Short Communication

Dopamine Agonist Action of Phencyclidine

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ABSTRACT Although the psychotomimetic action of phencyclidine is often used to model a hypoglutamate theory of psychosis or schizophrenia, work also exists showing that phencyclidine has a significant affinity for the dopamine D2 receptor. The present study was done to determine whether phencyclidine has a direct functional dopamine-like action on cells. The effect of phencyclidine was tested on the release of prolactin from rat cultured anterior pituitary cells. It was found that the release of prolactin was 50% inhibited by 4 nM phencyclidine. This strong dopamine-like agonist action at the functional high-affinity state of the dopamine D2 receptor by the phencyclidine psychotomimetic is consistent with the dopamine hypothesis of psychosis. Synapse 58:275–277, 2005. © 2005 Wiley-Liss, Inc.

INTRODUCTION

Although the anti-dopamine actions of antipsychotic drugs are compatible with the hyper dopamine hypothesis of psychosis and schizophrenia (Seeman, 1987; Van Rossum, 1967), the psychosis caused by the glutamate antagonist phencyclidine suggests a hypoglutamate contribution to psychosis (Goff and Coyle, 2001; Jentsch and Roth, 1999; Tamminga et al., 1995). At the same time, however, phencyclidine lowers plasma prolactin (Lozovsky et al., 1983) and elicits rotation (Mele et al., 1998), suggesting a direct or indirect-mimetic action of phencyclidine.

Phencyclidine is not selective for the glutamate NMDA receptor (Kapur and Seeman, 2002), because it has a high affinity (Seeman 2004) for the functional high-affinity state (George et al., 1985) of the cloned D2 receptor, or the D2High receptor.

[3H]Domperidone is a selective ligand for D2 that readily permits the accurate detection of D2High receptors by competition with dopamine agonists (Seeman et al., 2003, 2005). In addition, there is no information on the direct action of phencyclidine on isolated cells that are normally sensitive to dopamine-like drugs. Although it is known that phencyclidine lowers the secretion of prolactin in rats in vivo (Meltzer et al., 1985), it is not known whether the action is direct or indirect, because glutamate pathways modify the release of prolactin (Login, 1990; Pampillo et al., 2002).

Therefore, the present study was done to determine whether the action of phencyclidine may have a direct dopamine-like agonist component.

METHODS

Anterior Pituitary Cell Culture

The effect of phencyclidine was tested on cultured anterior pituitary cells (Caruso et al., 2004). Briefly, rat anterior pituitary glands (posterior pituitaries removed) were sliced and dispersed enzymatically and mechanically by extrusion through a Pasteur pipette in Krebs buffer without Ca2+ and Mg2+. The cells were cultured for 72 h (37°C, 5% CO2–95% O2 in air) in DMEM-S with 10% FBS. After the culture period, the medium was replaced and a range of phencyclidine concentrations added and incubated for 4–24 h. At the end of the incubation period, the media were

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aspirated and stored at –20°C until assayed for prolactin determination.

**Prolactin RIA**

Prolactin was measured by a double-antibody RIA, with reagents provided by the National Hormone and Pituitary Program. Rat PRL-RP-3 was used as the standard, and NIDDK-antirPRL-S-9 was used as antisemum. Cross-reactivity with other pituitary hor- mones was negligible. The sensitivity of the assay was 0.1 ng/ml. Hormone concentration was expressed as nanograms per well.

**RESULTS AND DISCUSSION**

The release of prolactin from the rat cultured anterior pituitary cells was readily inhibited by phencyclidine concentrations above 0.1 nM. The phencyclidine concentration to inhibit 50% (IC 50%) was 4 nM. Vertical bars indicate the s.d. The number of measurements is given below each point. Each value is expressed as a percent of the control measurement.

The data in Figure 1, however, illustrate that phencyclidine acts as a direct potent dopamine-like agonist to inhibit the release of prolactin at 4 nM. The release of prolactin is predominantly controlled by the D2[^2] receptor (Borgundvaag and George, 1985; George et al., 1985).

Although the anterior pituitary gland also contains a low density of dopamine D3 receptors (4.2 pmol/g, as measured by the D3-selective ligand [3H]PD 128,907; this laboratory, unpublished), the dissociation constant of phencyclidine for the D3 receptor exceeds 10,000 nM (this laboratory, unpublished), indicating that the phencyclidine inhibition of prolactin release is not via D3 receptors.

Considering that the psychotomimetic phencyclidine acts on both dopamine D2 and NMDA receptors, phencyclidine is not sufficiently selective for testing theories of psychotomimetic action, as had been thought (Svenningsen et al., 2004). Although prolactin release from hemi-pituitary glands in vitro was not directly inhibited by 1 μM phencyclidine (Meltzer et al., 1985), it is possible that phencyclidine has better access to the isolated pituicytes.

The present data are consistent with the dopamine hypothesis of psychosis. That is, the clinical agonist actions of phencyclidine in eliciting psychotic symp- toms are selectively treated in the hospital emergency room by haloperidol and other dopamine D2-selective antagonists (Giannini et al., 1984, 1984–1985, 2000), supporting the idea that dopamine D2 receptors are the primary target for eliciting psychotic symptoms.

The serum phencyclidine concentration that elicits psychotomimetic action is of the order of 10 nM (Javitt and Zukin, 1991). This is exactly the active range of phencyclidine that directly stimulates D2[^2] to inhibit prolactin release (Fig. 1). In contrast, the NMDA receptor has phencyclidine Ki values of 97 nM and 124 nM on rat brain membranes, and 196 nM on the human cloned NMDA receptor (Grimwood et al., 1996; Murray et al., 2000).

Ögren and Goldstein (1994) have shown that three dopamine antagonists (haloperidol, raclopride, and remoxipride) blocked locomotion elicited by phencyclidine. Because these three dopamine antagonists have very low affinity for the NMDA receptor, and raclo- pride and remoxipride being highly selective for dopamine D2 receptors, dopamine is clearly an important component in the phencyclidine model of schizophrenia.

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