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Comparison of the long-term consequences of withdrawal from repeated amphetamine exposure in adolescence and adulthood on information processing and locomotor sensitization in mice

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Abstract
Repeated administration of the indirect dopamine receptor agonist amphetamine (AMPH) produces robust locomotor sensitization and additional behavioral abnormalities. Accumulating evidence suggests that the developmental timing of drug exposure can critically influence this effect. The present study compared the consequences of withdrawal from repeated AMPH exposure in adolescence and adulthood on information processing and locomotor sensitization in C57BL/6 mice. Animals were injected daily with AMPH (1 or 2.5 mg/kg) or vehicle on 7 consecutive days starting either from postnatal day 35 to 42, or from postnatal day 70 to 77, following which they were given a 4 week withdrawal period before behavioral and pharmacological testing commenced. We found that withdrawal from the higher dose of AMPH (2.5 mg/kg/day) given either in adolescence or adulthood similarly disrupted selective associative learning as measured by the latent inhibition paradigm. None of the AMPH withdrawal groups displayed alterations in sensorimotor gating in the form of prepulse inhibition. Withdrawal from adult AMPH exposure at both doses induced marked locomotor sensitization, whereas adolescent pre-treatment with the higher (2.5 mg/kg/day) but not lower (1 mg/kg/day) dose of AMPH potentiated the locomotor-enhancing effects of acute AMPH re-challenge. Our study suggests that withdrawal from repeated AMPH exposure in adolescence and adulthood has similar consequences on selective associative learning, but the two manipulations differ with respect to their efficacy to induce long-term locomotor sensitization to the drug. The latter finding supports the hypothesis that the precise developmental timing

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determines, at least in part, the impact on long-term dopamine-associated sensitization processes.

1. Introduction

Repeated administration of the indirect dopamine receptor agonist amphetamine (AMPH) is known to produce robust sensitization, a process whereby exposure to a particular stimulus such as a drug induces a potentiated response at subsequent exposures (Robinson and Becker, 1986). AMPH sensitization is expressed when initial exposure to the drug leads to an enhanced response to a subsequent drug challenge and typically involves a potentiation of dopamine-associated behaviors and neurotransmission such as increased locomotor responses and striatal dopamine release. Such potentiation can occur even if the initial and subsequent AMPH challenges are separated by a prolonged phase of drug withdrawal (Robinson and Becker, 1986; Paulson et al., 1991; Peleg-Raibstein et al., 2009). In addition to the enduring sensitized response to a subsequent AMPH challenge, withdrawal from repeated AMPH exposure is associated with long-term behavioral dysfunctions, including abnormalities in selective associative learning, sensorimotor gating, visual attention and attentional set shifting (Murphy et al., 2001; Russig et al., 2002, 2003, 2005; Tenn et al., 2003, 2005; Fletcher et al., 2005, 2007; Peleg-Raibstein et al., 2006a,b, 2008, 2009). In keeping with these behavioral manifestations, AMPH withdrawal models in rodents have also been widely used to experimentally explore and support the endogenous dopamine sensitization hypothesis of schizophrenia, which postulates that sensitization of the mesolimbic dopamine system may underlie the development of dopamine-associated psychotic abnormalities (Lieberman et al., 1997; Laruelle, 2000).

Numerous rodent studies show that the efficacy of AMPH withdrawal to induce behavioral dysfunctions is critically influenced by several experimental parameters, including duration of the drug withdrawal period, the precise AMPH dosing and administration regimen, and specific rat strain used (Murphy et al., 2001; Russig et al., 2002, 2003, 2005; Tenn et al., 2003, 2005; Fletcher et al., 2005, 2007; Peleg-Raibstein et al., 2006a,b, 2008, 2009). In addition, the developmental timing of drug exposure also seems to critically influence the nature and/or severity of behavioral sensitization to psychostimulant drugs (reviewed in Tirelli et al., 2003; Kuhn et al., 2010). With respect to this, there is an ongoing debate as to whether adolescent subjects are more vulnerable to psychostimulant-induced behavioral sensitization and neuronal adaptations compared to adult subjects. In favor of this interpretation, some experimental studies in rodents show that exposure to dopamine-related psychostimulant drugs such as AMPH or cocaine induce more robust behavioral and dopamine-related neuronal sensitization when given in adolescence as compared to equivalent drug exposure in adulthood (Laviola et al., 2001; Mathews et al., 2009, 2011; Kameda et al., 2011). These age-dependent effects parallel the observations of increased risk of drug abuse in adult human subjects who initiated first use in adolescence (Merline et al., 2004; Doremus-Fitzwater et al., 2010). However, other rodent studies report an increased potential for sensitization to dopamine stimulating drugs when given in adulthood as compared to exposure in adolescence (Kolta et al., 1990; Collins and Izenwasser, 2002; Frantz et al., 2007). Moreover, there is a relative lack of studies directly comparing the long-term consequences of (repeated) AMPH exposure in adolescence and adulthood on long-term behavioral functions other than locomotor sensitization to the drug. Additional direct comparisons between the long-term consequences of repeated psychostimulant drug exposure in adolescence and adulthood are thus clearly warranted.

The present study addressed this issue by comparing the consequences of withdrawal from repeated AMPH exposure in adolescent and adult mice on information processing and locomotor sensitization. Information processing was studied using the paradigms of prepulse inhibition (PPI) and latent inhibition (LI). PPI refers to the reduction of startle reaction to a startle-eliciting stimulus (pulse) when it is shortly preceded by a weak stimulus (prepulse) (Braff et al., 2001). It is an operational measure of sensorimotor gating which reflects the ability to filter or gate intrusive sensorymotor information, and it is disrupted in numerous neuropsychiatric disorders, including schizophrenia, autism, obsessive-compulsive disorder and Huntington's disease (Braff et al., 2001). LI is a form of selective associative learning, in which non-reinforced pre-exposures to a to-be-conditioned stimulus (CS) retards subsequent conditioning between the same CS and the unconditioned stimulus (US) (Lubow, 2005). LI is considered to index an organism's capacity to ignore irrelevant stimuli and is disrupted in at least a subset of schizophrenic patients, especially in acutely ill subjects experiencing marked positive symptoms (Weiner 2003; Lubow, 2005; Weiner and Arad, 2009). The paradigms of PPI and LI were selected because they can sensitively capture the behavioral effects of withdrawal from repeated AMPH exposure in rats (Murphy et al., 2001; Russig et al., 2002, 2003, 2005; Tenn et al., 2003, 2005; Fletcher et al., 2005, 2007; Peleg-Raibstein et al., 2006a,b, 2008, 2009). In addition to the assessment of PPI and LI, we measured locomotor activity in response to AMPH re-exposure in order to confirm the presence of locomotor sensitization to AMPH following AMPH withdrawal across adolescence or adulthood.

2. Experimental procedures

2.1. Animals

The subjects were naïve male C57BL/6 mice bred in a specific pathogen free (SPF) breeding facility (Physiology and Behavior Laboratory, ETH Zurich, Schwerzenbach, Switzerland). All breeding pairs were originally obtained from Charles River Laboratories (Sulzfeld, Germany). All animals used in this study were weaned