever was located at waist level. The task was initiated by the monkey pressing the lever. After a fixed period of 3.0 s, the LED was turned on to green, indicating the warning phase. After a variable period of time (1.5–3.5 s), the LED turned from green to red, indicating the go phase. The monkey released the lever within 600 ms after the onset of the go signal to receive a drop of juice as a reward. The reward phase lasted for 1.5 s after delivery of the reward. Eye movements that were consistently related to the task events were not observed by EOG recording. The monkeys performed ~1500 trials in each recording session of ~2–3 h. The reaction time from the go signal to the onset of lever release was ~350–400 ms with a SD of ~40–60 ms for one subject and ~320–380 ms with a SD of ~50–70 ms for the other subject.

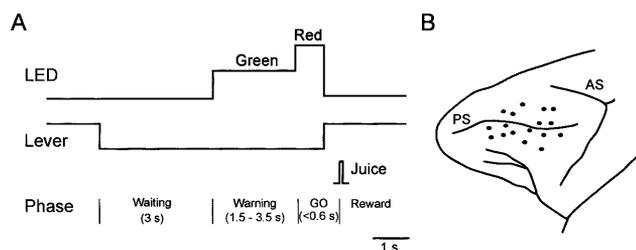


Fig. 1. (A) Time sequence of the visual reaction time task. The task was initiated by the monkey pressing a lever. After a 3.0 s waiting phase, a light-emitting diode (LED) was turned on (green) to indicate the onset of the warning phase. After a variable period of 1.5–3.5 s, the LED turned from green to red, indicating the go signal (go phase), he was rewarded with a drop of juice 0.3 s after lever release (reward phase). (B) Sites of penetration by the electrodes, illustrated on the surface of the left prefrontal cortex. A total of 17 penetrations were made in four hemispheres of two monkeys. The sites on the right hemisphere were homotopically transferred to the left side. PS, principal sulcus. AS, arcuate sulcus.

2.2. Recording, iontophoresis and data analysis

Multibarreled glass micropipettes were used for extracellular recording of neuronal activity and iontophoretic application of drugs. The central barrel of the micropipette contained a carbon-fiber filament (7 μm in diameter; T300, Toray, Tokyo, Japan), and was filled with 0.1 M NaCl and was used for the recording of neuronal activity. Surrounding barrels were used for iontophoretic application of the following drugs: BMI (0.01 M, dissolved in saline, pH = 5–6; Sigma, St. Louis, MO); GABA (0.01 M, dissolved in saline, pH = 5–6; Sigma); and 0.1 M NaCl (to balance the current). BMI was used in all penetrations of the micropipette ($n = 17$), but GABA was used in only four penetrations: since exactly the same results were obtained in either case, we pooled the data obtained with these penetrations.

While the monkeys performed the task, the micropipette was inserted into the dorsolateral PFC contralateral to the hand used for task performance, and the activities of single neurons were recorded. The micropipette was inserted using a pulse-motor-driven micromanipulator (MO-90, Narishige, Tokyo, Japan). To prevent leakage of drugs, a backing current (2–5 nA) was always applied to each barrel before and between drug applications. Neuronal activity was converted from analog to digital by a window-discriminator (DIS-1, BAK Electronics, Germantown, MD, USA) and the discharge rate during each phase of the task was compared with the background discharge rate during the waiting phase on a trial-by-trial basis. When the discharge rate of a neuron during at least one task-phase differed significantly from the background discharge rate (Mann-Whitney's U-test, $P < 0.05$), the neuron was considered to be task-related. When task-related neuronal activity was encountered, it was recorded during more than eight successive trials. Drugs were then applied with currents of 5–30 nA during more than eight successive trials to examine the influence of the drugs on task-related neuronal activity. Drug applications were separated by more than 2–3 min to allow for the recovery of neuronal activity. When the discharge rate of a neuron changed significantly during the application of a drug (Mann-Whitney's U-test, $P < 0.05$), the neuron was judged to be responsive to the drug. The amplitude of spikes of a neuron was similar between the predrug control period and during BMI application (see Fig. 3); for 10 typical neurons whose activities were increased by the iontophoretic (10 nA) application of BMI, the average amplitude did not significantly differ between these periods; 104.2 ± 26.1 (SD) μV for the control period and 106.5 ± 25.1 μV for the period with BMI application (paired t -test, $P > 0.05$, NS). As mentioned below, during some penetrations, the tip of the micropipette

was positioned at various depths in the PFC, at which no neuronal activity was observed for more than 3 min, and BMI was applied with currents of 5–30 nA to uncover the activity of certain ‘silent’ neurons that showed no activity for more than 3 min during performance of the task. In addition, the activity of silent neurons was sometimes uncovered by the application of BMI at sites where the activity of task-related neurons was recorded.

2.3. Histology

At the end of the recording sessions, the monkeys were deeply anesthetized with sodium pentobarbital and perfused with saline followed by 10% formalin. The points of penetration by electrodes were detected on the surface of the formalin-fixed brains. Fig. 1B shows the 17 sites of penetration on the surface of the left prefrontal cortex; the sites on the right hemisphere were homotopically transferred to the left side. The points were scattered throughout the periprincipal sulcal area and the immediately adjacent cortex in the PFC, which has cytoarchitectural features of Walker’s area 46 (Walker, 1940).

3. Results

3.1. Types of task-related neurons and the effects of BMI on their activities

We recorded the activities of a total of 95 task-related neurons, and these neurons showed changes in activity during the warning phase ($n = 25$), the go phase ($n = 19$), both the warning and the go phases ($n = 41$), and the reward phase ($n = 10$) of the visual reaction time task. These neurons were classified, as in previous studies (Sawaguchi, 1987a,b; Sawaguchi et al., 1989b), as W (warning)-, GO (go)-, WG (warning and go)-, and RE (reward)- type neurons, respectively. Fig. 2 shows examples of each type of neuron. These task-related neurons were spontaneously active, and the average frequency of their background discharge during the waiting phase was 8.1 ± 6.9 (SD) spikes/s ($n = 95$). Iontophoretic application of BMI increased the activity of all of the task-related neurons. Fig. 3 shows an example of the effects of BMI and GABA on the activity of a W-type neuron, in which averaged histograms for the activity before (control) and during the application of GABA (with 20-nA current) and BMI (with 10-nA current) are shown separately. As shown in Fig. 3B, the iontophoretic application of GABA reduced the activity, whereas BMI increased both the task-related and background activities. The properties of task-related activities themselves did not change during BMI application except that overall discharge rates were increased, as shown in the example in Fig. 3B.

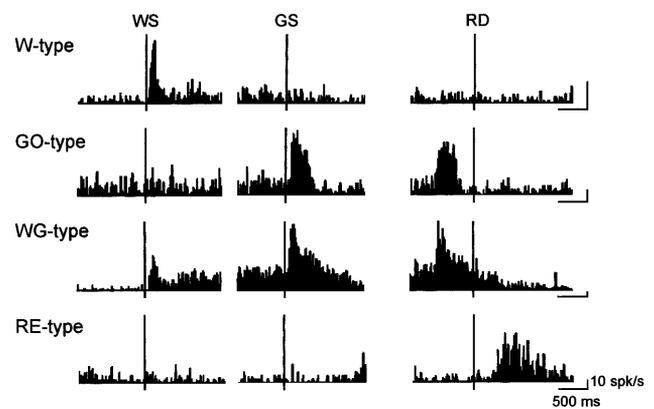


Fig. 2. Types of neuronal activity related to the task. Averaged histograms, aligned at the onset of the warning signal (WS), go signal (GS) and reward delivery (RD), are shown (sampling rate, 20 ms). From top to bottom: a neuron that showed a change in activity during the warning phase (W-type) (average of 23 trials); a neuron that showed a change in activity during the go phase (GO-type) (average of 17 trials); a neuron that showed changes in activity during the warning and go phases (WG-type) (average of 25 trials); and a neuron that showed a change in activity during the reward phase (RE-type) (average of 19 trials).

3.2. Unmasking of silent ‘task-related’ neuronal activity by BMI

While examining the effects of the drugs on task-related neuronal activity, we recognized that normally silent neurons became active during the application of BMI, and that these neurons were invariably task-related. Therefore, during eight penetrations of the micropipette, its tip was moved away from the site where task-related neurons were recorded to positions at various depths in the PFC at which no neuronal activity was observed for 3 min or more, and BMI was applied with currents of 5–30 nA. At a total of 19 such sites, the application of BMI uncovered the activities of silent neurons, which were related to the task. Fig. 3C shows an example of this result. The neuron in Fig. 3C, whose activity was recorded at a site $\sim 180 \mu\text{m}$ deeper than that at which the activity shown in Fig. 3B was recorded (see Fig. 3A-b), showed no activity during performance of the task for more than 3 min. However, it began to show activity during the application of BMI, and this activity was related to the warning phase of the task (i.e. W-type). Such originally silent but subsequently task-related neurons, i.e. silent ‘task-related’ neurons, during the application of BMI were usually found near the standard task-related neurons during the same penetration of the electrode, as seen in Fig. 3.

Silent ‘task-related’ neurons were also found at sites where the activities of standard task-related neurons were recorded. Fig. 4 shows an example of this situation. The activity of one neuron was observed before

the application of BMI (Fig. 4A-a). Another neuron, which was silent for more than 3 min prior to the application of BMI, showed activity during the application of BMI (Fig. 4A-b, arrow). The initial active neuron showed a tonic change in activity during the warning phase (i.e. W-type, Fig. 4B-a), and the previously silent neuron also showed a tonic change in activity during the warning phase (Fig. 4B-b).

The effect of BMI on silent task-related neurons appeared to be dose-dependent as far as we examined this point for six neurons. A typical example is shown

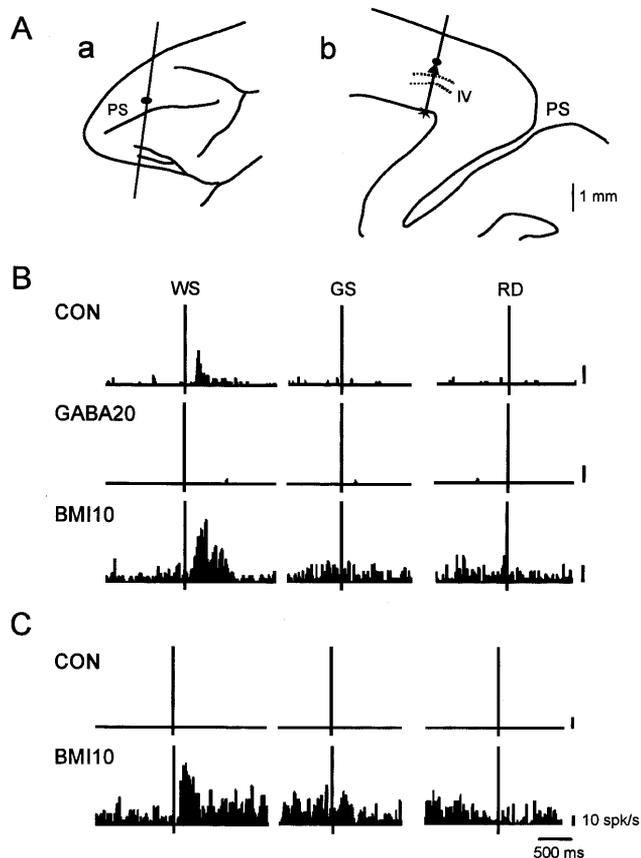


Fig. 3. Effects of iontophoretically applied GABA and bicuculline methiodide (BMI) on neuronal activity during performance of the task. (A) Recorded sites. (a) Penetration point of the electrode. The oblique line shows the coronal plane at which the section shown in b was cut. (b) Recording sites illustrated on the coronal section. The oblique line shows the track of the electrode. The filled circle and filled triangle show sites at which the neuronal activities shown in B and C were recorded, respectively. The asterisk indicates the deepest point of the electrode, marked by carbon deposits of the electrode (see Sawaguchi et al., 1989a,b). The space between the dotted lines indicates layer IV. (B) The effects of GABA and BMI on the activity of a task-related neuron. CON, neuronal activity without any drugs (average of 10 trials). GABA20, activity during the application of GABA with 20 nA (8 trials). BMI10, activity during the application of BMI with 10 nA (10 trials). (C) An example of the effects of the application of BMI on a silent 'task-related' neuron. The neuron did not show any activity prior to the application of BMI (CON, 25 trials), but showed activity related to the task during the application of BMI with 10 nA (BMI10, 18 trials). Conventions are as in Fig. 2.

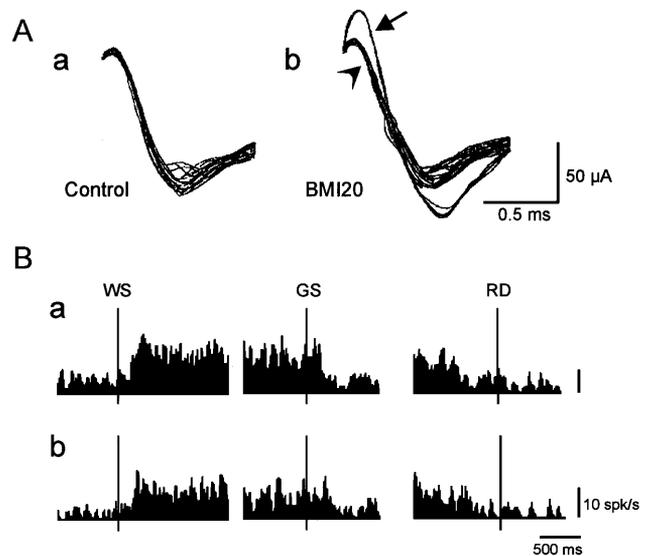


Fig. 4. An example of the effects of the application of BMI on silent neurons that were located at the same sites as where task-related neurons were recorded. (A) Superimposition of traces of spikes of neuron(s) prior to (a, Control) and during the application of BMI with 20 nA (b, BMI20). Note that spikes, which did not appear in the control, appeared during the application of BMI (arrow in b). (B) Averaged histograms of the activities of neurons whose spikes are shown in A. (a) Activity of a neuron that showed activity both in the control state and during the application of BMI (arrowhead in A-b, 18 trials with the application of BMI). (b) Activity of a neuron that was silent in the control state and began to show activity during the application of BMI (arrow in A-b, 18 trials with the application of BMI). Conventions are as in Fig. 2.

in Fig. 5, in which raster displays and averaged histograms of the activity of a silent 'task-related' neuron are shown for trials during the predrug control period lasting for ~4 min and during BMI application with current intensities of 10 and 20 nA. As shown, this neuron showed no activity during the predrug control period, whereas it began to show a warning phase-related activity during the application of BMI with a 10 nA current. After the termination of BMI application, the activity gradually disappeared. When BMI was then applied with a larger current of 20 nA, the activity appeared again, and the discharge rate was significantly larger than that during BMI application with a 10 nA current (mean \pm SD spikes/s; 3.9 ± 2.4 for 10 nA current vs. 7.6 ± 3.9 for 20 nA current, $P < 0.01$, U-test). Similar results were obtained for all of the six neurons examined with different intensities for the iontophoretic application of BMI.

3.3. Distribution, by type, of silent 'task-related' neurons

A total of 40 silent 'task-related' neurons were found. Of these, 19 were found at sites different from, and 21 were found at the same sites as active task-related

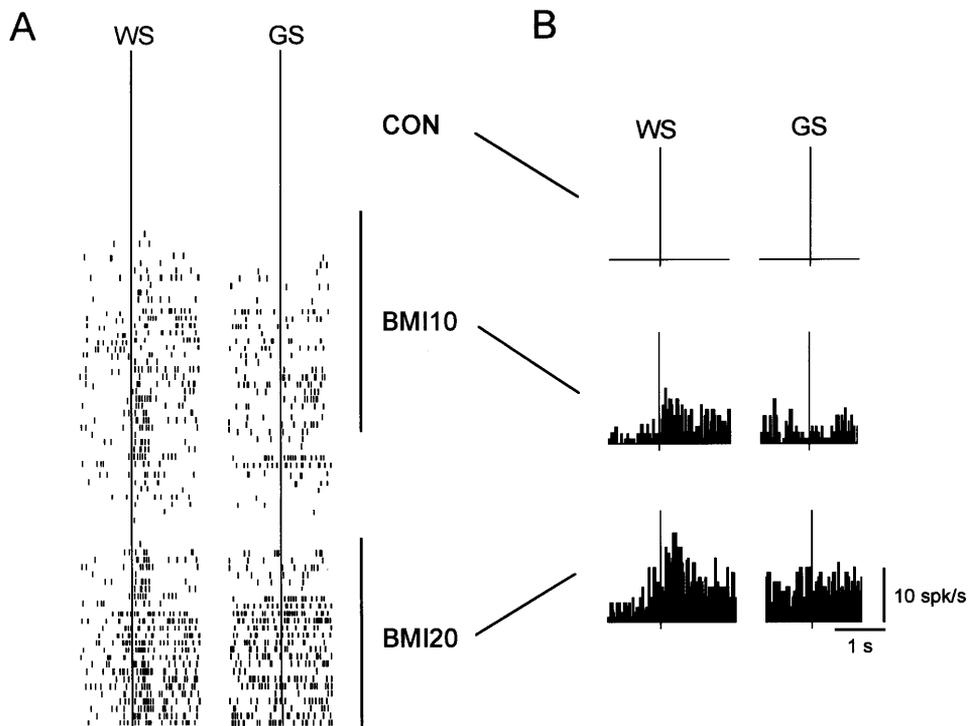


Fig. 5. Dose-dependent effect of the application of BMI on a silent neuron. Raster display (A) and averaged histograms (B) are shown for the activity of a silent neuron that showed no activity during the predrug control period (CON) and showed warning phase-related activity during the application of BMI with current intensities of 10 and 20 nA. Conventions are as in Fig. 2.

neurons (of these, 34 neurons were found during penetrations without GABA). Similar to the task-related neurons, the silent 'task-related' neurons consisted of W-, GO-, WG-, and RE-type neurons. Table 1 compares the distribution, by type, of standard task-related neurons and silent 'task-related' neurons. The distribution of silent 'task-related' neurons differed significantly from that of standard task-related neurons ($\chi^2 = 14.42$, $df = 3$, $P < 0.001$), and the most common silent 'task-related' neurons were W-type. The proportion of silent W-type neurons among the silent 'task-related' neurons (21/40, 53%) differed significantly from that among the standard task-related neurons (25/95, 26%) ($\chi^2 = 7.47$, $df = 1$, $P < 0.01$). This was the case for silent 'task-related' neurons that were found where active task-related neurons were found (11/21, 52% vs. 25/95, 26%; $\chi^2 = 4.31$, $df = 1$, $P < 0.05$).

3.4. Similarities of silent 'task-related' neurons to nearby task-related neurons

The activities of silent 'task-related' neurons tended to be similar to those of nearby task-related neurons, as seen in the examples in Fig. 3 and Fig. 4. To confirm this finding, we examined the distribution of task-related neurons at various distances from sites at which silent 'task-related' neurons were found during each penetration of the electrode. Table 2 shows the distribu-

tion of each type of task-related neuron, found at various distances from the silent 'task-related' neurons. In Table 2, the distances have been arbitrarily divided into four classes: 0 μm (the same site), 1–200 μm , 201–400 μm , and over 400 μm (> 400 μm). Each of the task-related neurons contributed to two or more data points when two or more silent 'task-related' neurons were found during the same penetration. As shown in Table 2, the task-related neurons that were found near the silent 'task-related' neurons more frequently showed

Table 1
Distribution, by type, of active task-related neurons and silent 'task-related' neurons

Type	Task related neurons	Silent 'task-related' neurons		
		Same sites ^a	Nearby sites ^b	Total
W-type	25	11*	10*	21**
GO-type	19	2	1	3
WG-type	41	5	3	8
RE-type	10	3	5	8
Total	95	21	19	40

^a Number of silent 'task-related' neurons that were found at the same sites as task-related neurons.

^b Number of silent 'task-related' neurons that were found at sites different from task-related neurons. * $P < 0.05$, ** $P < 0.01$: significantly different from the distribution of standard task-related neurons (χ^2 -test, $df = 1$).

Table 2
Distribution of task-related neurons at various distances from each type of silent 'task-related' neuron during the same penetration of the electrode

Types of silent neurons	Distances (μm)	Types of active task-related neurons				Total
		W	GO	WG	RE	
W-type ($n = 21$)	0 ^a	9	0	2	0	11
	1–200	15	0	6	1	22
	201–400	7	2	0	2	11
	Subtotal	31	2	8	3	44
	>400	22	10	28	4	64
GO-type ($n = 3$)	0 ^a	0	2	0	0	2
	1–200	1	3	1	0	5
	201–400	1	1	1	0	3
	Subtotal	2	6	2	0	10
	>400	6	4	11	1	22
WG-type ($n = 8$)	0 ^a	1	0	4	0	5
	1–200	2	0	10	0	12
	201–400	2	3	6	2	13
	Subtotal	5	3	20	2	30
	>400	16	5	24	4	49
RE-type ($n = 8$)	0 ^a	0	0	0	3	3
	1–200	1	2	0	5	8
	201–400	1	0	1	2	4
	Subtotal	2	2	1	10	15
	>400	11	14	31	1	57

^a Numbers of active neurons that were found at the same sites as silent 'task-related' neurons.

the same type of activity as that of the nearby silent 'task-related' neurons. Most of the task-related neurons showed the same type of activity as that of the silent 'task-related' neurons that were recorded at the same sites (18/21, 86%). Two-thirds of the task-related neurons that were recorded at sites less than 400 μm (including 0 μm) from those of silent 'task-related' neurons showed the same type of activity as silent neurons (67/99, 68%). This ratio (67/99, 68%) differed significantly from that (51/192, 27%) for task-related neurons that were more than 400 μm from silent 'task-related' neurons ($\chi^2 = 44.11$, $df = 1$, $P < 0.001$).

3.5. Cortical distribution of silent 'task-related' neurons

Silent 'task-related' neurons were found during all penetrations of the micropipette, and there was no obvious clustering or ordering of their cortical distributions in the dorsolateral PFC. However, with regard to depth distribution, silent 'task-related' neurons appeared to be more numerous in the superficial layers (II–IV) than in the deep layers (V and VI). Among silent 'task-related' neurons ($n = 32$) whose laminar distributions could be estimated with the methods described previously (Sawaguchi and Matsumura, 1985; Sawaguchi et al., 1986, 1989b), most were found in the superficial layers ($n = 24$) with a relatively small number in the deep layers ($n = 8$). This corresponds to the fact that most of the silent 'task-related' neurons were W-type (see above), and W-type neurons are relatively

numerous in the superficial layers, as demonstrated previously (Sawaguchi et al., 1989b).

4. Discussion

Iontophoretic application of BMI uncovered the 'task-related' activity of silent neurons in the dorsolateral PFC which did not show any activity during the performance of a visual reaction time task for over 3 min. It is unlikely that these silent 'task-related' neurons are actually involved in, or responsible for, performance of the task, since they did not show any activity during several trials (i.e. more than ~ 20 trials) of the task. Although these silent 'task-related' neurons might be considered an artifact due to the leakage of GABA from the tip of the electrode, this possibility is unlikely since (1) a backing current was always applied to prevent leakage of the drugs; (2) most of the silent 'task-related' neurons were found during penetrations without GABA; and (3) the mean discharge rate of the background activity of the task-related neurons in the present study (8.1 spikes/s) was similar to that examined in a previous study of prefrontal neurons (8.6 spikes/s) which used the same type of electrode and task but not GABA or BMI (Sawaguchi, 1987a). Similar (7.6–8.1 spikes/s) or slightly lower values (4–6 spikes/s) for the mean discharge rate of the background activity in prefrontal neurons of monkeys have been reported in studies using metal electrodes and tasks

different from that in the present study (Quintana et al., 1988; Funahashi et al., 1989; Koch and Fuster, 1989). Thus, the present data suggest that the 'task-related' activity of some prefrontal neurons is continuously suppressed by GABA so that they are silent during task performance for several minutes, although it is unknown how long they are actually silent during task performance or whether or not they are active in relation to the performance of tasks other than the present task.

The silent neurons found in the present study should receive substantial excitatory input during task performance, since, with the reduction of GABA inhibition with the application of BMI, they showed background as well as task-related activities. Thus, more neurons are spontaneously active and responsive to the task events when GABA inhibition is reduced during task performance. GABA may limit the population of prefrontal neurons that are involved in a behavioral task over several minutes, thereby organizing the prefrontal neuronal activity associated with the behavioral task. This possible role of GABA in the PFC should be mediated by GABA_A receptors, since BMI is a GABA_A antagonist and the primate cerebral cortex contains a high level of GABA_A receptors (Schwartz et al., 1988). GABA could also play a similar role in other cerebral cortical areas for organizing neuronal activities, since both GABA neurons and GABA_A receptors are widely distributed in the cerebral cortex (Hendry et al., 1987; Schwartz et al., 1988) and local injection of BMI induces abnormal bursting activity in other cortical areas, such as the premotor and motor cortices of monkeys (Matsumura et al., 1991; Sawaguchi et al., 1996). Indeed, local injections of BMI into the motor or premotor cortex induced a disorder of behavior related to each of these cortices (Matsumura et al., 1991; Sawaguchi et al., 1996); these findings also support the present notion that GABA limits and organizes neuronal activities associated with a behavioral task.

The distribution, by type, of the silent 'task-related' neurons differed from that of neurons related to the task. This was true for both silent 'task-related' neurons found at the same sites as standard task-related neurons and those found at sites different from where standard task-related neurons were recorded. Among the silent 'task-related' neurons, W-type neurons were found most frequently. These findings indicate that the suppression of neuronal activity by GABA is selective or preferential, and that W-type neurons are the most frequently suppressed by GABA during performance of the visual reaction time task. W-type neurons are relatively numerous in the superficial layers (II–IV) of the dorsolateral PFC (Sawaguchi et al., 1989b) and GABA neurons in this area are distributed more densely in the superficial layers (II–IV) than in the deep layers (V and VI) (Jones, 1993). Therefore, it is likely that the inhibi-

tion of prefrontal neurons by GABA may be stronger in the superficial layers than in the deep layers, and, as a result, W-type neurons may be the most frequently suppressed during task performance. Furthermore, the activities of silent 'task-related' neurons were in most cases similar to those of task-related neurons that were found nearby or at the same site. Anatomical studies of the monkey have demonstrated that neurons that project their axons to the same regions form clusters or columns in the PFC (Arikuni et al., 1983; Schwartz and Goldman-Rakic, 1984). Taken together, these findings suggest that some particular neurons within neuronal clusters, which have similar physiological properties and project their axons to similar regions, are continuously suppressed by GABA via GABA_A receptors and are therefore silent during behavioral tasks over several minutes. This continuous and preferential suppression by GABA via GABA_A receptors within neuronal clusters may be critical for organizing neuronal activities for behavior mediated by the PFC.

Thus, the present study is the first to demonstrate that a substantial number of prefrontal neurons are silent during a behavioral task and are latent related to the task over several minutes, and appear to be continuously and preferentially suppressed by GABA via GABA_A receptors. Since GABA neurons and GABA_A receptors are widely distributed in the cerebral cortex (Hendry et al., 1987; Schwartz et al., 1988) and columnar/modular organization is common across various neocortical areas, the present findings and conclusions may be applicable to neocortical areas other than the PFC; the continuous and preferential/selective suppression by GABA within neuronal clusters/columns is likely to be a critical/general mechanism for the organization of neocortical neuronal activities that are associated with various behavioral tasks/information processing. Indeed, GABAergic inhibitory control in the formation of receptive fields is well known in somatosensory and visual cortices (Dykes et al., 1984; Sillito, 1984; Crook et al., 1996, 1997, 1998), and, in motor cortices, GABAergic inhibition plays a role in organizing movement-related activities (Matsumura et al., 1992).

The PFC is involved in the learning of behaviors, and neural activities of the PFC show flexible changes depending on the behavioral context (Petrides, 1982; Sasaki and Gemba, 1982; Gemba and Sasaki, 1984; Kubota and Komatsu, 1985; Watanabe, 1990; Gemba et al., 1995; Petrides, 1997; Asaad et al., 1998). The present findings may allow us to hypothesize that preferential/selective suppression by GABA underlies this flexibility of the PFC, in particular, fast and reversible learning mediated by the PFC. In this regard, a previous finding with *in vivo* optical imaging demonstrated that modular activation of neurons by ICMS was accompanied by modular suppressions in the frontal cor-

tex of monkeys, which suggests that some functional modules are suppressed when a functional module is activated (Sawaguchi, 1994). It is likely that different populations (or 'modules') of PFC neurons are deployed in different behavioral contexts during which many other neurons are silent due to GABAergic inhibition; many functional modules are already present and some are selected with GABAergic inhibition in a given context. This hypothesis is worth considering for further studies of the neuronal mechanism of the flexible control and learning of behaviors, which are mediated by the PFC.

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