

ORIGINAL ARTICLE

**SHORT LATENCY AFFERENT INHIBITION
IN SCHIZOPHRENIA PATIENTS**

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Abstract

Objective: The objective of this study was to test our preliminary in vivo evaluations of central cholinergic abnormalities in schizophrenia patients. Short latency afferent inhibition (SAI) is based on coupling peripheral nerve stimulation with motor cortex Transcranial Magnetic Stimulation (TMS), which has been shown to be a putative marker of central cholinergic activity. ***Methods:*** We evaluated SAI in 5 patients with schizophrenia and 5 healthy subjects. ***Results:*** The level of SAI was significantly lower in the patients with schizophrenia than in the controls ($p=0.008$). ***Conclusion:*** Our findings suggest involvement of central cholinergic neurotransmission in schizophrenia, which indicates a possible approach for treatment of cognitive dysfunction related to the disease. *ASEAN Journal of Psychiatry, Vol. 14 (2): July – December 2013: XX XX.*

Keywords: Schizophrenia, Short Latency Afferent Inhibition (SAI), Transcranial Magnetic Stimulation (TMS)

Introduction

Although the pathogenesis of schizophrenia is unclear, recent discoveries have indicated dysfunction of diverse cortical neurotransmissions in affected patients, such as glutamate and gamma-aminobutyric acid (GABA), as well as the classical dopamine hypothesis (1). In addition, several lines of evidence suggest that the cholinergic system may be disrupted in schizophrenia, as post-mortem studies have demonstrated alterations in nicotinic and muscarinic receptors, as well as their availability or expression in patients with schizophrenia (2, 3, 4, 5). Therefore, agents that target cholinergic function, such as acetylcholinesterase inhibitors, and nicotinic and muscarinic receptors agonists, have been considered as possible approaches for treatment of cognitive dysfunction in affected patients (6).

In vivo measurements such as neurotransmitter changes can also be helpful for treatment of the disease, of which transcranial magnetic stimulation (TMS) is a noninvasive technique that stimulates a restricted part of the cortex and allows examination of the excitability of the motor cortex based on muscle responses.

By use of paired pulse TMS protocols or coupling peripheral nerve stimulation with TMS of the contralateral motor cortex, it is possible to recruit several neuronal circuits of the human brain (7). For example, short interval intracortical inhibition (SICI) is measured with paired-pulse TMS involving a subthreshold conditioning stimulus applied ipsilateral to the test stimulus over the primary motor cortex at an interstimulus interval (ISI) of 1–5 ms and is thought to be mediated via the GABA type A receptor (GABAAR) (8). Several studies have

reported SICI abnormalities in schizophrenia patients, which supports the GABAergic dysfunction hypothesis for disease pathogenesis (9, 10, 11, 12).

Another form of motor cortical inhibition is short latency afferent inhibition (SAI). Muscle responses recorded in hand muscles after TMS of the motor cortex can be suppressed by electrical stimulation of the median nerve if the time interval between stimulation of median nerve and motor cortex is 2-8 ms longer than the time taken by the peripheral nerve afferent input to reach the cortex (13). In that study, direct demonstration of the cortical origin of SAI was provided through recordings of descending corticospinal volleys from conscious patients with high cervical epidural electrodes. SAI is decreased by the muscarinic receptor antagonist scopolamine in normal subjects (14), and also reduced in Alzheimer's disease and restored by an acetylcholinesterase inhibitor, thus it is considered to be a non-invasive means of testing central cholinergic activity (15, 16). To the best of our knowledge, SAI in schizophrenia has not been investigated. Hence, the present study was conducted as a preliminary evaluation of central cholinergic abnormalities in vivo in patients with schizophrenia as a possible approach for treatment of cognitive dysfunction related to the disease.

Methods

Five patients (3 females, 2 males; mean age 37.2 ± 16.5 years) with a diagnosis of schizophrenia and 5 control subjects (2 females, 3 males; mean age 28.6 ± 5.3 years) were investigated. The patients were recruited at the Department of Neuropsychiatry, Wakayama Medical University, and the diagnosis of schizophrenia was made according to DSM-IV criteria. There were no significant differences between the groups regarding age ($t=1.112$, $df=8$, $P=0.318$). All subjects were right-handed. The main clinical and demographic characteristics of the subjects are shown in Table I. Each subject provided informed written consent according to the Declaration of Helsinki and the study was approved by the ethics committee of our university.

Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation was performed with a Magstim 200 stimulator (Magstim Co., Whitland, Dyfed, UK). A figure-8 coil with external loop diameters of 9 cm was held over the left motor cortex at the optimum scalp position to elicit motor responses in the contralateral first dorsal interosseous (FDI) muscle. Motor evoked potentials (MEPs) were recorded via two 9-mm diameter Ag-AgCl electrodes, with the active electrode applied over the motor point of the muscle and the reference on the metacarpophalangeal joint of the index finger. Motor responses were amplified and filtered (bandwidth 3-3000 Hz) using a Neuropack ΣMEB508 (Nihon Kohden Co. Ltd., Tokyo, Japan).

Short latency afferent inhibition (SAI)

SAI was investigated using the technique described by Tokimura and colleagues (13). The conditioning stimulus was a single pulse (200 μ s) of electrical stimulation (cathode positioned proximally) applied through bipolar electrodes to the median nerve at the wrist. The intensity of the conditioning stimulus was set just above the motor threshold necessary to evoke a visible twitch of the thenar muscles. The intensity of the unconditioned magnetic test pulse given to the left motor cortex was adjusted to evoke an MEP in the contralateral relaxed FDI with an amplitude of approximately 1 mV peak to peak. Interstimulus intervals (ISIs) were determined relative to the latency of the N20 component of the somatosensory evoked potential evoked by stimulation of the median nerve. To record somatosensory evoked potentials, the active electrode for recording the N20 potential was attached 3 cm posterior to C3 (according to the 10-20 International EEG system) and the reference was Fpz. Five hundred responses were averaged to identify the latency of the N20 peak. ISIs from the latency of the N20 component plus 2 ms to the latency of the N20 component plus 7 ms were investigated in steps of 1 ms. Eight stimuli were delivered at each ISI. We calculated the average MEP value obtained after the cortical magnetic stimulation alone (test MEP) and the MEP value obtained by the conditioning cortical magnetic stimulus with peripheral stimulus to the median nerve at the

wrist at the 6 different ISIs studied (conditioned MEP). The amplitude of the conditioned MEP was expressed as the percentage of the amplitude of the test MEP. The percentage inhibition of the conditioned responses at the 6 different ISIs was averaged to obtain a grand mean. Subjects were given audio-visual feedback to assist in maintaining complete relaxation. The electrophysiological parameters of the patients were analyzed separately and compared with those of the control subjects

using Mann-Whitney tests. The level of significance was set at 0.05.

Results

There were no significant differences between the groups for age ($t=1.112$, $df=8$, $P=0.318$). The mean doses of medications and number of patients taking each drug are presented (NA: not applicable).

Table 1. Demographic characteristics of the subjects

	Schizophrenia (n=5)	Control (n=5)
Age (years)	37.2 ± 16.5	28.6 ± 5.3
Gender (male, female)	2/3	3/2
Antipsychotic dose (mg) (chlorpromazine equivalent)	539.2 ± 459.2 (n=5)	NA
Anticholinergic dose (mg) (biperiden equivalent)	2.5 (n=1)	NA
Benzodiazepine dose (mg) (diazepam equivalent)	5.3 ± 3.6 (n=4)	NA

MEPs in the control subjects were inhibited at all ISIs corresponding to the N20 latency plus 2 ms to N20 latency plus 7 ms. The level of SAI was significantly lower in the patients with schizophrenia (mean responses reduced to

84.6 ± 19% of test size) than in the normal controls (mean responses reduced to 50.8 ± 15% of test size; $P=0.008$, Mann-Whitney test, $N1=5$, $N2=5$) (Fig. 1, Fig. 2).

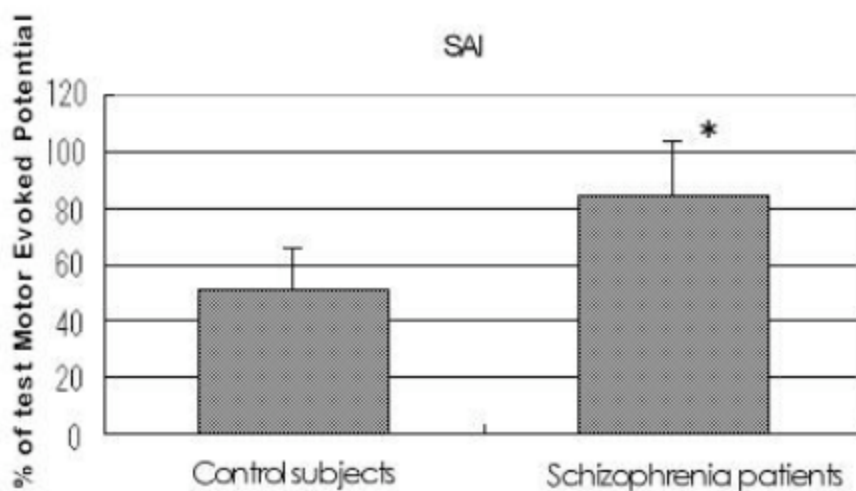


Fig. 1. Column graph showing grand mean values for short latency afferent inhibition (SAI) in the patients with schizophrenia and control subjects

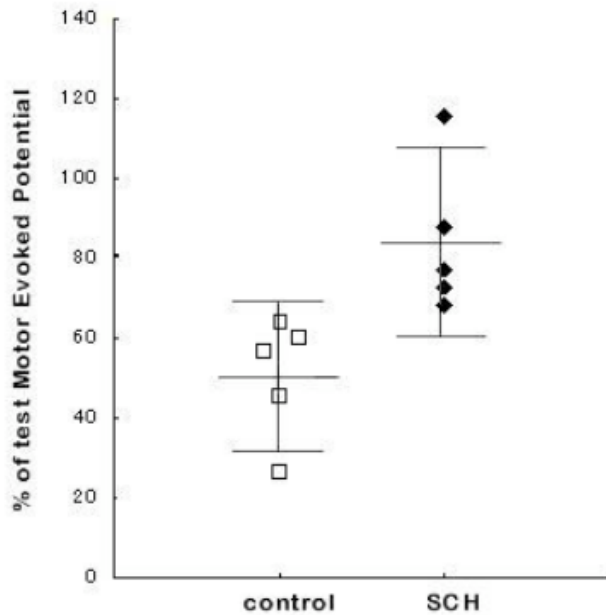


Fig. 2. Scatterplot showing individual values for short latency afferent inhibition (SAI) in the patients group (SCH) (◆ filled diamond, n=5) and control subjects (□ open squares, n=5). The amplitude of the conditioned motor evoked potential (MEP) is reported as a percentage of the test MEP. Error bars show standard deviations. Control: control subjects, SCH: patients with schizophrenia.

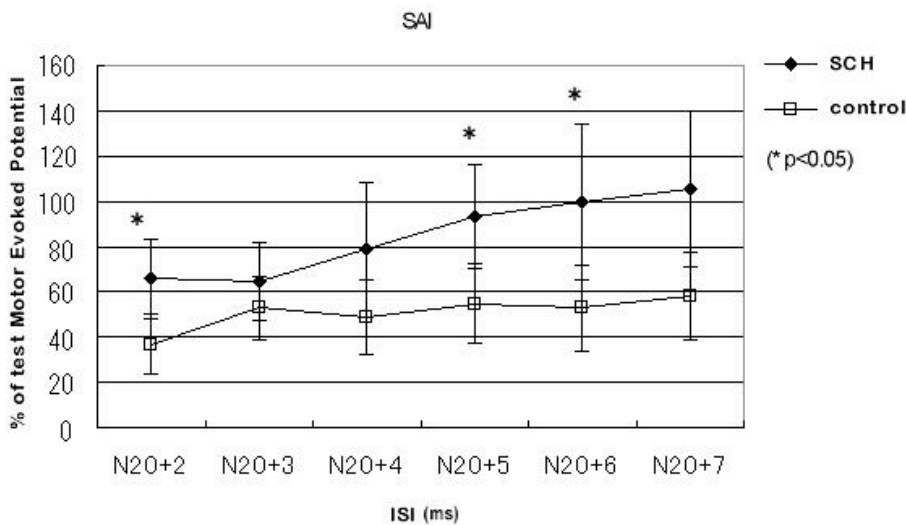


Fig. 3. Short latency afferent inhibition (SAI) at single interstimulus intervals (ISIs) in patients with schizophrenia and control subjects

The amplitude of the conditioned motor evoked potential (MEP) is reported as a percentage of the test MEP. SAI was significantly reduced in

the patients group (◆ filled diamond) at ISIs of N20+2 ms, N20+5 ms, and N20+6 ms when compared with the control subjects (□ open

squares) (*P<0.05, Mann-Whitney test). Error bars show standard deviations. SAI: short latency afferent inhibition, ISI: interstimulus intervals, Control: control subjects, SCH: patients with schizophrenia

Furthermore, SAI was significantly reduced in the patients with schizophrenia as compared

with the controls for ISIs of the N20 latency plus 2 ms, plus 5 ms, and plus 6 ms (P-values: 0.016, 0.032, and 0.032, respectively, Mann-Whitney test) (Fig. 3). There were no significant differences in terms of N20 latency and mean test MEP amplitude. The obtained data are summarized in Table 2.

Table 2. Electrophysiological data for controls and patients with schizophrenia (all values are expressed as the mean ± SD)

	Schizophrenia (n=5)	Controls (n=5)	p-value
N20 latency (ms)	18.8±1.9	18.8±0.4	0.841
tMEP amplitude (μV)	676.2±564.6	852.6±224.8	0.15
SAI (%)			
ISI: N20+2	65.8±17.5	36.8±13.1	0.016 *
ISI: N20+3	64.7±17.2	53±13.9	0.421
ISI: N20+4	78.5±29.8	48.6±16.6	0.151
ISI: N20+5	93.4±22.9	54.8±17.5	0.032 *
ISI: N20+6	99.6±34.5	52.9±19.1	0.032 *
ISI: N20+7	105.3±34.4	58.2±19.5	0.056
SAI (grand mean) (%)	84.6±19	50.8±15	0.008 *

SAI was calculated by the mean amplitude of conditioned MEP expressed as a percentage of the mean amplitude of the test MEP (see text). SAI was significantly reduced in the patients group at ISIs of N20+2 ms, N20+5 ms, and N20+6 ms intervals when compared with the control group (bold type) (*P<0.05, Mann-Whitney test).

ISI: interstimulus interval, SAI: short latency afferent inhibition, tMEP: test motor evoked potential.

Discussion

In the present study, SAI was found to be reduced in patients with schizophrenia, which could be interpreted in a number of different ways. One possible explanation is that reduced SAI suggests dysfunction of cholinergic neuronal circuits in patients with schizophrenia, as supported by data from post-mortem studies (2, 3, 4, 5). On the other hand, it has been suggested that SAI is dependent on the integrity

of circuits linking sensory input and motor output, rather than cholinergic function (17). Also, sensorimotor gating deficits in patients with schizophrenia have been demonstrated by other neurophysiological measures, such as P50 evoked potential, and linked to the alpha7 nicotinic receptor system (18). Together, it can be speculated that reduced SAI is involved in sensorimotor gating deficits, cholinergic dysfunction, and cognitive impairment in schizophrenia.

It has been reported that different neurotransmitters such as GABA or dopamine may be involved in the regulation of SAI (19, 20, 21). Furthermore, GABA-mediated inhibition may play a role in modulating SAI at a presynaptic level (20). Dopaminergic changes could also modulate SAI via the cortical or subcortical level (21). Thus, in conditions that impair dopamine or the GABA system, SAI modifications may occur. In addition, these neurotransmitters appear to have a modulatory function toward each other in the brain (22).

Therefore, reduced SAI may reflect abnormalities of several such neurotransmitters in patients with schizophrenia.

This study has some limitations. The small sample size may be insufficient to take into account factors that have an influence on the results, such as age and sex. Although there was tendency for the patient group to be older than the control group, no effect of age on SAI has been shown in previous studies. Second, the influence of concomitant medication should also be considered. All of our patients were taking antipsychotic medications, while some were also taking anticholinergic drugs or benzodiazepines. Therefore, we cannot deny the possibility that these drugs contributed to SAI changes by modulation of the cholinergic, GABAergic, or dopaminergic systems in the patients group. Third, we only examined SAI and not other distinct TMS measures such as SICl. As discussed above, it might be argued that impaired SAI does not necessarily reflect exclusive cholinergic dysfunction because other neurotransmitters such as GABA or dopamine may modulate SAI. A previous study indicated that pharmacological profiling distinguishes SAI from SICl: For example, the muscarinic receptor antagonist scopolamine decreases only SAI but not SICl (14), whereas different GABAAR modulators (lorazepam, diazepam, and zolpidem) show dissociated patterns, suggesting involvement at the level of GABAAR subtypes (19, 20). In addition, results of an experimental study suggested that SICl and SAI are mediated through 2 distinct and reciprocally connected subtypes of GABAergic inhibitory interneurons with convergent projections onto the corticospinal neurons (23). Thus, abnormalities such as different neuronal circuits in schizophrenia might be segregated by the combination of SAI with SICl.

In conclusion, our findings demonstrated a reduction of SAI in patients with schizophrenia. Further study is needed to clarify whether our results are related to cholinergic abnormalities in schizophrenia or a different state.

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