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Increased affective ultrasonic communication during fear learning in adult male rats exposed to maternal immune activation

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ABSTRACT

Maternal exposure to infection during pregnancy greatly increases the risk of psychopathology in the offspring. In support of clinical findings, rodent models of maternal immune activation (MIA) show that prenatal exposure to pathogens can induce phenotypic changes in the offspring associated with schizophrenia, autism, depression and anxiety. In the current study, we investigated the effects of MIA via polyinosinic:polycytidylic acid (poly I:C) on emotional behavior and communication in rats. Pregnant rats were administered poly I:C or saline on gestation day 15 and male offspring were tested in an auditory fear conditioning paradigm in early adulthood. We found that prenatal poly I:C exposure significantly altered affective signaling, namely, the production of aversive 22-kHz ultrasonic vocalizations (USVs), in terms of call number, structure and temporal patterning. MIA led to an increase in aversive 22-kHz USVs to 300% of saline controls. Offspring exposed to MIA not only emitted more 22-kHz USVs, but also emitted calls that were shorter in duration and occurred in bouts containing more calls. The production of appetitive 50-kHz USVs and audible calls was not affected. Intriguingly, alterations in aversive 22-kHz USV emission were observed despite no obvious changes in overt defensive behavior, which highlights the importance of assessing USVs as an additional measure of fear. Aversive 22-kHz USVs are a prominent part of the rat's defensive behavioral repertoire and serve important communicative functions, most notably as alarm calls. The observed changes in aversive 22-kHz USVs show that MIA has long-term effects on emotional behavior and communication in exposed rat offspring.

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1. Introduction

Epidemiological studies show that maternal infection during pregnancy is associated with an increased prevalence of neuropsychiatric disorders, such as schizophrenia and autism, in the offspring (Brown & Derkits, 2010; Patterson, 2011). Rodent models of maternal immune activation (MIA) have been developed in attempt to elucidate the relationship between prenatal exposure to infection and the emergence of adult psychopathology (Meyer & Feldon, 2012). Polyinosinic:polycytidylic acid (poly I:C) is a viral mimic used as an immunostimulatory agent because it evokes a maternal immune response, namely pro-inflammatory cytokine release, without causing the full reaction normally observed after viral infection (e.g. production of antiviral antibodies) (Meyer & Feldon, 2012). In previous studies, poly I:C administration to pregnant mice or rats during specific gestational periods caused a number of behavioral, neuroanatomical and neurochemical deficits in offspring (reviewed in Boksa, 2010). The most consistent behavioral finding is a deficit in sensorimotor gating (Boksa, 2010). Other studies have reported disruptions in social behavior (Baharnoori et al., 2010; Ehninger et al., 2012; Malkova et al., 2012; Patterson, 2011; Smith et al., 2007). Thus, the poly I:C model of MIA has gained acceptance as a model of neurodevelopmental disorders such as schizophrenia and autism (Meyer & Feldon, 2012; Patterson, 2011).

Recent evidence suggests that the MIA model may also be applicable to mood and/or anxiety disorders. Specifically, MIA via poly I:C was shown to induce anxiety- and depressive-like behavior in rodents. This includes a reduction in exploration and time spent in center in the open field test (Smith et al., 2007), decreased social interaction (Bitanihirwe et al., 2010; Ehninger et al., 2012; Malkova et al., 2012; Smith et al., 2007), lower sucrose consumption (Bitanihirwe et al., 2010) and decreased time spent in open arms on the elevated plus maze (Abazyan et al., 2010; Yee et al., 2011a).

Despite the fact that communication is affected in a number of severe neuropsychiatric diseases associated with maternal infection,

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including autism and schizophrenia as well as affective disorders (American Psychiatric Association, 2000; DeLisi, 2001; Frith & Happe, 1994; Püschel et al., 1998; Stassen et al., 1995), very little is known about the effects of MIA on communication in rodent models. So far, communication has only been assessed in mice and almost exclusively during the very first days of postnatal life (Baharnoori et al., 2010; Malkova et al., 2012; Patterson, 2011).

The goal of the present study was to investigate the effects of MIA on defensive behavior and affective communication in adult rats during fear conditioning. We hypothesized that rats exposed to MIA during fetal development would display an anxiety-like phenotype with increased affective communication in adulthood. In rats, freezing is the most commonly used behavioral measure in fear conditioning tests and serves to exemplify fear and defensive behavior, as well as the subject's emotional state (Blanchard & Blanchard, 1969; Fendt & Fanselow, 1999). Besides performing a detailed analysis of the rat's overt defensive behavioral repertoire, including freezing, we also sought to investigate ultrasonic vocalizations (USVs) as a measure of affective communication. Depending on the emotional valence of the context (Knutson et al., 2002), adult rats produce two distinct types of USVs: 50-kHz USVs in appetitive situations, such as play (Knutson et al., 1998) or reward anticipation (Knutson et al., 1999) and 22-kHz USVs in aversive situations, such as predator exposure (Blanchard et al., 1991) or fear conditioning (Borta et al., 2006; Wöhr et al., 2005). Aversive 22-kHz USVs are a prominent part of the rat's defensive behavioral repertoire. Both appetitive 50-kHz USVs as well as aversive 22-kHz USVs serve important communicative functions. Playback experiments have shown that USVs induce call-specific behavioral responses in the receiver. Appetitive 50-kHz USVs induce social approach behavior (Wöhr & Schwarting, 2007), which supports the notion that they serve as social contact calls. In contrast, aversive 22-kHz USVs lead to freezing behavior, which indicates an alarm function: namely, to warn conspecifics about external danger (Blanchard et al., 1991; Endres et al., 2007; Wöhr & Schwarting, 2007; Wöhr & Schwarting, 2010). These opposite behavioral responses are paralleled by distinct patterns of brain activation. Aversive 22-kHz USVs induce activation in the brain areas implicated in fear and anxiety, including the amygdala and periaqueductal gray, while appetitive 50-kHz USVs activate the nucleus accumbens, which is highly relevant for reward processing (Parsana et al., 2012; Sadananda et al., 2008).

We utilized an established rat model of MIA via poly I:C treatment to pregnant rats on gestation day (GD) 15 and subjected the offspring to fear conditioning testing in early adulthood. Overt behavior and detailed USV analyses were carried out to examine the effects of prenatal poly I:C exposure.

2. Methods

All experiments were performed in accordance with the European Communities Council Directive of November 24, 1986 (86/EEC), including the Recommendation 2007/526/EC of June 18, 2007 and approved by the Lower Saxony Federal State Office for Consumer Protection and Food Safety, Germany.

2.1. Animals and prenatal treatment

Experimental animals were generated at Harlan Laboratories (Horst, the Netherlands) as described by Yee et al. (2011a). Briefly, 3-month-old female Sprague Dawley rats were mated and the day after copulation was defined as day 1 of pregnancy. On GD 15, pregnant rats were slightly anesthetized with 2.5% isoflurane and given a single tail vein injection of poly I:C (4.0 mg/kg, Sigma, Germany) dissolved in saline or an equivalent volume of saline alone. Male offspring of poly I:C- and saline-treated rats were sent to the German Primate Center (Göttingen, Germany) at age 21 days. Rats were separated from littermates and distributed into cages designated as "poly I:C" ($n = 7$) or "saline" ($n = 6$) groups. They were group-housed (3-4/cage) under a 12-h reverse light cycle (lights on at 18:00).

2.2. Fear conditioning protocol

When rats reached adulthood (age 71 days), they underwent an auditory fear conditioning paradigm known to be efficient at eliciting aversive 22-kHz USVs, as described by Wöhr et al. (2005). Fear conditioning was conducted in a shock chamber (33.5 × 35 × 38 cm) made of gray and transparent plastic walls. A loudspeaker was mounted in one wall to present the tone stimulus (conditioned stimulus, CS; 3-kHz sine wave tone of 20 s duration and about 72 dB). The floor of the shock chamber consisted of stainless steel rods spaced 1 cm apart. The chamber was housed within a sound-attenuating isolation cubicle (Colbourn Instruments, Whitehall, PA, USA) equipped with a black-and-white CCD camera (Conrad Electronics, Hirschau, Germany) for video recording. A stand-alone shocker (Med Associates, St. Albans, VT, USA) administered the shock stimulus (unconditioned stimulus, US) via the rod floor. The US was a 0.5 mA scrambled shock (120 V peak-to-peak amplitude) of 500 ms duration. Stimulus timing and delivery were controlled by the Presentation program (Neurobehavioral Systems, Albany, CA, USA).

The fear conditioning procedure was carried out over 3 days. On day 1 (habituation), a rat was placed into the shock chamber for 11 min without CS or US presentation. Day 2 (fear conditioning) started with an initial 180 s pre-shock period (min 1–3), followed by six CS/US pairings (min 4–11); each pairing was followed by a 60-s inter-stimulus interval (ISI). The US was given during the last 500 ms of the 20-s CS. Day 3 (fear testing) started again with an initial 180-s context phase (min 1–3); then six tones (CS) were presented for 20 s each, with a 60-s ISI (min 4–11). All animals were tested between 8:00 and 17:00 in alternating (between groups) and randomized order.

2.3. USV recording and analysis

USVs were recorded for the entire testing duration on each day of the 3-day procedure using a condenser ultrasound microphone (CM16; Avisoft Bioacoustics, Berlin, Germany) mounted in the shock chamber roof and connected to a computer with recording software (Avisoft Recorder) via Avisoft UltraSoundGate hardware (USG416Hb; sampling rate: 250 000 Hz; format: 16 bit).

Avisoft SASLab Pro (Version 4.51; Avisoft Bioacoustics) was used for acoustic analysis of USV recordings (as in Wöhr et al., 2005). The latency to call and number of 22-kHz USVs and 50-kHz USVs were determined. For the 22-kHz USVs, calls were divided into those starting a bout vs. those within a bout according to the duration of the interval between two calls. A bout was defined as a call or a number of calls, separated from others by intervals longer than 320 ms (van der Poel & Miczek, 1991; van der Poel et al., 1989). The number of bouts and calls per bout were determined. Additionally, a detailed spectrographic analysis of call parameters was performed and call duration, peak amplitude and peak frequency were determined for each individual call based on the average spectrum of the entire call (Borta et al., 2006; Wöhr et al., 2005). Finally, the number of audible calls in response to US application was counted. Exemplary spectrograms of 22-kHz USVs, 50-kHz USVs and audible calls are shown in Fig. 1A–C, respectively.

2.4. Overt behavior

Overt behavior was scored from video recordings by an experienced observer blind to group assignment. The time spent

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