Molecular Mechanisms of DCS Induced Changes in Hippocampal Neuron Excitability

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Background

Arc gene expression has been used as a marker for neuronal activity (Tinselette, 2006; Gazeau&L., 1999). Specifically, arc gene expression has been correlated with the activity of hippocampal place-cells (Gazeau&L, 1999). Although D-cycloserine (DCS) is known to be a partial NMDA agonist (Hord, 1985; Millan, 1996; Pfeiffer, 1994), our lab has shown in vitro that DCS functionally acts as an NMDA antagonist (Donzis & Thompson, 2007), decreasing Schaffer collateral-evoked EPSPs in CA1, by competing for binding with the endogenous full agonists serine and glycine, which enhance EPSP amplitudes. Since increased NMDAR activity is correlated with increased place cell activity (Kentros, 1998), as well as arc expression (Bloomer, 2006), then administration of DCS acting as a partial agonist should decrease place-cell activity as well as decrease arc expression.

Methods

Drug Treatment: 3 – 5 mo male Long Evans rats were given a single injection or 21 daily injections of either saline vehicle (0.9% NaCl) or of D-cycloserine (2 mg/kg, i.p., 0.5 mL/250 mg, pH 7.4). The rats were sacrificed and brain tissue collected 1 h post-injection. Western Blotting Placing recipes (6 rats per condition) were recorded at intervals indicated post-injection. Place-Cell Recording and Data Analysis: Rats explored a radial-arm maze for 5 baseline (pre-injection) sessions. Post-DCS, place-cell firing rates were significantly reduced (p<0.003) for periods > 6 hr post injection, then returned to basal rates within 12 hr. Both out-of-field (non-specific) and in-field (location-specific) firing rates were reduced (Baker et al. DCS injected). Signal-to-noise ratios (i.e. ratios of in- to out-of-field firing) were actually enhanced by DCS (data not shown).

Results

Figure 1. Stable place-field activity was obtained from five or more baseline sessions from 63 CA1 complex-spiking place-cells from 7 rats. Post-DCS, place-cell firing rates were significantly reduced (p<0.003) for periods > 6 hr post injection, then returned to basal rates within 12 hr. Both out-of-field (non-specific) and in-field (location-specific) firing rates were reduced (Baker et al. DCS injected). Signal-to-noise ratios (i.e. ratios of in- to out-of-field firing) were actually enhanced by DCS (data not shown).

Discussion

• DCS administration transiently decreases the firing activity of complex spike place cells.
• Both chronic and acute administration of DCS decrease arc protein expression, but do not alter pAkt or total Akt expression.
• DCS in vivo functionally acts as a NMDAR agonist, competing for binding to NMDA receptors.

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Figure 2: Acute DCS injections reduced arc protein expression but not pAkt in the hippocampus

Figure 3: Chronic DCS injections reduced arc protein expression in the hippocampus (*p<0.05).