Cocaine-induced Changes in Functional Connectivities between Simultaneously Recorded Single Neurons in the SI Cortex and the VPL Thalamus of Conscious Rats

Hyung-Cheul Shin[1], Hyoung Jin Park[1], Yang Seok Oh[2] and John K. Chapin[3]

*Department of Physiology[1], School of Medicince, Experimental Animal Center[2], Hallym University,
1 Okchun-dong. Chunchon, Kangwon-do, Korea 200-702, Department of Physiology and Biophysics,
Hahnemann University[3]. Broad and Vine Sts., Philadelphia, Pennsylvania, USA 19102*

= ABSTRACT =

The present study was carried out to determine the effects of cocaine (0.25, 1.0, 10.0 mg/kg, i.p.) on the interactions between spontaneously active neurons within ensembles of simultaneously recorded neurons in the primary somatosensory cortex (SI, n= 20) and the ventroposterolateral (VPL, n= 16) thalamic nucleus of awake rats. Spike-triggered cross-correlation histograms were constructed between pairs of simultaneously recorded neurons. Among 101 neuronal pairs analyzed, 22.7% showed correlations indicative of various functional connections among the cortical cells, two corticothalamic interactions and one thalamocortical excitatory interaction. There were also 15 cofiring activities among SI cortical cells. These functional connectivities appeared to be modulated (weakened, abolished, or strengthened) during the 5 to 30 min following cocaine injection. The effects of saline were tested as a control, but it did not appear to alter the functional connectivities. In general, cocaine-induced changes of the functional interactions were mainly due to the concomitant alterations of the uncorrelated background discharges. These resluts suggest that the biphasic effects of cocaine on the spontaneously established neural networks among the SI cortical and the VPL thalamic cells of conscious rat were mainly indirect. However, various changes of the functional interactions by different doses of cocaine appeared to be a possible neural network mechanism for the cocaine-induced modulation of afferent somatosensory transmission.

Key Words: Cocaine, Somatosensory cortex, VPL thalamus, Functional connectivity, Neural network

INTRODUCTION

Cocaine is an alkaloid derived from the leaves of Erythroxylon coca. Behaviorally, cocaine produces a variety of amphetamine-like stimulant effects in humans (Byck & Van Dyke, 1977; Fischman & Schuster 1982, Johanson & Fischman, 1989). The effects of euphoria, arousal, hyperactivity and increased capacity for mental and physical work are commonly reported in humans after administration of the drug. It is because of these properties that cocaine abuse has become widespread (Weiss & Mirin, 1987; Gawin, 1991). At higher doses, cocaine produces paranoid delusions, visual, auditory, and tactile hallucinations and stereotyped behaviors (Post, 1975).

Animals under the influence of cocaine demonstrate an increased motor responsiveness to auditory, visual and tactile stimuli (Wilson et al, 1976; Scheel-Kruger et al, 1977; Davis,

1985). While these observations suggest an in-fluence of cocaine on the perception of signals transmitted through the major sensory systems, they do not clarify the circuit mechanisms of the effects of cocaine on the sensory processing within neural networks. Recently, we have re-ported that systemic application of cocaine sig-nificantly alters afferent sensory transmission in the primary somatosensory cortex (SI) and the ventroposterolateral (VPL) thalamus of awake, behaving rats (Shin et al, 1993). Lower doses (1.0 mg/kg) of cocaine counteracted movement-induced suppression of afferent sen-sory transmission, whereas higher doses (10 mg /kg) of cocaine further suppressed sensory in-flow during movement.

To further elucidate the neural circuit mecha-nism(s) of cocaine action on the somatosenso-ry processing, we have simultaneously recorded many single units from ensembles of neurons of the SI cortex and the VPL thalamus of awake rats through chronically implanted microwires. Three different doses of cocaine (0.25, 1.0, 10.0 mg/kg) were systemically applied. Spike-triggered cross-correlation analysis was per-formed between pairs of simultaneously record-ed neurons. The results indicated that cocaine has a biphasic effect on the excitability of spontaneoulsy active cells, an initial increase followed by decrease. In general, various func-tional connectivities within spontaneously active neural networks of somatosensory neu-rons appeared to be initially weakened and then either recovered or strengthened following cocaine administration.

METHODS

Microwire electrode implantation

The subjects were Long-Evans (hooded) rats weighing from 250 to 300 g at the time of sur-gery. Animals were housed individually in a 12 hour on/12 hour off light-dark room. They were trained to run on an electronically timed varia-ble-speed treadmill (Chapin & Woodward,

1982a, b; Shin & Chapin, 1990b, d). Several (7 ~10) days prior to experiment animals were prepared for awake single unit recording. Rats were anesthetized with pentobarbital (40~ 50 mg/kg, i.p.) and surgically implanted with re-cording microwire electrodes (n=9, 25 μm di-ameter stainless steel teflon coated, California Fine Wire, Grover City, CA) in the forepaw area of the somatosensory nuclei (Shin & Chapin, 1990d). Implantations in the cortex in-volved removing a small piece of overlying cra-nium and dura, and stereotaxically lowering an array of microwires to a given depth in the SI cortex (1.0 mm anterior ~0.5 mm posterior to bregma, 3.0 mm~4.5 mm lateral from midline, 0.6 mm~1.5 mm deep from brain surface). For thalamic recording the microwire bundles were stiffened with dental acrylic, leaving about 1 mm of teflon coated free wire at the tip. This bundle was then stereotaxically driven to the correct location (2.3 mm~4.3 mm posterior to bregma, 2.0 mm~3.5 mm lateral from midline, and 5.0 mm~7.0 mm deep from brain surface). The recording microwire bundle was rigid enough to pierce the pia, and penetrate brain tissue without bending (Shin & Chapin, 1990d). The final position of electrodes within the brain was well predicted by the stereotaxic surgery and by recording somatosensory recep-tive fields from the microwires, since the VPL thalamus and the SI cortex contain fine grain maps of the cutaneous periphery (Wall & Egger, 1971; Angel & Clarke, 1975; Chapin & Lin, 1984). Follow-up histology was used as the final criterion for localization of the recording sites. Typically, the total 9 implanted wires were divided approximately equally between cortex and thalamus (i.e. either a 5/4 or a 4/5 ratio). Units acceptable for this study fulfilled the following requirements: 1) a signal/noise ratio of more than 3, 2) possession of a cutane-ous receptive field on the contralateral forepaw and 3) responsiveness to stimulation through the stimulating electrodes implanted in the forepaw. Over several months, the time in which some of these animals were kept, the units recorded on a particular wire would often
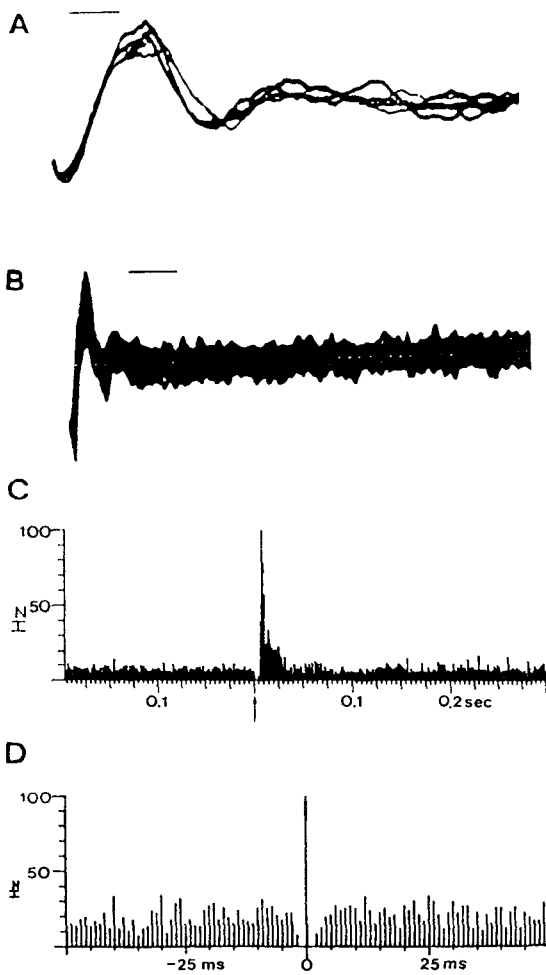
A

B

C

D

Fig. 1. A and B: oscilloscope photographs of typical extracellullarly recorded action potentials of a single neuron in the rat SI cortex using a 25 μm microwire. A: 5 superimposed sweeps triggered on the initial negative deflextion of the action potential. Bar=0.2 msec. B: 10 superimposed sweeps of the same unit, shown at a longer time base (bar=1.0 msec). The unfiltered amplitude of action potential was about 250 μV. C: sensory responses of VPL thalamic cell indicated by a peri-stimulus time histogram trggered by electrical paw stimulation (at arrow) during rest. Y axis tickes=10 spikes/s. Bins =1 msec, Small X axis ticks=5 msec. D: an autocorrelogram for a SI cortical neuron recorded through microwire electrodes. Bins=1 msec, Y axis ticks=10 spikes/sec, small X-axis ticks=5 msec, large X-axis ticks=25 msec.

be lost, and after a few days, another would appear. Thus, some of the different units used here were recorded on the same microwire, but several days or weeks aprat.

The oscilloscope photographs in Fig. 1 show superimposed extracellular action potentials of a typical unit recorded in the SI cortex using this technique. Interestingly, this good isolation of single units is typically not achieved until at least several days after surgery. Once achieved, however, these recordings are extremely stable during movement and over time. The reason for the improvement of recording quality is not known. It may be that the partial covering of the electrode tip with fibrous tissue produces a smaller recording surface, which is now embedded stably near a neuron. The shape of the waveform of this action potenital reflects a relatively high frequency notch (1~3 KHz), implemented with active filters. This is sometimes necessary to suppress the large local field potential caused by sensory paw stimulation.

General procedure

During experimentation, an implanted rat was placed in a recording enclosure. A multi-wire recording harness was plugged into a small "hat" connector chronically implanted on the rat's head (Shin and Chapin, 1990d). The wire harness plug proximal to the rat's head contained an array of FET transistors (one for each microwire) to be used as cathode followers. Each signal was then separately amplified (1K gain), actively filtered (0.5~5 KHz), spike-height discriminated, and then fed into the computer (Data General Micro-Eclipse S-20 computer) for storage and display.

The activities of SI cortical and VPL thalamic single units with cutaneous receptive fields on the palm of the contralateral forepaw were simultaneously monitored through chronically implanted microwire electrodes in the forepaw area of the VPL thalamus and the SI cortex while the animal was on the treadmill (Fig. 1C, 10 sec ON/10 sec OFF, for 50 min). Animals were subjected to three different doses (0.25, 1.0, 10.0 mg/kg, free weight) of cocaine-HCl via

an IP injection with a 3 to 7 days interval between injections. In control experiments, the effects of saline were tested. After an initial 10 min recording period, cocaine, or saline was administered and recording was continued up to 40 min post-injection. Behavior was recorded throughout experimental sessions on video tape (33 field-frames/sec) which was used to determine possible behavioral changes elicited by the drugs. The computer was synchronized with the video camera through an electrical pulse sent from the camera to the computer at the beginning of each frame exposure. In frame-by-frame analysis of videotapes, the frame numbers associated with the initiation and termination of appropriate movement event were fed into the computer.

Data analysis

Spike-triggered cross-correlation analysis was performed on the stored data. Spike-triggered cross-correlation histograms (SCHs) were constructed for every cell pair recorded simultaneously. Peaks, troughs, and periodicities in the SCH provided information about the temporal relationship of the two spike trains and permitted inferences about functional connectivity between the neurons (Perkel et al, 1967; Moore et al, 1970; Bryant et al, 1973). The following formula was used to calculate the instantaneous firing rate in an epoch: (No. of spikes/No. of sweeps) × (1000/No. of msec in epoch). A numerical value K was calculated for selected

pairs as an index of the effectiveness of a given functional correlation. It was defined as the ratio (K=P/BD) of the peak counts (P) in the SCH to the mean counts (BD) in a region away from the peak (-45 to -10 msec from 0, Sears & Stagg, 1976). Another numerical value A was calculated as an index of the magnitude of the correlated peak. This A value (A=P-BD) was expressed as the mean discharge rate of the correlated peak, minus the uncorrelated background discharge rate. The cocaine-induced changes of a functional interaction was expressed in terms of the percent change (K%, A%) from either the K or A value measured during the pre-drug period (i.e. $100 \times (K'-K)/K$ or $100 \times (A'-A)/A$). An autocorrelation histogrm (ACH) was also computed for each neuron as an aid in the interpretation of functional correlations (Moore et al, 1970; Bryant et al, 1973) and to ensure that the isolation of the waveform from background activity was adequate (Fig. 1D).

RESULTS

A total of 36 recorded neurons were used in this study (including 20 in the SI cortex and 16 in the VPL thalamus). Among 101 neuronal pairs (combinatory analysis: !n/(n-r)!.1/r!, maximum 36 pairs in an animal which had 9 recordable wires in an experimental session) analyzed, 28 between the SI cortical neurons, 54

Table 1. Somatosensory neurons recorded in the SI cortex and the VPL thalamus through implanted microwires and various functional connections observed between cells during pre-drug resting period

	SI Cortex	VPL Thalamus	Between SI & VPL	Total
Recorded Neurons	20	16		36
Neuronal Pairs Tested	28	19	54	101
Functional Connections				23
Corticocortical	5			
Cofiring	15			
Corticothalamic			2	
Thalamocortical			1	

between neurons in the SI cortex and the VPL thalamus, 19 among the VPL thalamic neurons (Table 1). Correlations indicating functional interactions were detected in 23 cell pairs (22.7 %). Excitatory interactions were indicated by narrow peaks to one side of the triggered time of the SCHs (Moore et al, 1970). In the present data set, five pairs of excitatory functional connections were found among the SI cortical cells. Two cortico-thalamic and one thalamocortical excitatory interactions were observed between the SI cortical cells and the VPL thalamic cells. Correlations between pairs of neurons indicating shared inputs were also indicated by a broader peak straddling the trigger time (Segera & Shanon, 1985; Kruger & Aiple, 1988). These were often (n=15) observed simultaneously with the more direct functional connections.

In general relative effectiveness (defined by the ration between correlated discharge and uncorrelated firing) and the strength (defined by correlated discharge minus uncorrelated firing) of these functional connections were not changed by saline, but they were weakened or abolished during running behavior. Here, we present changes of functional connectivities induced by cocaine during the quiet resting state, since most of the functional connectivities found in this study were present during rest and they were gated out during movement state. In this study, no behavioral changes were observed from the administration of either 0.25 mg/kg or 1.0 mg/kg doses of cocaine, but intermittent locomotor activites (such as rearing, exploratory movement, and standing) were noted following 10.0 mg/kg doses of cocaine administration. These drug-induced movement periods were not included for the data analysis. Simple interpretations of SCHs are presented for the sake of clarity.

Changes of functional connection by lower doses of cocaine

Figure 2 illustrates an experiment in which two SI cortical cells (2 and 5) and one VPL thalamic cell (T1) were recorded simultaneously. Analysis of SCHs indicated that two SI cortical

cells (2 and 5) were driven by unknown common driver (s) (×, Moore et al, 1970; Kruger & Aiple, 1988) and a VPL thalamic cell (T1) was driven by SI cortical cell 2 during resting period prior to cocaine administration (SCH 1 *2 & 2*1). In general the excitabilities (inferred from uncorrelated discharge rates) of these cells were heightened (87~300%) during the 5 min post-drug period and then they were decreased (−60~−70%) during the 10 min post-drug period. During the first 5 min post-drug (0.25 mg/kg) resting period the strength of the corticothalamic connection (2−>1) appeared to be diminished (K%, −68%; A%, −53%) and the cofiring of two SI cortical cells (2 and 5) was also weakened (K%, −75%; A%, −48%). During the 10 min post-drug period, the efficacy of the corticothalamic connection (2−>1) was strengthened (K%, +95%), but the peak actually correlated was not completely recovered (A%, −9.3%). At this time, a new corticocortical connection (2−>5; measured between 0~2 ms away from 0, K=77.2%, K%, 498%; A%, 92%) was established. The strength of the cofiring activity (2 and 5) was also increased (K%, 245%; A%, 11%). Results from another experiment with lower doses of cocaine showed no change of a cofing activity between two SI cortical cells, while strengthening a thalamocortical connection during the 20~30 min post-drug period.

Modification of functional connections by middle doses of cocaine

Middle doses (1.0 mg/kg) of cocaine also appeared to alter several functional interactions. In one experiment, three SI cortical cells (1, 2, 5) and one thalamic cell were simultaneously recorded. The analysis of SCHs indicated a cofiring activity among three SI cortical cells. This cofiring activity was abolished during the 6~10 min post-drug period. Cofiring activity between cell 1 & 2 began to reappear during the 11~20 min post-injection period. Strengthening of the original cofiring activity among three SI cortical cells was observed during the 30~40 min following cocaine injection.
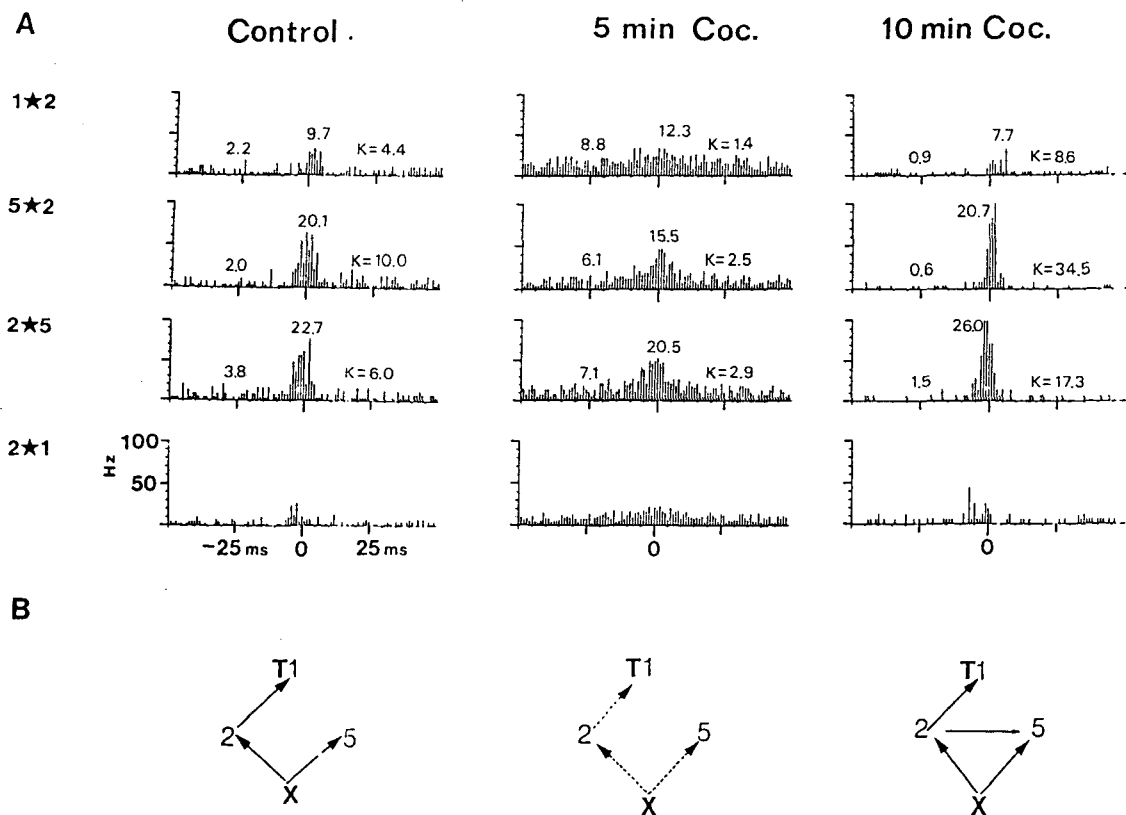
Fig. 2. *Changes in functional connectivity induced by lower doses (0.25 mg/kg, IP) of cocaine. A: Spike-triggered cross-correlation histograms (SCHs) were constructed to measure the strength of functional connections between pairs of simultaneously recorded three neurons. Cell No. before star symbol stands for target cell and cell No. after the symbol for reference cell. Central peaks in SCHs 5*2 suggested unknown common input(s) to the two SI cortical cells and SCHs 1*2 indicated that VPL thalamic cell 1 was driven by SI cortical cell 2 during pre-drug period. Cocaine induced changes of these functional connections are described in the text. Vertical scalse are normalized for constant instantaneous firing rate per bin and are equal for all histograms: small X-axis ticks=5 msec, large X-axis ticks=25 msec, Y-axis ticks-10 spikes/sec. Bins=1 msec. 2000 sweeps. B: connectional strength (solid line: stronger, dotted line: weaker) and patterns are also shown diagramatically at the bottom panel (X stands for common input).*

Figure 3 illustrates another experiment in which two SI cortical cells (3 and 5) and one VPL thalamic cell (T1) were recorded simultaneously through implanted microwire electrodes. Analysis of SCHs indicated that two SI cortical cells (3 and 5) shared inputs from unknown common source ($\times$) and the VPL thalamic T1 cell was driven by SI cortical cell 5 (5 −>1, K=7.5) during the first five minute pre-

drug period. A corticocortical connection was also noticed between SI cortical cells 3 and 5 (3 −>5, K=11.1) during this pre-drug period. The excitabilities of these cells were heightened (207-246%) during the 6-10 min post-drug period and then were decreased (−48~ −62%) during the 11~15 min post-drug period. During the first 5 min post-drug period the corticothalamic interaction (5−>1) was dimin-
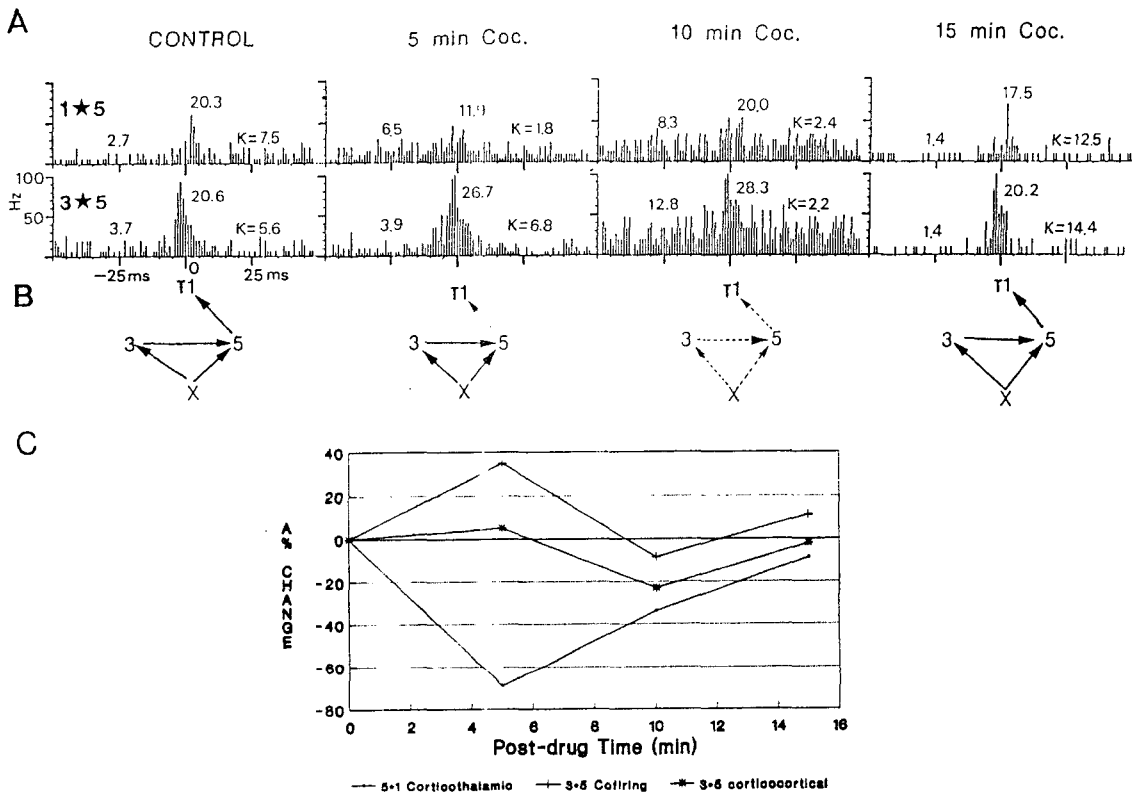
Fig. 3. *Modulation of functional connectivities by middle (1.0 mg/kg) doses of cocaine. A: SCHs constructed among two SI cortical cells (3 and 5) and a VPL thalamic cell 1 before and after cocaine administration. small X-axis ticks=5 msec, large X-axis ticks=25 msec, Bins=1 msec, Y-axis ticks=10 spikes/sec. 2000 sweeps. Connectional patterns are shown diagramatically in B and changes of connectional strength are shown graphically in C. (X stands for unknown common input).*

ished (K%, −76%; A%, −69%), while the cofiring (3 and 5) activity was strengthened (K %, 21.4%; A%, 35%) and the cortico-cortical (3 − >5) activities were left intact (K%, 0%; A%, 5%, Fig. 3C). During the next 5 min period (6-10 min post-drug), the cofiring of cortical cells (3 and 5, K%, −61%; A%, −8.3%) and the cortico-cortical connection (3− >5, K=3.3, K %, −70%, A%, −23%) were also weakened. The corticothalamic connection (5− >1) remained suppressed (K%, −68%; A%, −34%). The original evoked connectivities among these cells were almost recovered from 11 to 15 min post-drug period (cofiring: A%, +11.2%; 3− >

5; A%, −2%; 5− >1; A%, −8.5%), while the effectiveness of these connections was significantly increased (cofiring: K%, 157%; 3− >5: K%, 147%, 5− >1: K%, 67%).

Changes of functional connections by higher doses of cocaine

Higher doses of cocaine (10.0 mg/kg) differenatially weakened some of the cofiring activities among neurons. Figure 4 illustrates that all four SI cortical cells (1, 2, 4, 5) were driven by an unknown common source(s) during the pre-drug periods. The maximum reductions of the strength (SCH 4 ∗ 1: K%, −77%, A
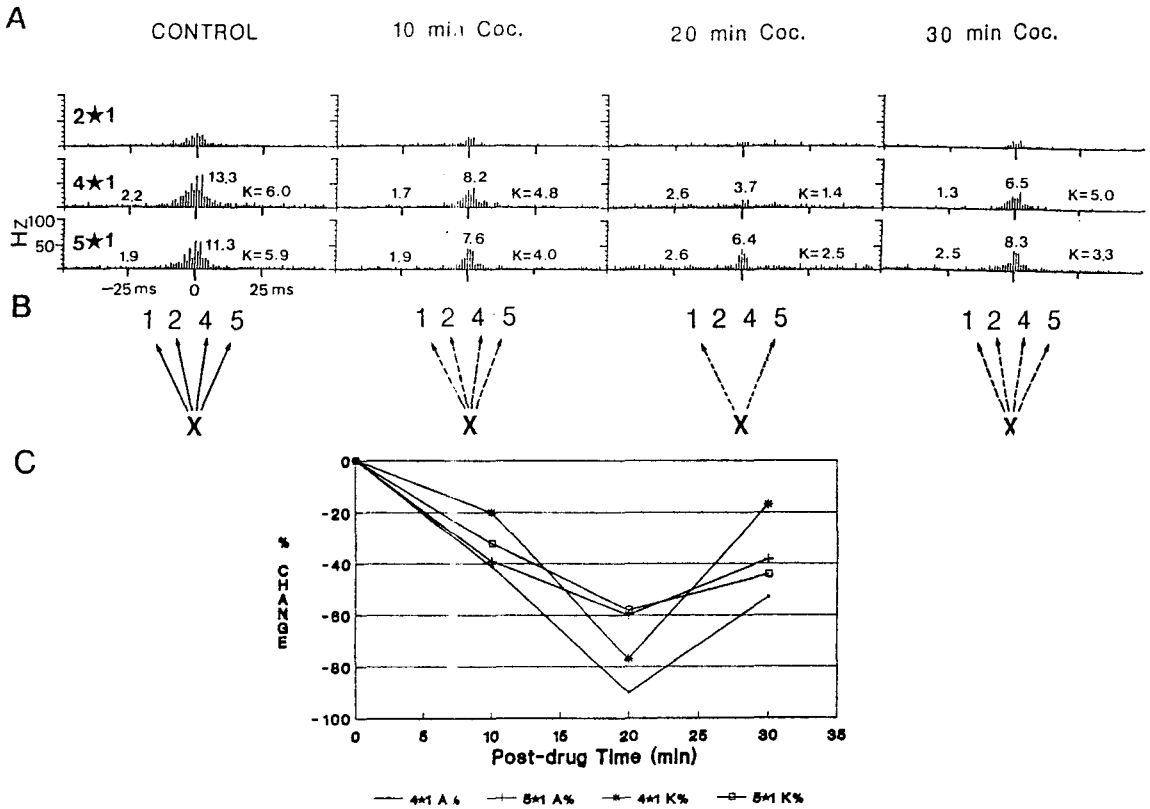
Fig. 4. Changes of functional connectivities by high (10.0 mg/kg) doses of cocaine. Cofiring activities driven by unknown common driver(s) among four SI cortical cells were suggested from central peaks in SCHs 2*1, 4*1 and 5*1 during pre-drug period. Changes of these functional connections after cocaine administration are described in the text and they are also shown in B and in C. (X stands for unknown common input). Bins= 1 msec, Y-axis ticks= 10 spikes/sec. X-axis ticks= 25 msec, 2000 sweeps.

%, −90%; SCH 5 * 1: K%, −58%, A%, −60 %, Fig. 4C) of the cofirng activities were observed during the 10-20 min post-drug period. At this time, there was no correlation observed between cell 2 and 4. During this period both the decrease of the height of the correlated central peaks and the increase of the uncorrelated background firing rates (18~37%) were responsible for the weakening of the cofiring activities among these cells. This cofiring pattern among these four SI cortical cells did not completely recover (K%, −17 ~ −44%; A%, −38~ −53%) until 20~30 min post-drug period.

DISCUSSION

The results of this study indicated that interactions between spontaneously active neurons within ensembles of simultaneously recorded single neurons in the VPL thalamus, and the SI cortex were strongly modulated after cocaine administration. The effectiveness (K value) of functional connectivities, defined by the signal (correlated peak of a SCH) to noise (uncorrelated firing) ratio, was often initially weakened

and then strengthened after low and medium doses of cocaine administration. The strength (A value) of functional interactions, defined by firing rate of a correlated peak minus uncorrelated discharge rate, was mainly weakened and then recovered, regardless of the doses of cocaine injected, except in one case where a cofiring pattern was facilitated following injection of middle doses of cocaine. The duration of the waning phase was short (5 min) at lower doses and was long (30 min) at higher doses of the drug. These cocaine-induced changes of the functional connectivities were mainly due to the initial increase and the following decrease of the uncorrelated spontaneous firing activities without significant alteration of the correlated peaks of the SCHs. In anesthetized animals, a similar suppression of the spontaneous firing by low doses of cocaine (0.25 mg/kg, ip, iv) has been reported in the dopaminergic neurons within the substantia nigra and ventral tegmental area, in the noradrenergic neurons of the locus coeruleous, and in the serotonergic neurons of the dorsal raphe nucleus (Pitts & Marwah, 1987). Recently, suppression of the spontaneous firing was also oberved in the SI cortex within 3∼20 min after systemic injection of 0.5 mg/kg cocaine (Jimenez-Rivera & Waterhouse, 1991). In this study, cocaine had initial facilitating effects on the spontaneous firing, which have not been observed in previous studies. This discrepancy may be due to the depressant effects of general anesthesia. In fact, a minor (4 of 21 cells) facilitating effect on somatosensory cortical neuron spontaneous discharge has been noticed after local application of cocaine via microiontophoresis in anesthetized rats (Jimenez-Rivera & Waterhouse, 1991). Higher doses of cocaine decreased the heights of the correlated central peaks and increased the uncorrelated background firing rates, resulting in the weakening of the cofiring activites among SI cortical cells. A similar mode of cocaine action has been reported in anesthetized rats following administration of analgesic doses (25 mg/kg) of cocaine. Belczynski et al. (1987) showed an increase of the spontaneous discharge (background firing) and a decrease of the evoked activity (correlated firing) of neurons in the medullary reticular formation.

The mode of cocaine action on the spontaneously active SI cortical and VPL thalamic cells was quite different from that on the evoked neuronal activity. Previously, we have reported that cocaine has biphasic effects on the peripherally evoked afferent sensory transmission in the SI cortex and the VPL thalamus of awake rats during movement (Shin et al, 1993). Lower doses of cocaine (1.0 mg/kg) facilitated afferent sensory transmission to counteract movement-induced suppression of afferent sensory transmission (Shin and Chapin, 1990d), whereas higher doses of cocaine (10 mg/kg) further suppressed sensory inflow during movement. Similar biphasic effects of cocaine on evoked neuronal activities have been reported in the SI cortex of anesthetized animals (Jimenez-Rivera & Waterhouse, 1991). Thus, peripherally evoked afferent sensory connections (thalamocortical and cuneothalamic) were directly modulated by cocaine during movement, while the strength of the spontaneously established connections (corticocortical, corticothalamic, cofiring) were indirectly influenced by cocaine during rest, except in two cases (suppression of cofiring activities among SI cortical cells by higher doses of cocaine and facilitation of a cofiring pattern between two SI cortical cells after middle doses of cocaine administration). However, the polarities of cocaine actions on either spontaneous activity or peripherally evoked activity were similar, that is both neuronal activities were dependent on the doses of cocaine administered.

The number of cell pairs (n=23, 22.7% of 101 pairs analyzed) indicating functional interactions in this study was much higher than the predicted values, the synaptic input offered by any one presynaptic cell, which is likely to be quite low. A small proportion of cell pairs (7% of the 255 pairs) were functionally interactive in respiratory neurons in the brainstem of cat (Segers et al, 1985). However, if the indi-

vidually counted functional connections, indica-
tive of cofiring among many neurons, were con-
sidered as one connection, then the number of
the functional interactions was actually much
smaller (14 cell pairs, 13.9%).

Common input

Concurrent excitation may occur if cells
share common input(s) and cells are likely to
fire conjointly (Perkel et al, 1967). The central
peaks observed in this study were 9~19 ms
wide. Similar but wider central peaks (60 ms)
have been observed in the monkey striate cor-
tex, and were attributed to a common input
from the retinogeniculate pathway (Kruger &
Aiple, 1988). The weakening of common input
(s), which may be thalamocortical input(s), to
groups of SI cortical cells after cocaine
administration may have the effects of isolating
the cortex from external somatic inputs
(Chapin & Woodward, 1982a; Shin and
Chapin, 1990b, d). It is quite reasonable that
this suppression of common input(s) was
responsible for the previously observed depres-
sion of the afferent sensory transmission in the
SI cortex of awake moving rats (Shin et al,
1993). The increase of uncorrelated firing after
cocaine administration is reminiscent of the
deafferentation-induced increase of spontane-
ous discharge of the SI cortical neurons (Dykes
& Lamour, 1988). On the other hand, the
strengthening of common input(s), which was
definitely shown following middle doses of co-
caine administration in this study, may enable
simultaneous global activation of many SI corti-
cal cells to process thalamocortical afferent sen-
sory inflow. Previously observed facilitation of
afferent sensory transmission after injection of
similar doses of cocaine may be possible by the
strengthening of common input(s) observed in
this study.

Corticothalamic connection

The corticothalamic projections (Price &
Webster, 1972; Jacobson & Trojanowski, 1974;
Wise & Jones, 1977; Shin & Chapin, 1990a, c)

were postulated to subserve movement or
arousal related afferent sensory modulation ob-
served in the ventral posterior thalamus
(Hayward, 1975; Coquery, 1978; Shin &
Chapin, 1990b, d). The weakening of corti-
cothalamic feedback connections following the
administration of low and middle doses of co-
caine may represent a possible release of the
predominant SI cortical descending inhibitory
actions on the afferent sensory transmission,
which have been observed most strongly at 30
msec after SI cortical stimulation in the VPL
thalamus of anesthetized rats (Shin and
Chapin, 1990c). In this regard, this kind of
disinhibition on the thalamocortical inflow via
weakening of the corticothalamic excitatory
connection may also be a feasible circuit mech-
anism responsible for the facilitation of the af-
ferent sensory transmission we have observed
in the SI cortex of awake rats after similar
doses of cocaine administration (Shin et al,
1993).

**Possible mechanisms of the changes of
functional connections**

Available biochemical evidence indicates that
the primary action of cocaine in the CNS is to
elevate synaptic levels of biogenic amines by
blocking reuptake of norepinephrine (Ross &
Rentyi, 1987), dopamine (Hadfield & Nugent,
1983), and serotonin (Taylor & Ho, 1978). The
significant increase of uncorrelated background
firing rates from both reference and target cells
before recovery phase could be related to a gat-
ing action of norepinephrine (Ferron et al,
1985; Waterhouse et al, 1988) on subthreshold
synaptic stimuli which were uncorrelated to the
observed functional connection. Alternatively,
this initial increase and following decrease of
background firing rates by cocaine injection
may represent the general property of local an-
esthetics, which are known to excite CNS ini-
tially and then to depress (Covino, 1987). The
decrease of the height of correlated peaks may
be enabled by direct inhibitory effects of seroto-
nin (Bloom et al, 1972) and norepinephrine
(Hoffer et al, 1971, Parfitt et al, 1988). The

majority of strengthened effectiveness of the functional interactions observed during low and middle doses of cocaine administration was accomplished by the reduction of the target cell's background firing rates without significant changes of the correlated peak. A similar enhancement of the signal to noise ratio of SI cortical excitatory responses was reported by iontophoretically applied norepinephrine (Waterhouse & Woodward, 1980). The selective enhancement of the shared input between two SI cortical cells following middle doses of cocaine administration was done without concomitant increase of the uncorrelated discharges. In the SI cortex of anesthetized rats, similar mode of cocaine action has been reported and it was attributed to the noradrenergic modulatory mechanisms rather than to those of dopamine or serotonin (Jimenez-Rivera & Waterhouse, 1991).

ACKNOWLEDGEMENTS

REFERENCES

Angel A & Clarke KA (1975) An analysis of the representation of the forelimb in the ventrobasal thalamic complex of the albino rat. *J Physiol (London)* **249**, 399-423

Belczynski CR, Pertovaara A, Morrow TJ & Casey KL (1987) Cocaine: neurophysiological effects on bulboreticular projection neurons. *Soc Neurosci Abstr* **13**, 1588

Bloom FE, Hoffer BJ, Siggins GR, Barker JL & Nicoll RA (1972) Effects of serotonin on central neurons: microiontophoretic administra-

tion. *Fed Proc* **31**, 97-106

Bryant HL Jr. Marcos AR & Segudo JP (1973) Correlations of neuronal spike discharge produced by monosynaptic connections and by common inputs. *J Neurophysiol* **36**, 205-255

Byck R & Van Dyke C (1977) What are the effects of cocaine in man? In Cocaine: *(NIDA Research Monograph #13)*, Petersen RC & Stillman RC (ed) Washington, D.C.: U.S. Government Printing Office, p97-118

Chapin JK & Woodward DJ (1982a) Somatic sensory transmission to the cortex during movement. I. Gating of single cell responses to touch. *Exp Neurol* **78**, 654-669

Chapin JK & Woodward DJ (1982b) Somatic sensory transmission to the cortex during movement. II. Phasic modulation over the locomotor step cycle. *Exp Neurol* **78**, 670-684

Chapin JK & Lin CS (1984) Mapping the body representation in the SI cortex of anesthetized and awake rats. *J Comp Neurol* **229**, 199-213

Coquery JM (1978) Role of active movement in control of afferent input from skin of the cat and man. In: *Gordon G (ed) Active Touch.* Pergammon press. Oxford. p161-179

Covino BG (1987) Toxicity and systemic effects of local anesthetic agents. In: *Strichartz GR (ed) Handbook of experimental pharmacology.* Springer-Verlag, New York. p187-212

Davis M (1985) Cocaine: excitatory effects on sensorimotor reactivity measured with acoustic startle. *Psychopharmacol* **86**, 31-36

Dykes RW & Lamour Y (1988) An electrophysiological studies of single somatosensory neurons in rat granular cortex serving the limbs: a laminar analysis. *J Neurophysiol* **60**, 703-724

Ferron A, Siggins GR & Bloom FE (1985) Vasoactive intestinal polypeptide acts synergistically with norepinephrine to depress spontaneous discharge rate in cerebral cortical neurons. *Proc Natl Acad Sci* **82**, 8810-8812

Fischman MW & Schuster CR (1982) Cocaine self-administration in humans. *Fed Proc* **41**, 241-246

Gawin FH (1991) Cocaine: Psychology and neurophysiology. *Science* **251**, 1580-1586

Hadfield MG & Nugent EA (1983) Cocaine: comparative effect on dopamine uptake in

extrapyramidal and limbic systems. *Biochem Pharmacol* **32,** 744-746

Hayward JM (1975) Response of ventrobasal thalamic cells to hair displacement on the face of the waking monkey. *J Physiol* **250,** 385-407

Hoffer BJ, Siggins GR & Bloom FE (1971) Studies on norepinephrine-containing afferents to Purkinje cells of rat cerebellum. II. Sensitivity of Purkinje cells to norepinephrine and related substances administered by microiontophoresis. *Brain Res* **25,** 522-534

Jacobson S & Trojanowski JQ (1974) Corticothalamic neurons and thalamocortical terminal fields: An investigation in rat using HRP and autoradiography. *Brain Res* **58,** 385-401

Jimenez-Rivera CA & Waterhouse BD (1991) Effects of systemically and locally applied cocaine on cerebrocortial neuron responsiveness to afferent synaptic inputs and glutamate. *Brain Res* **546,** 287-296

Johanson CE & Fischman MW (1989) The pharmacology of cocaine related to its abuse. *Pharmacol Rev* **41,** 3-52

Kruger J & Aiple F (1988) Multimicroelectrode investigation of monkey striate cortex: spike train correlations in the infragranular layers. *J Neurophysiol* **60,** 798-828

Moore GP, Segundo JP, Perkel DH & Levitan H (1970) Statistical signs of synaptic interaction in neurons. *Biophys J* **10,** 876-900

Parfitt KD, Freedman R & Bickford-Wimer PC (1988) Electrophysiological effects of locally applied noradrenergic agents at cerebellar purkinje neurons: receptor specificity. *Brain Res* **462,** 242-251

Perkel DH, Gerstein GL & Moore GP (1967) Neuronal spike trains and stochastic point processes. II. Simultaneous spike trains. *Biophys J* **7,** 419-440

Pitts DK & Marwah J (1987) Cocaine modulation of central monoaminergic transmission. *Pharmacol Biochem Behav* **26,** 453-461

Post RM (1975) Cocaine psychoses: a continuum model. *Am J Psychiat* **132,** 231-255

Price TR & Webster KE (1972) The corticothalamic projection from the primary somatosensory cortex of the rat. *Brain Res* **44,** 636-640

Ross SF & Rentyi AL (1987) Inhibition of the uptake of tritiated catecholamines by antidepressants and related agents. *Eur J Pharmacol* **2,** 181-186

Scheel-Kruger J, Braestrup C, Nielsen M, Golembiowska R & Mogirnicha E (1977) Cocaine: discussion of the role of dopamine in the biochemical mechanism of action. *In Cocaine and Other Stimulants.* Ellinwood EH & Kilbey MM (ed) New York: Plenum Press, p373-407

Sears TA & Stagg D (1976) Short-term synchronization of intercostal motorneurone activity. *J Physiol (London)* **263,** 357-381

Segers LS, Shanon R & Lindsey BG (1985) Interactions between rostral pontine and ventral medullary respiratory neurons. *J Neurophysiol* **54,** 318-334

Shin HC & Chapin JK (1990a) Mapping the effects of motor cortex stimulation on ventroposterolateral thalamic nucleus in rat: Direct response and afferent modulation. *Brain Res Bull* **24,** 257-265

Shin HC & Chapin JK (1990b) Modulation of afferent transmission to single neurons in the ventroposterior thalamus and somatosensory cortex during movement in rats. *Neurosci Lett* **198,** 116-120

Shin HC & Chapin JK (1990c) Mapping the effects of SI cortex stimulation on somatosensory relay neurons in the rat thalamus: direct responses and afferent modulation. *Somatosen & Motor Res* **7,** 421-434

Shin HC & Chapin JK (1990d) Movement-induced modulation of afferent transmission to single neurons in the ventroposterior thalamus and somatosensory cortex in rat. *Exp Brain Res* **81,** 515-522

Shin HC, Raymond SA, Oh UT, Park HJ & Chapin JK (1993) Cocaine-induced changes in sensory responsiveness of simultaneously recorded single neurons in the VPL thalamus and the SI cortex of behaving rats. *Exp Neurobiol* **1,** 47-59

Taylor D & Ho BT (1978) Comparison of inhibition of monoamine uptake by cocaine, methylphenidate and amphetamine. *Res Commun Chem Pathol Pharmacol* **21,** 67-75

Wall PD & Egger MD (1971) Formation of new connections in adult rat brains after partial deafferentaion. *Nature (London)* **232,** 542-545

Waterhouse BD & Woodward DJ (1980) Interac-

tion of norepinephrine with cerebro-cortical activity evoked by stimulation of somatosensory afferent pathways. *Exp Neurol* **67**, 22-34

Waterhouse BD, Sessler FM, Cheng JT, Woodward DJ, Azizi SA & Moises HC (1988) New evidence for a gating action of norepinephrine in central neuronal circuits of mammalian brain. *Brain Res Bull* **21**, 425-432

Weiss RD & Mirin SM (1987) Cocaine. Washington DC: *American Psychiatric Press*

Wilson MC, Bedford JA, Buelke J & Kibbe AH (1976) Acute pharmacological activity of intravenous cocaine in the rhesus monkey. *Psychopharm Comm* **2**, 252-262

Wise SP & Jones EG (1977) Cells of origin and terminal distribution of descending projections of the rat somatic sensory cortex. *J Comp Neurol* **175**, 129-158