Effects of LSD on the dopaminergic neurons of Ventral Tegmental Area. An in vivo electrophysiological study

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Background: The effects of the hallucinogen D-lysergic diethilamide (LSD) are described as a 'mystical experiences', 'sensory journeys', pseudo-hallucinations, affective changes, enhancement of past memories. It was firstly synthetized in 1938 by A. Hofmann, but its mechanism of action has not yet completely elucidated. It is well known that LSD interacts with the serotonin (5-HT) system binding to 5-HT_1 and 5-HT_2 receptors (Peroutka and Solomon, 1973), decreasing the activity of 5-HT neurons in the Dorsal Raphe Nucleus (DRN) (Trulson and Jacobs, 1979) and increasing the firing rate of cortical neurons in the somatosensory cortex in rats (Marek and Aghajanian, 1996). However, little is known of its potential interactions with the dopamine (DA) neurons of the Ventral Tegmental Area (VTA). In this study, we first evaluated the effects of LSD on DA neuron activity in the parabrachial nucleus of VTA, and second, we compared these effects to those produced on 5-HT neurons in the DRN. Third, we pretreated rats with p-chlorophenylalanine (PCPA), an inhibitor of 5-HT synthesis, or with the 5-HT_{1A} antagonists WAY-100635, to test whether the effects of LSD on DA neurons are mediated by the 5-HT system. **Methods:** Using *in vivo* electrophysiology, we studied the effects of cumulative doses of LSD (10-90 ug/kg, i.v.) on DRN 5-HT and VTA DA neurons in Sprague Dawley male adult rats. A second group of rats was pretreated with PCPA (350 mg/kg, i.p.) 48-h and 24-h before VTA DA recordings and a third group was pretreated with the WAY-100635 (0.5 mg/kg, i.v.). **Results:** LSD induced a significant decrease of DRN 5-HT firing activity at the dose of 10 ug/kg, and switched off the firing at 20 ug/kg (n=6). These doses did not affect DA neuronal activity. At the dose of 60 ug/kg, LSD decreased DA firing activity (vehicle: 2.42 ± 0.95 Hz; LSD 60 ug/kg: 1.44 ± 0.61 Hz, n=6), while at 90 ug/kg it completely shut down VTA DA activity ($p<0.05$ versus vehicle, n=6). Notably, the injection of cumulative doses of the selective D2 antagonist haloperidol (0.05-15 mg/kg, i.v.) was able to reinstate the activity of DA neurons (1.53 ± 1.23 Hz, $p<0.05$, n=6). In PCPA-pretreated rats, LSD decreased the activity of VTA DA neurons similarly to non-treated rats (vehicle: 2.04 ± 0.64 Hz; LSD 60 ug/kg: 0.40 ± 0.29 Hz, $p< 0.05$, n=4), but in this case, haloperidol (0.05-0.25 mg/kg, i.v.) was not able to reinstate DA neuronal activity. The previous injection of WAY-100635 prevented the inhibitory effects of LSD on DA activity. **Discussion:** These results suggest that LSD modifies the DA system independently from the 5-HT system integrity. However, the 5-HT_{1A} receptor controls the effects of LSD over DA system. Furthermore, it confirms that the 5-HT system plays an inhibitory role on VTA DA neurons through the modulation of D2 receptor.