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Short Communication

Increased proportion of high-affinity dopamine D2 receptors in rats with excitotoxic damage of the entorhinal cortex, an animal model of schizophrenia

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Abstract

Excitotoxic lesions of the left entorhinal cortex (EC) cause dopamine supersensitivity. In order to determine if these lesions selectively alter the high-affinity state of dopamine D2 receptors ($D2^{High}$), these high-affinity states were measured by competition between dopamine and [^{3}H]domperidone in striata from lesioned rats and sham-operated animals. The proportion of $D2^{High}$ sites was significantly elevated by 200% in the EC-lesioned rats while that of the $D1^{High}$ sites, measured by dopamine/[^{3}H]SCH23390 competition, was unaltered. These results provide a biochemical basis for behavioral supersensitivity in rats with EC lesions.

Theme: Disorders of the nervous system
Topic: Neuropsychiatric disorders

Keywords: Entorhinal cortex; Excitotoxic lesion; Dopamine; High-affinity state of D2 receptor; Supersensitivity; Schizophrenia

Dopamine (DA) supersensitivity has been assumed to be a neurochemical basis underlying psychotic symptoms of neuropsychiatric disorders, such as schizophrenia [11,14,15]. Since morphological studies report left dominant reductions in the volume of temporal lobe structures, including parahippocampal gyrus, or the entorhinal cortex (EC; anterior portion of parahippocampal gyrus), in subjects with schizophrenia [1,2,7], we have conducted a series of studies on the effect of excitotoxic damage of the left EC on DA transmission in the rat [4,6,16–19]. Thus, lesions of the left EC by quinolinic acid resulted in increased tissue concentrations of DA and its metabolites in several subcortical brain regions [4,6,17], as well as augmented DA release in the amygdala after injection of a moderate dose of methamphetamine (MAP; 2 mg/kg) [17,19] or exposure to physical or psychological stress [18]. In a recent study [16], we found enhanced locomotor activity after administration of a small dose (1 mg/kg) of MAP in the EC-lesioned rats while this dose of MAP did not augment DA release in the accumbens nucleus. These observations have led us to hypothesize that excitotoxic lesions of EC would produce supersensitivity of DA receptors in some regions of the brain [16].

Seeman et al. (2003, 2005) have developed a method to measure the high-affinity state, or the functional state, of DA receptors, using competition between DA and a radioactive ligand such as [^{3}H]domperidone for D2 receptors ($D2^{High}$ sites) [13,14]. This method has revealed increased proportions (140–370% relative to control subjects) of $D2^{High}$ in the

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striata of rats by various manipulations, such as chronic administration of phencyclidine, treatment with a clinically relevant dose of antipsychotic drugs, and neonatal hippocampal lesions [14]. These results indicate a correlation of the increased amount or proportion of $D2^{High}$ sites with the pathophysiology of some of the psychosis-related signs. The purpose of the present study, therefore, was to determine if excitotoxic lesions of the left EC produce a selective increase in the proportion of $D2^{High}$ sites, but not other sites, such as $D1^{High}$ sites, in the striata of rats.

The procedure of lesioning of the left EC of rats was based on our previous reports [4,6,16,18,19]. Male young adult (postnatal 7 weeks) Wistar rats (Sankyo Labo Service Inc., Japan) weighing 210–230 g at the time of surgery were housed at temperature-controlled environment on a daily light (07:00–19:00 h)/dark schedule of 12/12 h with free access to food and water. The procedure was in compliance with the National Institutes of Health *Guide for Care and Use of Laboratory Animals*, and was reviewed and approved by the Committee of Animal Research, Toyama Medical and Pharmaceutical University. After induction of anesthesia with pentobarbital (30 mg/kg, i.p.), the animals were placed in a stereotaxic apparatus with 30 ga stainless steel tubing directed into the left EC. The coordinates used were: AP −7.6 mm, ML 5.0 mm, VD −7.3 mm, with respect to the bregma [8]. Quinolinic acid (Sigma Chemical Co.; 75 nmol) (lesion group) or 0.1 M phosphate-buffered saline (pH 7.4) (sham group) in a total volume of 0.5 ml was administered into the left EC using a Model 22 microdialysis pump (Harvard Apparatus Inc., MA, U.S.A.) at a rate of 0.1 ml/min. The injection cannulae were left in place for an additional 5 min after the end of the infusion. Rats were allowed to recover and were housed in groups of 5. On the 28th postoperative days, animals were sacrificed by

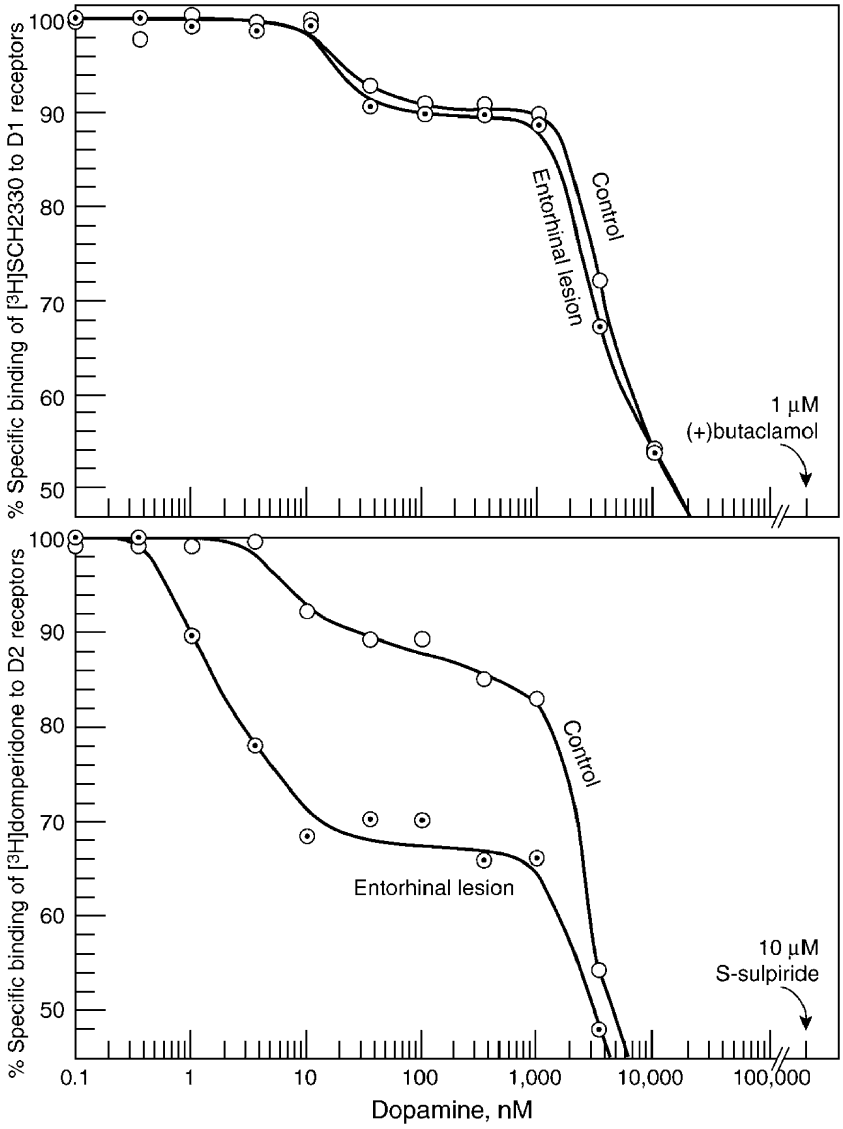

Fig. 1. Representative competition curves between dopamine and [^{3}H]SCH23390 (top) and those between dopamine and [^{3}H]domperidone (bottom) using rat striata.