



Prenatal exposure to modafinil alters behavioural response to methamphetamine in adult male mice



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ABSTRACT

Modafinil is a psychostimulant drug prescribed for treatment of narcolepsy. However, it is used as a “smart drug” especially by young adults to increase wakefulness, concentration and mental performance. Therefore, it can also be used by women with childbearing potential and its developmental effects can become a concern. The aim of this study was to assess behavioural and immune effects of prenatal modafinil exposure in mice and to evaluate the reaction to methamphetamine exposure on these animals in adult age.

Pregnant female mice were given either saline or modafinil (50 mg/kg orally) from gestation day (GD) 3 to GD 10 and then a challenge dose on GD 17. The male offspring were treated analogously at the age of 10 weeks with methamphetamine (2.5 mg/kg orally). Changes in the spontaneous locomotor/exploratory behaviour and anxiogenic profile in the open field test were assessed in naïve animals, after an acute and 8th modafinil dose and the challenge dose following a 7-day wash-out period. One month after completion of the behavioural study, the leukocyte phagocytosis was examined by zymosan induced and luminol-aided chemiluminescence assay *in vitro*.

The modafinil prenatally exposed mice showed basal hypolocomotion, increased anxiety, lower locomotor effect of acute methamphetamine and increased vulnerability to behavioural sensitization. The leukocyte activity did not show significant differences.

Prenatal modafinil exposure alters basal behavioural profile, decreases acute effect of methamphetamine and enhances vulnerability to development of behavioural sensitization at adulthood. This may lead to higher vulnerability to development of addiction.

1. Introduction

Modafinil is a psychostimulant drug indicated for treatment of narcolepsy (Abad and Guilleminault, 2017; Barateau et al., 2016). However, modafinil is used also as a “smart drug” by wide populations (Vargo and Petroczi, 2016) to increase wakefulness, concentration and overall mental performance (Wood et al., 2014). The mechanism of action is complicated but the main effect seems to be exerted similarly as in cocaine or amphetamines via blockade of dopaminergic transporter (DAT), preventing re-uptake of dopamine (DA) back to the presynaptic neuron (Bobak et al., 2016). Histamine, orexin/hypocretin (Dell’Osso et al., 2014) and adenosine systems’ involvement was also recently suggested (Lazarus et al., 2017). Modafinil has certain addictive potential (Volkow et al., 2009) but it is generally considered safe when not used regularly (Wisor, 2013).

In preclinical studies modafinil was shown to cause a robust hyperlocomotion in rodents comparable with the effect of amphetamine, methamphetamine (Simon et al., 1995) or MDMA (3,4-

methylenedioxymethamphetamine, “ecstasy”) (Machalova et al., 2012). However, it had a different ethological profile in the mouse model of agonistic behaviour where modafinil produced anxiolytic-like and antiaggressive-like effects (Machalova et al., 2010). D1 receptor appears to exert a primary role in modafinil-induced effects on spontaneous exploration (Young et al., 2011) while D2 agonistic profile probably contributes to its antidepressant-like properties observed in the Porsolt test (Mahmoudi et al., 2015).

Similarly as cocaine or amphetamine-like psychostimulants modafinil was shown to exert behavioural sensitization (Paterson et al., 2010; Slais et al., 2010), a phenomenon described as increased behavioural response (usually locomotor) to a repeated intermittent administration of a stable dose of addictive substance (Landa et al., 2014; Robinson, 1984; Schmidt and Beninger, 2006). This phenomenon may lead to decreased drug consumption which should not be mistaken for a treatment effect (Kucerova et al., 2009, 2012). Pre-clinical studies use a variety of paradigms to develop behavioural sensitization but they all assess the locomotor-exploratory activity at basal conditions before any

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Table 1
Study design.

	GD 3	GD 4	GD 5	GD 6	GD 7	GD 8	GD 9	GD 10	GD 11	GD 12	GD 13	GD 14	GD 15	GD 16	GD 17								
Mothers:																							
SAL (n = 15)		saline orally (SAL)																					
MDF (n = 15)		modafinil (50 mg/kg) orally (MDF)																					
Male offspring:	PND 70	PND 71	PND 72	PND 73	PND 74	PND 75	PND 76	PND 77	PND 78	PND 79	PND 80	PND 81	PND 82	PND 83	PND 84	PND 85	PND 86	PND 87	PND 88	PND 89	PND 90	PND 91	
prenatal-																							
postnatal																							
treatment																							
SAL-SAL (n = 12)	No treatment																						
SAL-METH (n = 12)						saline orally (SAL)		saline orally (SAL)															
MDF-SAL (n = 12)						methamphetamine (2.5 mg/kg) orally (METH)		methamphetamine (2.5 mg/kg) orally (METH)															
MDF-METH (n = 12)																							
Test	OF					OF																	

The tables show treatment schedule used in mothers and their male offspring. GD: gestation day, PND: postnatal day, SAL: saline, MDF: modafinil, METH: methamphetamine, OF: open-field test.

treatment, after an acute drug exposure, then after a chronic treatment and lastly following a challenge dose after a period of wash-out (Landa et al., 2006, 2008; Paterson et al., 2010). An acute dose of a psychostimulant leads to increased locomotion and further increase after chronic exposure to the drug is considered development of sensitization. Equally high or higher locomotor response to a challenge dose is supposed to reflect expression of behavioural sensitization known to be present long after the drug discontinuation (Landa et al., 2014). This is typically seen in methamphetamine and related substances such as MDMA (3,4-methylenedioxymethamphetamine or ecstasy) (Kucerova et al., 2006; Landa et al., 2009). A cross-sensitization to modafinil stimulatory effects on locomotor behaviour were also shown in mice after repeated treatment with methamphetamine (Merhautova et al., 2012) or cocaine (Wuo-Silva et al., 2016). This might support a suggestion that responses to modafinil stimulatory effects can be higher in psychostimulant abusers. Such evidence should be also taken into account when modafinil is off-label prescribed in drug abusers (Castells et al., 2016; Phillips et al., 2014).

Furthermore, modafinil as a wake-promoting agent might possess certain immunosuppressant effects analogously as a lack of sleep especially in patients using this drug for other than narcoleptic condition. Furthermore, a preliminary evidence shows an increase of C-reactive protein after an acute modafinil dose (Kim, 2012). However, the immunomodulatory properties of modafinil have not been described in detail.

Given that modafinil is quite often used as a smart drug due to its cognitive enhancing effects and moderate psychostimulation (Vargo and Petroczi, 2016; Wood et al., 2014) it can be taken by young women who may be or become pregnant. The prevalence of modafinil use in pregnancy is not established but it is recommended to avoid its use at early stages of gestation (Thorpy and Dauvilliers, 2015). Results from the pre-registration studies on reproductive and developmental toxicity revealed increased incidence in skeletal variations, embryo-foetal lethality and showed no teratogenic effect or impairment of growth or development of the offspring (EMA, 2016). However, these studies do not include behavioural profile as a marker of neurodevelopmental effects or immune changes. The current classification by the Australian categorisation system for prescribing medicines in pregnancy is B3, i.e. drugs which have been taken by only a limited number of pregnant women without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans (Administration, 2017).

Importantly, there is an extensive evidence of developmental toxicity of other psychostimulants, especially amphetamines. There are consistent clinical reports showing impaired pregnancy outcome, cognitive deficits and abnormal behaviour (Forray and Foster, 2015). Preclinical studies have shown analogous results, i.e. poor pregnancy results such as development of neonatal reflexes (McDonnell-Dowling and Kelly, 2015a) after oral or subcutaneous administration (McDonnell-Dowling and Kelly, 2016), memory impairment (Fialova et al., 2015; Macuchova et al., 2014; Slamberova et al., 2014) and increased anxiety in the adult offspring as assessed by different behavioural tests (Macuchova et al., 2016; Slamberova et al., 2015). In a similarly designed study a challenge dose of methamphetamine in adulthood in animals prenatally exposed to the same drug led to higher epileptiform neuronal activity in female rats (Matejovska et al., 2014). Furthermore, adult animals prenatally exposed to methamphetamine, but also methylphenidate, were shown to have higher perception of reward suggesting increased vulnerability to addiction (Lloyd et al., 2013).

To our knowledge no study has yet evaluated reactivity to abused psychostimulants in the prenatally modafinil-exposed individuals. Therefore, the aim of this study was to combine assessment of potential changes in the spontaneous locomotor/exploratory behaviour and

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