Short Communication

Methylphenidate has long-lasting metaplastic effects in the prefrontal cortex of adolescent rats

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HIGHLIGHTS

- Two week's methylphenidate (MPH) treatment enhanced LTP in the rat PFC in vivo.
- 15–18 days after the end of MPH treatment LTP remained strongly enhanced.
- Five months later LTP was no longer augmented.
- Could not be induced after high MPH doses.
- Doses of MPH that improved maze-learning also enhanced LTP in the same animals.

ABSTRACT

Methylphenidate (MPH) is widely used as a “nootropic” agent and in the treatment of disorders of attention, and has been shown to modulate synaptic plasticity \textit{in vitro}. Here we present \textit{in vivo} evidence that this MPH-induced metaplasticity can last long after the end of treatment. MPH (0, 0.2, 1 and 5 mg/kg) was administered daily to male rats from postnatal day 42 for 15 days. The animals were tested daily in a radial maze. Long-term potentiation (LTP), a marker of neural plasticity, was induced \textit{in vivo} in the prefrontal cortex after 2–3 h, 15–18 days or 5 months without treatment. The behavioral performance of the 1 mg/kg group improved, while that of animals that had received 5 mg/kg deteriorated. In the 1 and 5 mg/kg groups LTP induced 2–3 h after the last MPH treatment was twice as large as in the controls. Further, 15–18 days after the last MPH administration, in groups receiving 1 and 5 mg/kg, LTP was about fourfold higher than in controls. However, 5 months later, LTP in the 1 mg/kg group was similar to controls and in the 5 mg/kg group LTP could not be induced at all. No significant changes of LTP were seen in the low-dose group of animals (0.2 mg/kg). Thus, firstly, doses of MPH that improve learning coincide approximately with those that augment LTP. Secondly, MPH-induced increases in LTP can last for several weeks, but these may disappear over longer periods or deteriorate at high doses.

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Methylphenidate (MPH) is the most frequently used substance in the treatment of Attention Deficit Hyperactivity Disorder (ADHD; [1]). It is also widely used as a performance enhancing drug [2], helping to focus attention and maintain concentration particularly among adolescents and young adults [3]. Prolonged repetitive ingestion appears to modulate behaviors in adolescents in a lasting way [4]. In this context, it is possible that MPH induces lasting plastic changes in the neural circuitry underlying these modulations.

Animal behavioral studies have shown that MPH facilitates the acquisition of certain learning tests, albeit within a quite limited dose range. Berridge and Devilbiss [5] reported that in rats, a dose of 0.5 mg/kg improved performance of a delayed response task. But,