[S1-3] *[4/21/2000 (Fri) 11:10~11:50/Byulkwan Auditorium, Bldg 26]*

Understanding The Cause of and Developing New Drugs for Schizophrenia

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Since the introduction of chlorpromazine as an effective treatment agent of schizophrenia nearly five decades ago, dozens of antipsychotic drugs (APDs) have been introduced. Despite the proven efficacy in the treatment of schizophrenia, precise mechanisms and sites of action of APDs have remained to be elucidated. Delineation of sites of action of APDs is probably the best strategy of elucidating the action mechanism of APDs. To relate functional outcomes of APDs to their underlying actions in the nervous system, information about effects of APDs on neural activity is especially important. Previous studies have examined effects of APDs on activities of midbrain dopamine neurons. Chronic administration of APDs induces depolarization block in the A9 and A10 dopamine neurons. In spite of its importance in schizophrenia, however, effects of APDs on neural activities in the prefrontal cortex (PFC) have not been examined.

Several lines of evidence indicate involvement of the PFC in the pathophysiology of schizophrenia. Brain imaging studies have revealed functional as well as structural abnormalities in the PFC of schizophrenic patients. Furthermore, clinical response to clozapine, an atypical APD, was inversely related to prefrontal atrophy. These studies suggest the possibility that pathophysiology of schizophrenia involves abnormality in PFC neural activity and alterations in PFC neural activity induced by APDs contribute to antipsychotic actions of APDs. As an initial step toward investigating this possibility, we have been examining whether or not systemic injection of APDs changes spontaneous firing of single neurons in the PFC. Here we report acute effects of two APDs, haloperidol and clozapine, on neuronal activity in the PFC of the anesthetized rat. Both APDs significantly enhanced firing rates of PFC neurons, raising the possibility that enhancement of PFC neural activity underlies therapeutic effects of haloperidol and clozapine. The present results are being tested in behaving animals. Future

investigations should address effects of specific agonists/antagonists on PFC unit activity for development of a new therapeutic agent.

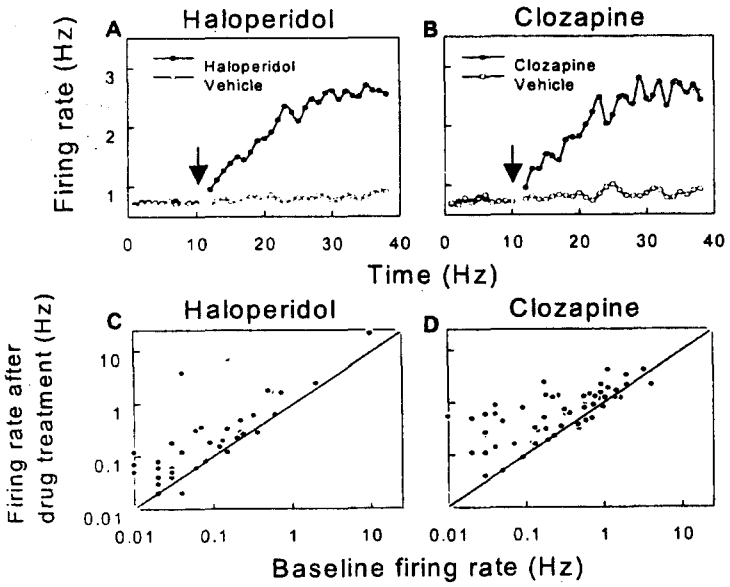

Figure: Effects of APDs on PFC neuronal activity. (A,B) Examples that show effects of haloperidol or clozapine on PFC unit activity. The arrow indicates the time of drug injection. (C.D) Distributions of firing rates before and after haloperidol or clozapine treatment are shown. Each point in the scatter plot indicates average firing rates for 10 min period before (abscissa) and after (ordinate) the drug treatment. Note that both abscissa and ordinate are in logarithmic scale.