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How various drugs affect anxiety-related behavior in male and female rats prenatally exposed to methamphetamine

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ABSTRACT

Different forms of anxiety-related behavior have been reported after a single drug use of many abused substances, however, less is known about how males and females are affected differently from exposure to various drugs. Furthermore, chronic prenatal methamphetamine (MA) exposure was shown to predispose the animal to an increased sensitivity to drugs administrated in adulthood. Using the Elevated plus-maze test (EPM), the first aim of the present study was to examine how male and female rats are affected by acute drug treatment with subcutaneously (s.c.) administrated (a) MA (1 mg/kg); (b) drugs with a similar mechanism of action to MA: amphetamine (AMP, 1 mg/kg), cocaine (COC, 5 mg/kg), 3,4-methylenedioxymethamphetamine (MDMA, 5 mg/kg); and (c) drugs with different mechanisms of action: morphine (MOR, 5 mg/kg), and Δ 9-tetrahydrocannabinol (THC, 2 mg/kg). The second aim was to determine if prenatally MA-exposed (5 mg/kg) animals show an increased sensitivity to adult drug treatment. The parameters analyzed were divided into two categories: anxiety-related behavior and anxiety-unrelated/exploratory behavior. Our results showed in female rats a decreased percentage of the time spent in the closed arms (CA) after MA, and an increased percentage of the time spent in the open arms (OA) after MA, AMP, and COC treatment, indicating an anxiolytic-like effect. In females, MDMA and THC treatment increased the percentage of the time spent in the CA. An increased percentage of the time spent in the CA was also seen after MOR treatment in females as well as in males, indicating an anxiogenic-like effect. As far as the interaction between prenatal MA exposure and adult drug treatment is concerned, there was no effect found. In conclusion, it seems that: (a) in some cases female rats are more vulnerable to acute drug treatment, in terms of either anxiogenic- or anxiolytic-like effects; (b) prenatal MA exposure does not sensitize animals to the anxiety-related effects of any of the drugs.

1. Introduction

Growing evidence based on animal studies have shown that there are differences between the sexes in their vulnerability to the effect of different drugs, with females found to be more vulnerable (Bisagno et al., 2003; Bobzean et al., 2014; Lynch et al., 2002; Macúchová et al., 2014; Roth et al., 2004; Schindler et al., 2002; Schutová et al., 2013; Šlamberová et al., 2013). It has been suggested that the higher responsiveness of females compared to males is based on different reactions of the serotoninergic (5-HT) and dopaminergic (DA) systems to drugs of abuse, and the effect of gonadal hormones on the neurotransmission (Bobzean et al., 2014; Lynch et al., 2002; Roth et al., 2004), as well as on gender differences in drug metabolism (Baba et al., 1988; Kato and Yamazoe, 1992; Roth et al., 2004). Moreover, female rats show a greater behavioral response to drugs in the estrus, when the striatal DA system is stimulated by gonadal hormones (Lynch et al., 2001; Peris et al., 1991; Sell et al., 2000). Similarly, women describe a greater subjective response to drugs in the follicular phase of the menstrual cycle, when levels of estrogen are rising and progesterone is at the lowest level (Bobzean et al., 2014).

There are several animal behavior paradigms used to model anxiety, from those the Elevated plus-maze test (EPM) is a test based on exploratory behavior and a natural aversion of an animal towards open and high places (Fernandez Espejo, 1997; Griebel, 1995; Pellow et al., 1985). The pivotal role in the anxiety-related process in the EPM has been demonstrated to be played, besides others, by the central nucleus of amygdala, hippocampus and raphe nuclei (File and Gonzalez, 1996; Killcross et al., 1997; Walker and Davis, 2002). As far as the neurotransmitters connected to anxiety-related behavior are concerned, interactions

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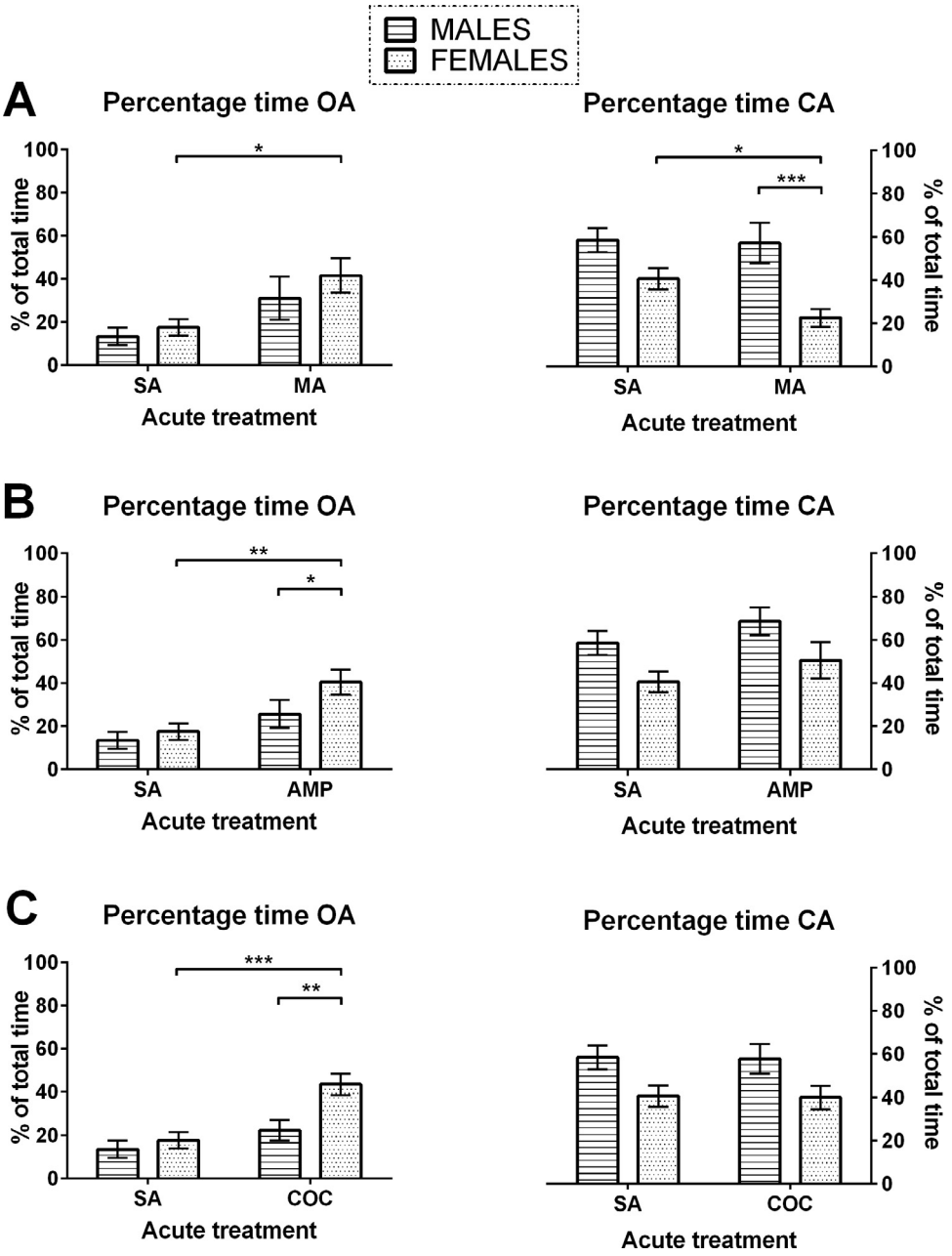

Fig. 1. The effect of MA (A), AMP (B), and COC (C) on two parameters of anxiety-related behavior of female and male rats in the EPM regardless of prenatal drug exposure. Left- percentage of the time spent in the open arms (OA). Females with drug vs females with SA * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; females with drug vs males with drug * $p < 0.05$, ** $p < 0.01$. **Right-** percentage of the time spent in the closed arms (CA). Females with MA vs females with SA * $p < 0.05$; females with MA vs males with MA *** $p < 0.001$.Values are means ± SEM, n = 16.

between DA and 5-HT have been shown to be responsible for its behavioral and physiological manifestations (Robinson et al., 2006). Both neurotransmitter systems, DA and 5-HT, are highly affected by acute treatment with different drugs of abuse. It has been well established that methamphetamine (MA), amphetamine (AMP), cocaine (COC), and 3,4-methylenedioxymethamphetamine (MDMA) increase extracellular levels of DA, 5-HT and noradrenaline (NA) neurotransmission (Rothman and Baumann, 2003). The monoamine transporter affinity differs for MA and AMP (NA □ DA □ 5-HT), whereas cocaine seems to have a higher affinity for 5-HT (Ritz and Kuhar, 1989). On the other hand, another derivative of amphetamine – MDMA – was shown to stimulate the 5-HT release the most from these three monoamine systems (Schmidt et al., 1987). The situation with the neurotransmitter release is different with acute treatment with morphine (MOR) and Δ 9-tetrahydrocannabinol (THC). MOR directly activates the opioid receptor, and THC primarily acts at the cannabinoid receptors, moreover, both drugs indirectly increase DA release (Johnson and North, 1992; Szabo et al., 2002), and also stimulate a 5-HT neurotransmission after acute treatment (Johnson et al., 1981; Yarbrough et al., 1973). As the first aim of the present study we decided to evaluate if male and female rats are affected differently by various drugs in terms of changes in anxiogenic and anxiolytic behavior. We tested the effect of an acute treatment with (a) MA; (b) drugs with similar mechanism of actions to MA: AMP, COC, and MDMA; and (c) drugs with different mechanisms of action to MA: MOR and THC.