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Enhanced prepulse inhibition of startle using salient prepulses in rats

Stephan Röskam *, Michael Koch [1]

Department of Neuropharmacology, Brain Research Institute, University of Bremen, P.O. Box 33 04 40, 28334 Bremen, Germany

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Abstract

Prepulse inhibition (PPI) of the startle reflex occurs when a non-startling stimulus is presented shortly prior to the startling stimulus. PPI is an operational measure for sensorimotor gating. PPI in humans is enhanced by attention, but there is no evidence yet for attentional modulation of PPI in animals. We here combined PPI and conditioned inhibition paradigms in order to investigate attentional modulation of PPI in rats. PPI was assessed before and after training for conditioned inhibition of fear with the conditioned stimulus (auditory CS) and conditioned inhibitor (visual CI) as prepulses. The CI significantly enhanced PPI after training, whereas presentation of the CS had no effect on PPI. These data suggest attentional modulation of PPI in rats by biologically salient prestimuli. This new paradigm may be useful for examining attentional modulation of PPI in animals and to compare attentional modulation in humans and animals.

Keywords: Acoustic startle response; Attention; Sensorimotor gating

1. Introduction

The acoustic startle response (ASR) is a fast brainstem-mediated reflex elicited by sudden noise. It consists of contractions of face, neck and skeletal muscles and is accompanied by changes in sympathetic activity. The ASR is found in many species and is considered as a defensive, protective reflex against predators and environmental threat (Yeomans et al., 2002).

The ASR can be reduced by presenting a non-startling tactile, visual or acoustic stimulus (prepulse) shortly prior to the startling stimulus (pulse) (Koch, 1999). This phenomenon is termed prepulse inhibition (PPI) and has been shown in a variety of species, including humans. Graham (1975) first described PPI in humans and hypothesized that it reflects a 'preattentive filter mechanism'. In its elaborated form, this hypothesis posits that the detection and early processing of the prepulse is protected by the activation of inhibitory mechanisms, which reduce further stimulation in order to facilitate stimulus processing and recognition. PPI has also been conceptualized as a 'sensorimotor gating mechanism', filtering out distracting stimuli in order to prevent sensory overload (Braff and Geyer, 1990). Interest in the mechanisms mediating and regulating PPI has been fueled by the fact that several neuropsychiatric disorders show impairments of PPI (Braff et al., 2001).

PPI occurs during the first prepulse–pulse presentation and is, therefore, not due to learning or habituation. Since PPI is found in decorticated (Ison et al., 1991) and anesthetized rats (Hammond and Ison, 1973) and in humans while sleeping (Silverstein et al., 1980), it probably reflects an automatic process without cognitive regulation and independent of attentional and voluntary modulations. However, there is evidence for attentional modulation of PPI in humans indicating that PPI is enhanced if the subjects attended to the prepulse (e.g., Dawson et al., 1993; Filion et al., 1993; Bohmelt et al., 1999; Filion and Poje, 2003; Heekeren et al., 2004). Filion et al. (1993) demonstrated that subjects who attended the prepulse showed enhanced PPI at an interstimulus interval (ISI) of 120 ms compared to subjects who ignored the prepulse, suggesting that at this short ISI attentional modulation already influenced PPI. They speculated that although PPI is primarily an automatic,

* Corresponding author. Tel.: +49 421 218 2438; fax: +49 421 218 4932.
E-mail addresses: stroesk@uni-bremen.de (S. Röskam), michael.koch@uni-bremen.de (M. Koch).
[1] Tel.: +49 421 218 7278; fax: +49 421 218 4932.

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preattentive mechanism, it might be affected by top-down attentional processes (Filion et al., 1998). It is worth mentioning that attentional effects on PPI were repeatedly found for long (e.g., >120 ms), but not for shorter ISIs (Filion et al., 1993; Hawk et al., 2002; Filion and Poje, 2003). A study by Bradley et al. (1993) revealed in a crossmodal experimental design that at an ISI of 300 ms the ASR is significantly reduced by focussing the attention on a visual prepulse, supporting the theory of attentional processes influencing PPI. Heekeren et al. (2004) introduced a novel paradigm for the study of attentional modulation of PPI, in which the subjects directed their attention both to the prepulse and the pulse and found an increased PPI at an ISI of 240 ms, but not at the shorter ISI of 100 ms. Taken together, these findings strongly support the idea that PPI can be influenced by attentional modulation.

PPI has been shown to be a cross-species, translational paradigm for the study of sensorimotor gating mechanisms in humans and in experimental animals (Swerdlow et al., 2001). Hence, it is surprising, that, except for one study published in abstract form (Varty et al., 1997), there are no studies examining attentional modulation of PPI in animals. This is particularly striking, since some PPI deficits induced by psychotomimetic drugs haven been attributed to attentional deficits rather than impairment of sensorimotor gating (Davis et al., 1990; Campeau and Davis, 1995).

Since the ASR is a sensitive measure of positive and negative emotional value (Lang, 1995), it is difficult in animal experiments to use behaviourally salient stimuli that would not affect baseline ASR magnitude. However, in conditioned inhibition of fear paradigms, the conditioned inhibitor (CI) signals that the conditioned stimulus (CS) will *not* be followed by a footshock. Therefore, the CI is certainly attended by the rat due to its salience as a predictor of the absence of shock, although it does not affect the ASR magnitude (Falls and Davis, 1997). The present study investigated attentional modulation of PPI in rats using a combined PPI/conditioned inhibition of fear paradigm. Unfortunately, the temporal characteristics of PPI and fear-conditioning are difficult to combine, because PPI dissipates at ISIs beyond 500 ms, whilst fear conditioning, and conditioned inhibition thereof, usually requires the presentation of the CS/CI for some seconds. Hence, we have to concede that the combination of these paradigms is mutually sub-optimal.

2. Methods

Male Wistar rats ($n=12$; 200–250 g; Harlan-Winkelmann, Germany) were housed in groups of six under standard ambient conditions under a 12-h light–dark cycle (lights on at 0700). They had free access to tap water and received 12 g of rat chow per day per rat (keeping the animals on approximately 85% of their free-feeding weights throughout testing). The experiments were performed in accordance with the NIH ethical guidelines for the care and use of laboratory animals for experiments, and were approved by the local animal care committee.

An automated commercial startle response system (TSE, Germany) was used for the measurement of the ASR, PPI and "freezing", as well as for fear-conditioning and conditioned inhibition thereof. This apparatus consisted of three sound-attenuated chambers equipped with movement-sensitive measuring platforms, two loudspeakers and a light emitting diode (LED) per chamber. Startle cages (27 cm × 9 cm × 10 cm) were equipped with a grid floor through which the unconditioned stimulus (US), a 300 ms 0.6 mA footshock, could be administered. The conditioned stimulus (CS) for fear-conditioning (paired with the US) was a 300 ms, 10 kHz, 72 dB SPL tone ($tone^+$ trials), the conditioned inhibitor (CI; predicting the absence of footshock) for conditioned inhibition training was a 300 ms light produced by the LED (intensity: 32 mcd) ($light \rightarrow tone^-$ trials). PPI was assessed before and after fear-conditioning and conditioned inhibition training with CSs and CIs as prepulses. The ISI between the prepulse (CS or CI) and the pulse was 300 ms. The ASR was elicited by a 100 dB white noise pulse (duration 20 ms, 0 ms rise/fall times). The background noise level was 60 dB sound pressure level (SPL).

On the first day, PPI was measured after an acclimatization time of 5 min, during which the rat received no stimulus except the background noise. Then 10 initial startle stimuli were presented first in order to habituate the rats to a stable ASR baseline. After habituation, the PPI experiment started with six different trial types presented in a pseudorandomized order: (1) trial: pulse alone, (2) trial: no stimulus, (3) trial: prepulse alone (tone, CS), (4) trial: prepulse alone (light, CI), (5) trial: prepulse–pulse (CS preceding the pulse without delay), (6) trial: prepulse–pulse (CI preceding the pulse without delay). A total of 15 presentations of each trial type was given in a pseudorandomized order at a mean intertrial interval (ITI) of 20 000–30 000 ms. PPI was calculated as the percent decrease of ASR in prepulse–pulse trials compared to pulse alone trials ($100 \times ((\text{pulse alone trial} - \text{prepulse–pulse trial}/\text{pulse alone trial}))$, where trial type 3 (tone/CS) and trial type 4 (light/CI) served as prepulses. On days 2 and 3, animals were placed in the startle chambers, and, after an acclimatization of 5 min, they received a fear-conditioning training with 10 $tone^+$ trials. The US was presented simultaneously with the tone CS at a mean ITI of 2 min (1.5–2.5 min). On days 4 and 5, the rats were trained for conditioned inhibition: they received 10 $light \rightarrow tone^-$ trials and five $tone^+$ trials in a pseudorandomized order at a mean ITI of 2 min (range 1.5–2 min). A $light \rightarrow tone^-$ trial consisted of a 300 ms light followed by a 300 ms, 10 kHz, 72 dB SPL tone. Twenty-four hours later (day 6), PPI was assessed. This test was identical to the PPI experiment conducted before fear-conditioning and conditioned inhibition training. The % PPI values were calculated