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Pharmacological and parametrical investigation of prepulse inhibition of startle and prepulse elicited reactions in Wistar rats

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ABSTRACT

Prepulse inhibition (PPI) is the inhibition of an acoustic startle response (ASR) that is observed when a weak prepulse is presented shortly before a startling stimulus. Here we studied in Wistar rats the dependence of PPI on variations of the interstimulus interval (ISI; from 25–1020 ms) after treatment with various drugs that are known to disrupt PPI. The motor response to the prepulse itself (prepulse elicited reaction, PER) was also studied. The direct dopamine receptor agonist apomorphine, the non-competitive NMDA glutamate receptor antagonist MK-801, and the cannabinoid CB1 receptor agonist WIN 55,212-2 all reduced PPI, depending on the ISI, with different effects on the PER and/or pulse alone. The serotonin 2A receptor agonist DOI tended to reduce PPI. The cannabinoid CB1 receptor antagonist AM 251 did neither affect PPI nor the responses to prepulses or startling noise pulses. Taken together this study supports the current notion of a pharmacologically complex pattern of regulation of PPI at different ISIs and suggests that the PER is a miniature ASR that does, however, not predict the level of PPI.

1. Introduction

Prepulse inhibition of startle (PPI) is a behavioural paradigm to assess sensorimotor gating mechanisms. Briefly, the normally occurring startle response to a sudden intense stimulus is reduced if a weak prepulse is presented shortly before the startling stimulus. PPI is frequently used in pharmacological studies testing pro- and antipsychotic drug treatment (Geyer et al., 2001). However, most of these investigations do not address the questions of how the drugs affect the response to the prepulse itself, and, whether the drug effects on PPI differ depending on different prepulse–pulse time intervals. It has to be noted, though, that some previous studies have shown drug effects on PPI using different prepulse–pulse intervals (Mansbach and Geyer, 1991) and also on PPI elicited by prestimuli of different sensory modalities (Weber and Swerdlow, 2008).

Recently, the interest in both the nature of the response to the prepulse (prepulse elicited reaction, PER) and in possible drug effects on this response has increased (Csomor et al., 2005; Dahmen and Corr, 2004; Yee et al., 2004; Yee and Feldon, 2009) because this might be important for the interpretation of PPI deficits, especially with respect to their relevance for the understanding of PPI impairments that occur in certain neuropsychiatric disorders (Braff et al., 2001). The behavioural response to the prepulse itself is still obscure. Frances Graham postulated that the prepulse triggers sensory-neuronal processing routines that need to be protected against disruption, so that the subsequent startling stimulus will be inhibited (Graham, 1975). Based on the time window for efficient PPI of approximately 30–800 ms it can be a variety of immediate responses, e.g. early sensory processing, an orienting response or an attentional shift response. However, the nature of the behavioural response related to the prepulse has never been investigated systematically. The definition of PPI as a phenomenon where a *non-startling* prepulse inhibits startle would preclude the idea that the prepulse itself elicits a startle response. If this were the case, PPI might not be strictly regarded as a sensorimotor gating process, where an additional circuit gates the primary startle circuit, but could also be regarded as a motor gating or a refractory effect occurring within the reflex pathway.

Another important issue in PPI research is the temporal relationship between the prepulse and the startling pulse. It has been shown that both in humans and in animals PPI is maximal when the interstimulus interval (ISI) between prepulse and pulse is in the range of 60–120 ms (Swerdlow et al., 2001). At these ISIs PPI is probably mediated by a pathway involving the pedunculopontine tegmental nucleus (PPTg) (Diederich and Koch, 2004; Fendt et al., 2001). Since the regulation of PPI by a corticolimbic–striatopallidal circuit appears to mainly target the PPTg (Fendt et al., 2001; Swerdlow et al., 2001), it would be interesting to know whether or not drugs that act on this regulating circuit influence PPI at ISIs other than 60–120 ms.

Therefore, the present study investigated the effects of different drugs on the motor response to the prepulse itself and on PPI at different ISIs.

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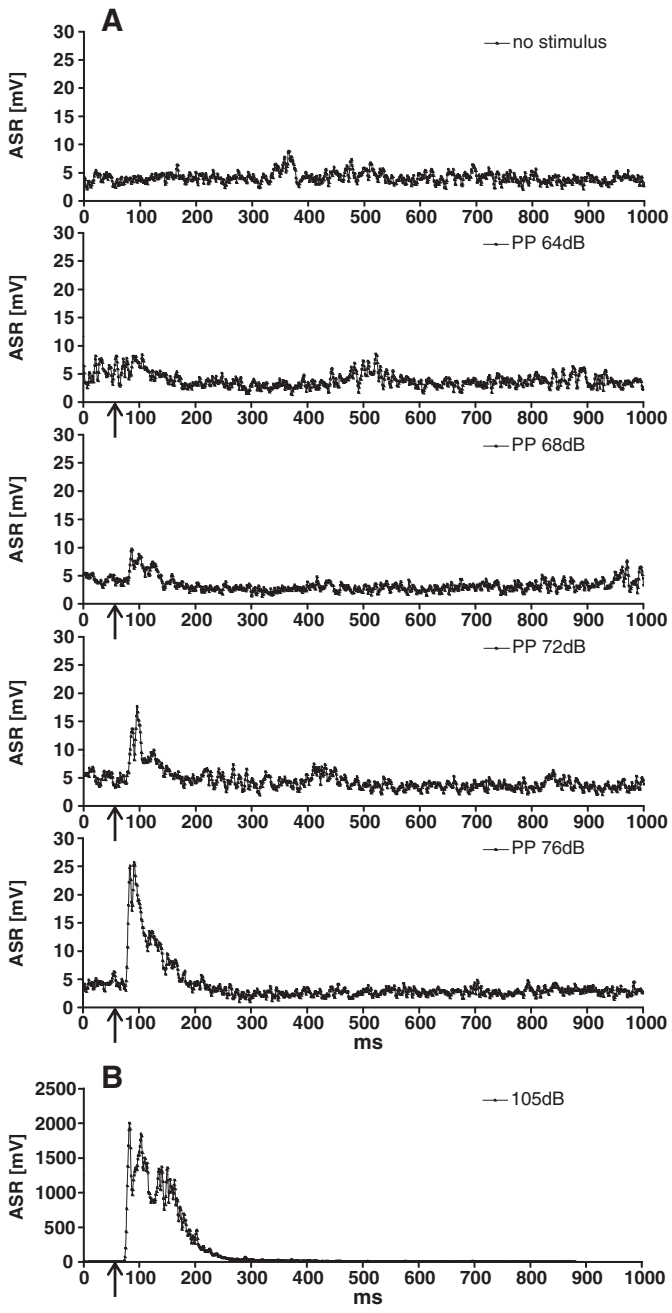

Fig. 1. Reaction of the rats (n = 10) to broadband noise stimuli of different intensities (0–45 dB above background). Stimulus onset occurred at 60 ms and was of 20 ms duration (arrow indicated pulse-onset). Whilst the animals displayed a strong startle reaction (ASR) to a 105 dB stimulus (i.e. 45 dB above background) (B), also lower pulse intensities of 12–16 dB above background were able to induce a miniature startle response as evidenced by a clear onset of the rats' motor reaction at 100 ms, i.e. 40 ms after stimulus onset (A) (see Table 1 for statistical evaluation).

Table 1
Effect of different prepulse intensities (64, 68, 72, and 76 dB) on the rats' PER magnitude. Stronger prepulse intensities lead to an increase in PER and induce a kind of miniature startle response (see also Fig. 1). Data are mean ± SEM. *Asterisks* indicate a difference of PER compared to no-stimulus. *Cross* indicates a difference to 64 dB. Data were analysed by one way RM ANOVA on ranks followed by Tukey tests ($p<0.05$).

Trial	PER magnitude
No-stimulus	18.2 (±3.5)
64 dB	23.6 (±4.0)
68 dB	25.5 (±4.3)
72 dB	35.6 (±6.1)*
76 dB	51.0 (±9.5)* +

2. Materials and methods

2.1. Animals

A total of 58 male adult Wistar rats (Hannover strain, Harlan-Winkelmann, Borchen, Germany) of 220–270 g were used. The rats were housed in groups of five animals in Macrolon cages (type IV) under standard conditions on a 12 h light–dark schedule (lights on 0700–1900 h). They received free access to tap water and were maintained on their body weight by controlled feeding of 12 g rodent chow/rat/day. Ten animals were used for experiment 1, nine to ten animals were assigned to each of the five drug treatment groups in experiment 2. Tests and treatments were done according to a within-subjects design with pseudorandomized treatment order.

The experiments were performed in accordance with the NIH ethical guidelines for the care and use of laboratory animals for experiments.

2.2. Drugs

The direct dopamine receptor agonist apomorphine (APO, Sigma-Aldrich, Steinheim, Germany) was dissolved in water with 0.1% ascorbic acid and injected subcutaneously (s.c.) at a dose of 1.0 or 2.0 mg/kg 5 min before testing. The non-competitive NMDA glutamate receptor antagonist MK-801 (Sigma-Aldrich, Steinheim, Germany) was dissolved in saline and injected s.c. in a dose of 0.075 and 0.15 mg/kg 10 min before testing. The cannabinoid CB1-receptor agonist WIN 55,212-2 (Sigma-Aldrich, Steinheim, Germany) was dissolved in Tween 80 and saline (1:99) and administered intraperitoneally (i.p.) at 0.6 and 1.2 mg/kg 10 min before testing. The cannabinoid CB1-receptor antagonist AM 251 (Sigma-Aldrich, Steinheim, Germany) was dissolved in Tween 80 and saline (1:99) and administered s.c. at 0.7 and 1.4 mg/kg 10 min before testing. The 5-HT2A/C-receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI, Sigma-Aldrich, Steinheim, Germany) was dissolved in saline and given in doses of 0.25 and 0.5 mg/kg s.c. 15 min before testing. Sterile water containing 0.1% ascorbic acid was used as vehicle control for all animals. Injection volume was 1 ml/kg and all drugs were freshly prepared before being used. Injection protocol was based on a randomised crossover design with at least 48 h resting-time in between the test sessions.

2.3. Experiments

Two experiments were conducted. In experiment 1 we investigated the PER at different prepulse intensities, whilst in experiment 2 the dependence of PPI on variations of the ISI as well as ASR and PER were tested after treatment with various drugs.

2.3.1. Experiment 1: parametric evaluation of PER

PER was measured using a four-unit automated SRLab startle system (San Diego Instruments, San Diego, USA). Startle-boxes consisted of non-restrictive plexiglass cylinders (9 cm in diameter) resting on a piezo-sensitive platform inside a sound-attenuated and ventilated chamber. Vibrations of the cylinder caused by the motor response of the rat to acoustic stimuli delivered through loudspeakers above the animal were transduced into analogue signals and then digitised and stored by a computer using the SRLab software (San Diego Instruments, San Diego, USA).

Each test session began with a 5 min acclimatisation period. During this period and the following sessions the animals were exposed to

60 dB broadband background noise. In the experiment a total of 105 trials were delivered in a pseudorandom order with an average intertrial interval (ITI) of 25 s. At the start of the session five single 20 ms pulse alone broadband noise stimuli with an intensity of 105 dB sound pressure level were presented. The 100 trials following the initial five pulses consisted of ten 105 dB pulse-alone trials, ten trials with no stimulus, 40 prepulse (64, 68, 72 or 76 dB) and 40 prepulse–pulse trials. Prepulse–pulse trials consisted of a single 105 dB pulse preceded by a broadband noise prepulse of 64, 68, 72 or 76 dB (duration 20 ms, 0 ms rise/fall time, and ISI 120 ms) to show that exerted prepulses induced PPI. In prepulse trials the PER of the rat to the 64, 68, 72 or 76 dB prepulse was recorded in a time window of 100 ms after onset of the stimulus.

2.3.2. Experiment 2: parametric and pharmacological evaluation of PPI, PER and ASR

PPI was measured using the SRLab startle system described above. At the beginning of each session animals were placed into the startle-boxes and exposed to a 60 dB broadband background noise during a 5 min acclimatisation period which continued for the remainder of the session.

A total of 80 trials were delivered in a pseudorandom order with an average ITI of 25 s. The first and last five trials consisted of single 20 ms pulse-alone broadband noise stimuli with an intensity of 105 dB sound pressure level. The middle 70 trials consisted of ten 105 dB pulse-alone trials, ten prepulse trials (78 dB), ten trials during which no stimuli were presented (no-stim trials), and 40 prepulse–pulse trials. Prepulse–pulse trials consisted of a single 105 dB pulse preceded by a broadband noise prepulse of 78 dB (duration 20 ms, 0 ms rise/fall time). In prepulse trials the PER of the rat to the 78 dB prepulse was recorded whilst in prepulse–pulse trials the stabilimeter readings after the pulse were measured. The maximal response in the prepulse or prepulse–pulse trials was measured in a time window of 100 ms after onset of the prepulse or startle stimulus. In order to test the effect of temporal variations on the expression of PPI four different ISIs (time between onset of prepulse and onset of pulse; 25, 120, 520 and 1020 ms) were used. The percentage of PPI (%PPI) was calculated as: $100-[(\text{startle amplitude on prepulse–pulse trial})/(\text{startle amplitude on pulse-alone trial})\times 100]$. In addition the magnitude of the ASR was measured. Within-session habituation was determined using the ASR magnitudes of the first five, middle ten, and last five pulse-alone trials. Measured values of experiments 1 and 2 represent the maximal motor response to acoustic stimuli (Vmax-value of the SR-Lab system).

2.4. Statistics

The descriptive statistics is based on means and variance is indicated by the standard error of the mean (±SEM). Data for experiment 1 were analysed by one-way analyses of variance (ANOVA) on ranks for repeated measures (RM). Post hoc Tukey tests were performed for pairwise comparisons. Data for experiment 2 were analysed by two-way RM ANOVA to (1) analyse the effect of drugs on PPI at different prepulse lead times and (2) to detect differences in the rats' habituation to the startle stimuli. Drug-effects on ASR and PER magnitudes were analysed by one-way RM ANOVA. Post hoc Duncan's tests were performed for pairwise comparisons. All analyses were performed with the statistical

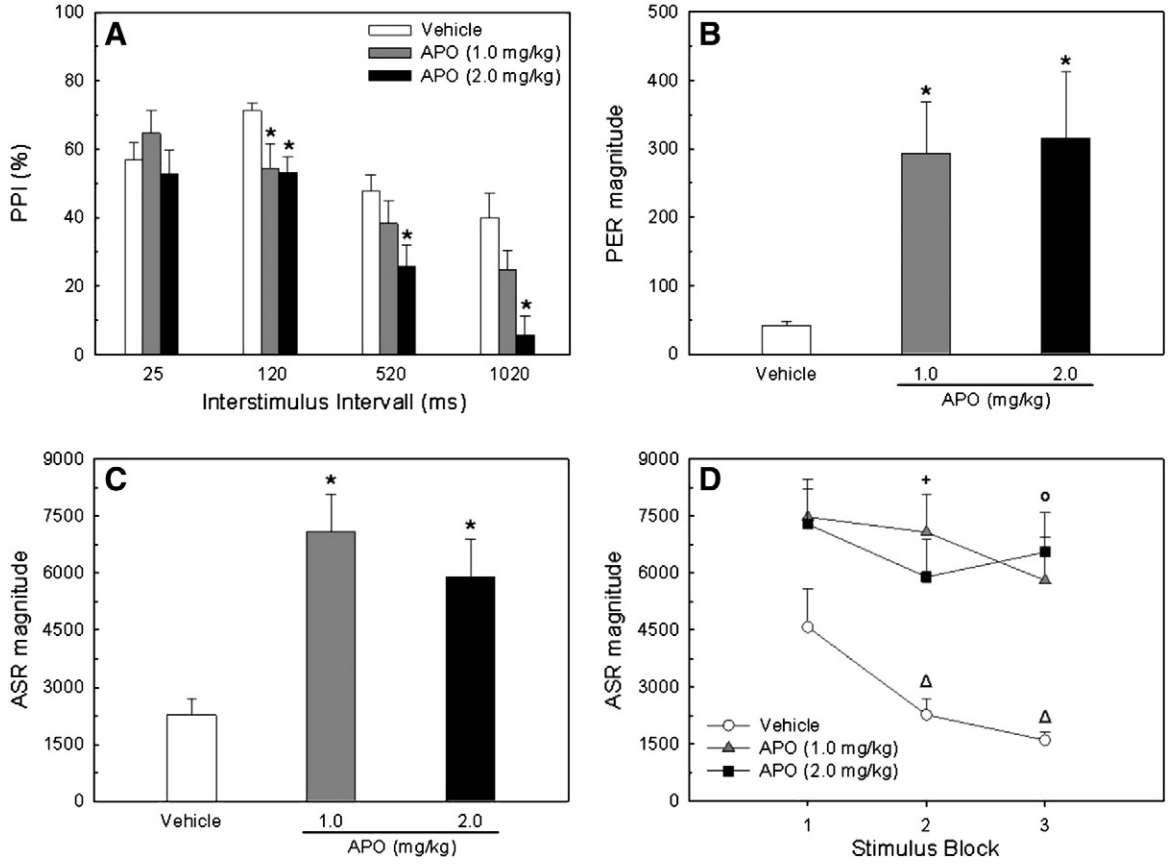

Fig. 2. Effect of variations of interstimulus interval (ISI) and systemic apomorphine treatment (APO; 1.0 or 2.0 mg/kg; s.c.) on the rats' PPI, ASR and PER magnitudes (n = 9). APO reduced PPI at ISIs of 120 ms or higher whilst it had no effect at an ISI of 25 ms (A). Both doses of APO increased the rats' PER (B) or ASR (C). Additionally, APO treatment altered habituation to the startle stimuli during the session (D). Data are mean ± SEM. *Asterisks* indicate treatment effect for the single ISIs, PER, or ASR. For habituation, *triangle*, *circle*, or *cross* indicates a difference to stimulus block 1 for the vehicle, APO 1.0, or APO 2.0 mg/kg group, respectively. Data were analysed by one- or two way RM ANOVAs followed by Duncan's test ($p<0.05$).

software SigmaStat (version 2.03 for Windows). A value of $P<0.05$ was considered to represent a significant effect.

3. Results

3.1. Experiment 1: parametric evaluation of PER

There is a strong correlation between the prepulse intensity and the observed PER (ANOVA; $p<0.001$) (Fig. 1A, Table 1). Post hoc analysis of the different prepulse intensities by Tukey tests showed that 72 dB and 76 dB prepulses increased PER compared to no stimulus. Furthermore, a distinct increase of PER was measured after presentation of 76 dB compared to 64 dB (Table 1). In general, the rats' PER was characterised by a maximum motor response 40 ms after stimulus onset, i.e. at 100 ms. Neither background noise nor prepulses of 64 dB or 68 dB were able to cause this kind of reaction. After presentation of the startle eliciting noise burst of 105 dB (Fig. 1B), the maximum peak of the motor response could again be observed at around 100 ms (40 ms after stimulus onset), but was approximately 100 times higher (i.e. 2000 mV) than after prepulse presentation, thereby characterising the PER as a kind of miniature startle response.

3.2. Experiment 2: parametric and pharmacological evaluation of PPI, PER and ASR

Here, we tested the effects of different drugs on the regulation of PPI and ASR when the prepulse–pulse interval was varied (25–1020 ms). Therefore, APO, MK-801, WIN 55,212-2, AM 251 and DOI were systemically injected prior to testing.

3.3. Effect of ISI variation and APO treatment on PPI, PER and ASR

APO dose-dependently reduced PPI at longer ISIs (ANOVA, $F2,48=6.818$; $p=0.007$). We also found a general effect of different ISIs on PPI (ANOVA, $F3,48=51.758$; $p<0.001$), as well as an interaction between APO and ISI ($F6,48=2.841$; $p=0.019$) (Fig. 2A). Further post hoc analysis of the different ISIs by Duncan's tests showed that neither dose of APO was effective at a short ISI of 25 ms whilst both 1 or 2 mg/kg APO significantly reduced PPI at an ISI of 120 ms. At longer ISIs of 520 or 1020 ms only the high dose of APO of 2 mg/kg significantly reduced PPI. In addition, the PER was enhanced by APO (ANOVA, $F2,26=4.869$; $p=0.022$) (Fig. 2B). Furthermore, APO significantly enhanced the ASR (ANOVA, $F2,16=10.375$; $p=0.001$) (Fig. 2C). Habituation of the ASR was impaired by both doses of APO (ANOVA, $F2,32=8.227$; $p=0.003$) across the session duration when compared to the control group (ANOVA, $F2,32=26.160$; $p<0.001$) (Fig. 2D).

3.4. Effect of ISI variation and MK-801 treatment on PPI, PER and ASR

MK-801 dose-dependently reduced the rats' PPI (ANOVA, $F2,48=3.860$; $p=0.043$). We also replicated the effect of ISIs on PPI (ANOVA, $F3,48=4.275$; $p=0.015$) (Fig. 3A). Post hoc analysis of the different ISIs by Duncan's test revealed that PPI at an ISI of 25 ms was sensitive to disruption by both doses of MK-801 whilst at 120 ms only the high dose of 0.15 mg/kg significantly reduced PPI. At longer ISIs (520 or 1020 ms) the PPI-reducing effects of MK-801 did not reach the level of significance. Both, PER and ASR magnitudes were unaffected by MK-801 when compared to vehicle treatment (Fig. 3B and C). Short-term habituation of the ASR was found after vehicle- but MK-801 reduced

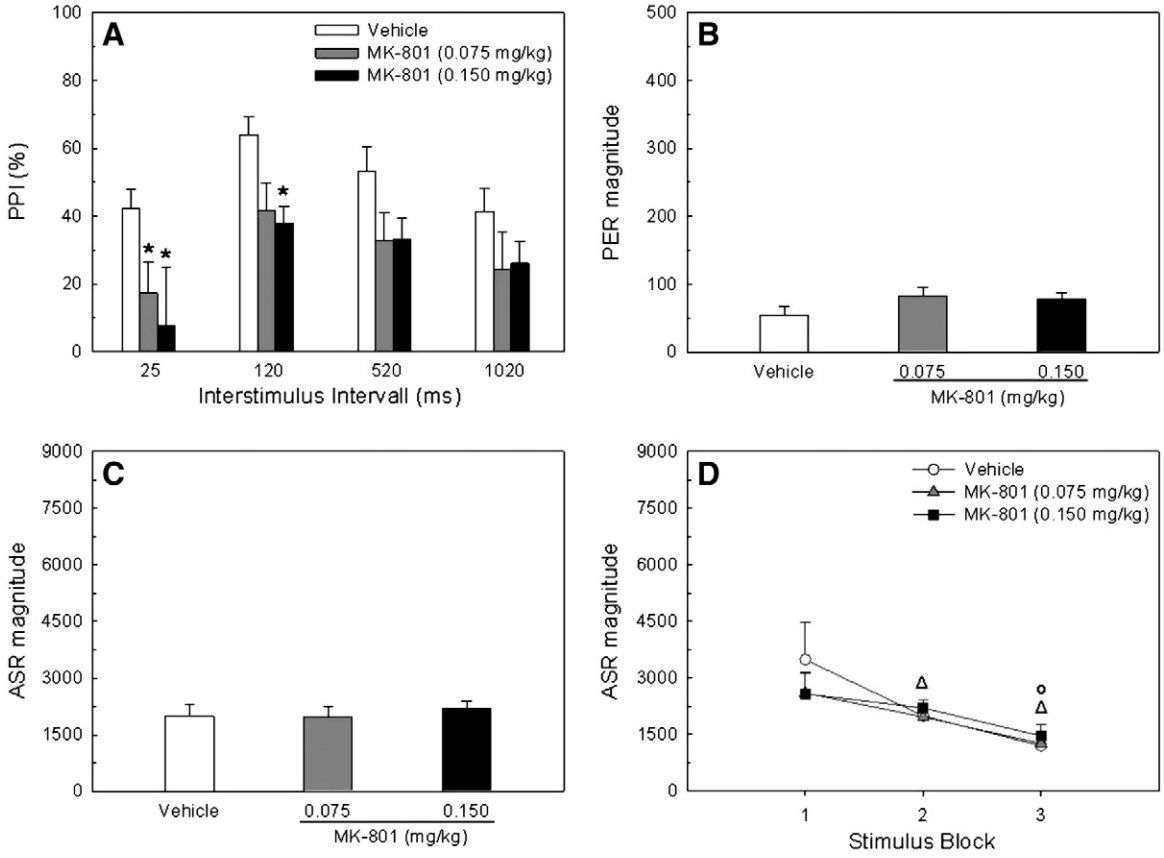

Fig. 3. Effect of variations of interstimulus interval (ISI) and systemic MK-801 treatment (0.075 or 0.150 mg/kg; s.c.) on the rats' PPI, ASR and PER magnitudes ($n=9$). MK-801 reduced PPI at ISIs of 120 ms or lower whilst it had no effect at ISIs of 520 ms or higher (A). Neither dose of MK-801 affected the rats' PER (B) or ASR (C). Habituation was dose dependently reduced by MK-801 (D). Data are mean ± SEM. *Asterisks* indicate treatment effect for the single ISIs. For habituation, *triangle*, or *circle* indicates a difference to stimulus block 1 for the vehicle or MK-801 0.075 mg/kg group, respectively. Data were analysed by one- or two way RM ANOVAs followed by Duncan's test ($p<0.05$).

habituation dose dependently (ANOVA, $F2,32 = 9.249$; $p = 0.002$) (Fig. 3D).

3.5. Effect of ISI variation and cannabinoid treatment on PPI, PER and ASR

Following WIN-treatment we found a general effect of different ISIs on PPI (ANOVA, $F3,54 = 14.044$; $p < 0.001$) as well as an interaction between WIN and ISI (ANOVA, $F6,54 = 6.242$; $p < 0.001$) (Fig. 4A). Post hoc analysis revealed an enhancement of PPI by WIN at ISIs of 25 ms and a reduction at 120 ms. WIN had no effect on PPI at any of the longer ISIs. Both, PER and ASR magnitudes were unaffected by WIN when compared to vehicle treatment (Fig. 4B and C). Habituation of the ASR was unaffected by the drug (Fig. 4D; ANOVA, $F2,36 = 7.572$; $p = 0.004$).

The CB1 receptor antagonist AM 251 had no effect on PPI whilst a general effect of different ISIs could be observed (ANOVA, $F3,54 = 17.296$; $p < 0.001$). Post hoc analysis by Duncan's test revealed a maximal PPI at 120 ms regardless of treatment (Fig. 5A). Both, PER and ASR magnitudes were unaffected by AM (Fig. 5B and C). Habituation of the ASR was dose dependently reduced by treatment (Fig. 5D; ANOVA, $F2,36 = 5.464$; $p = 0.014$).

3.6. Effect of ISI variation and DOI treatment on PPI, PER and ASR

DOI had no effect on PPI whilst a general effect of different ISIs could be observed (ANOVA, $F3,54 = 17.047$; $p < 0.001$). Post hoc analysis by Duncan's test revealed a maximal PPI at 120 ms (Fig. 6A). Additionally, the high dose of DOI (0.5 mg/kg) increased the rats' PER (ANOVA, $F2,29 = 5.730$; $p = 0.012$) when compared to the vehicle or low dose DOI groups (Fig. 6B) but decreased the ASR (Fig. 6C; ANOVA, $F2,29 = 4.413$; $p = 0.028$) and prevented habituation of the rats' ASR (Fig. 6D; ANOVA, $F2,89 = 4,387$; $p = 0.028$).

4. Discussion

The present findings confirm previous studies showing PPI deficits induced by drugs affecting different transmitter systems (Geyer et al., 2001; Schneider and Koch, 2002). Briefly, dopamine, 5-HT2 and CB1 receptor agonism, as well as NMDA receptor antagonism reduced PPI as shown before. The PPI deficit induced by the 5-HT2A/C agonist DOI did not reach the level of significance but showed only a trend, probably because we used too low doses of this drug. Interestingly, the CB1 receptor agonist WIN 55,212-2 facilitated PPI at the shortest ISI which is a novel finding. We can only speculate on the mechanisms responsible for the facilitation of PPI at short ISIs by WIN. Since CB1-receptors are heteroreceptors on a variety of inhibitory and excitatory transmitter systems (Wegener and Koch, 2009), we suggest that CB1-receptor agonist WIN facilitated the hitherto unknown mechanism by which prepulses affect the ASR at short ISI.

Our data also support the contention that the strong prepulse intensities elicit a motor response that – based on its latency – might reflect a miniature ASR (Yee and Feldon, 2009). However, our data also

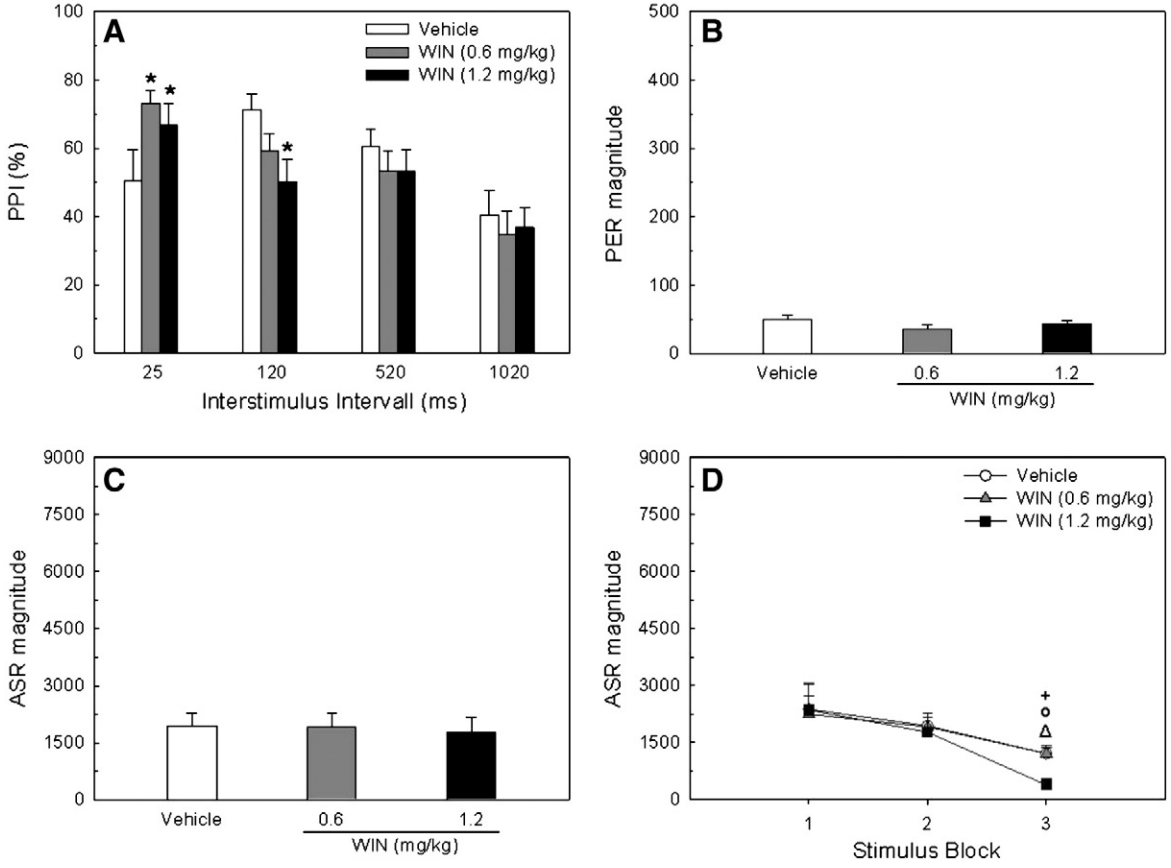

Fig. 4. Effect of variations of interstimulus interval (ISI) and systemic WIN 55,212-2 treatment (0.6 or 1.2 mg/kg; i.p.) on the rats' PPI, ASR and PER magnitudes ($n = 10$). WIN rescued PPI at ISIs of 25 ms whilst the high dose impaired PPI at an ISI of 120 ms. Longer ISIs remained unaffected by WIN treatment (A). Neither dose of WIN affected the rats' PER (B) or ASR (C) or had an effect on habituation to the startle noise (D). Data are mean ± SEM. *Asterisks* indicate treatment effect for the single ISIs. For habituation, *triangle*, *circle*, or *cross* indicates a difference to stimulus block 1 for the vehicle, WIN 0.6 or WIN 1.2 mg/kg group, respectively. Data were analysed by one- or two way RM ANOVAs followed by Duncan's test ($p < 0.05$).

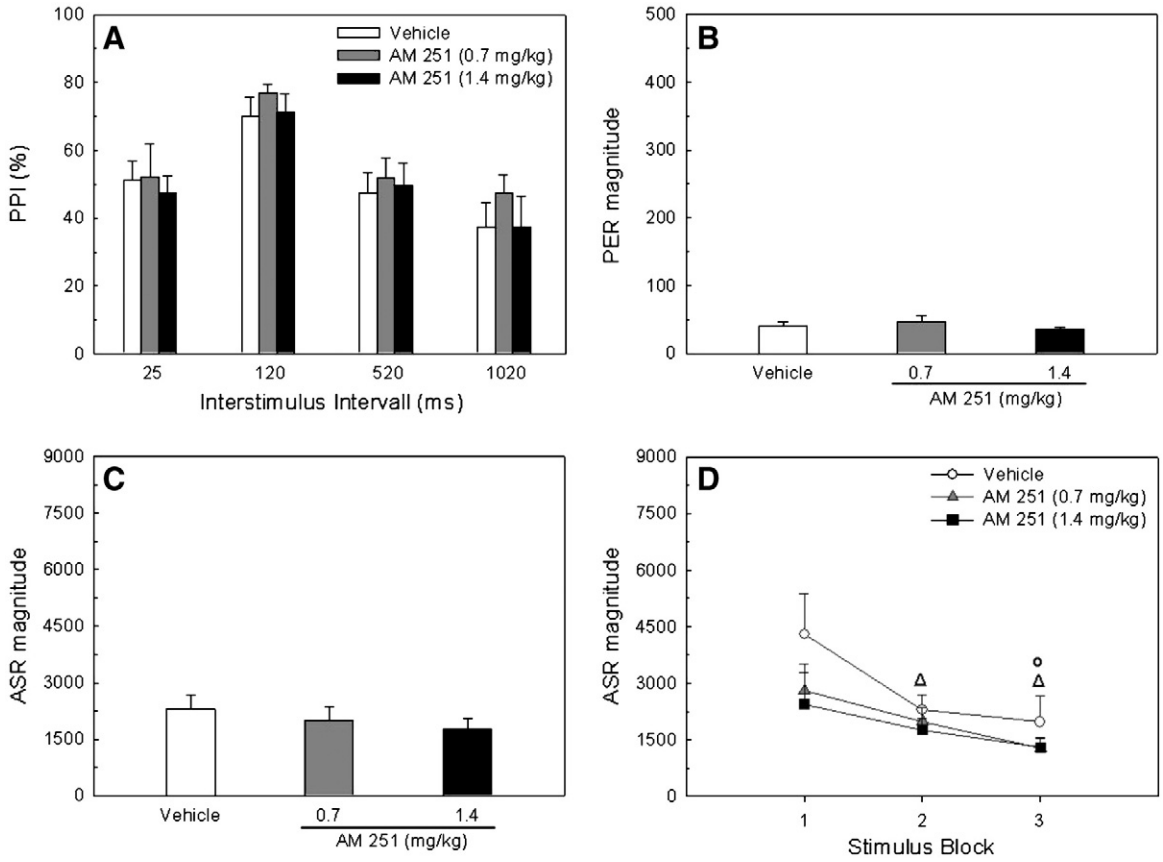

Fig. 5. Effect of variations of interstimulus interval (ISI) and systemic AM 251 treatment (0.7 or 1.4 mg/kg; s.c.) on the rats' PPI, ASR and PER magnitudes (n = 10). AM 251 had no effect on PPI at different ISIs (A). Neither dose of AM 251 affected the rats' PER (B) or ASR (C). Habituation was dose dependently reduced by AM 251 (D). Data are mean ± SEM. For habituation, *triangle* or *circle* indicates a difference to stimulus block 1 for the vehicle or AM 0.7 mg/kg group, respectively. Data were analysed by one- or two way RM ANOVAs followed by Duncan's test ($p<0.05$).

show that PPI is independent of this form of prepulse-induced motor response. This is also supported by the fact that PPI occurs at ISIs of only 25 ms although the first motor response that can be measured with the stabilimeter device is found at 40 ms. Hence, other mechanisms elicited by the prepulse which inhibit the ASR may have to be postulated. Previous studies have also shown that drugs such as APO reduce PPI elicited by prepulses that do not produce a PER (Swerdlow et al., 2004), suggesting the independence of PPI and PER drug effects.

It has been part of the classical definition of PPI that the prepulse itself does not elicit a startle response (Hoffman and Ison, 1980). However, the fact that the motor response elicited by the prepulse has the same latency as the ASR (about 40 ms, as measured in a stabilimeter device) strongly suggests that this response is also mediated by the ASR pathway (Koch, 1999), i.e. by the giant neurons of the caudal nucleus of the pontine reticular formation (PnC). Interestingly, electrophysiological data have shown that the firing threshold of PnC neurons is relatively low suggesting that the high level of acoustic input that is necessary to elicit an ASR is due to a high firing threshold of the cochlear root neurons that provide the fast input to the giant PnC neurons (Wagner and Mack, 1998). Since PnC neurons also receive direct input from the ascending auditory system, e.g. from the superior olivary complex and from the dorsal cochlear nucleus (Lingenhöhl and Friauf, 1992), we here suggest that the motor response elicited by the prepulse is mediated by the low firing threshold neurons of the ascending auditory nuclei projecting to the PnC. However, based on the present findings we cannot rule out an involvement of other short-latency bottom-up sensory mechanisms being involved in the PER. The motor response elicited by the prepulse could reduce the ASR by inducing some sort of refractory period within the reflex pathway, or by recruiting a motor gating pathway inhibiting the ASR.

Yee and Feldon have recently proposed that the PER must no longer be ignored, because it is important for the interpretation of drug-induced PPI deficits (Yee and Feldon, 2009). The present study supports this notion, but also shows that the magnitude of the PER does not predict the level of PPI. The most obvious finding was that APO elicits a strong PER and reduces PPI only at relatively long ISIs, whilst MK-801 can reduce PPI particularly at short ISIs without having an effect on the PER. However, one important methodological issue to be considered when interpreting the present data is that PPI and drug-effects on PPI are strain dependent, with Wistar rats, which were used here, usually showing relatively low PPI levels and blunted drug-effects on PPI (e.g. compared to Sprague Dawley rats). Hence, until comparable data are available on PER in other rat strains, our findings have to be considered more or less specific for the Wistar strain.

The "classical" pathway that mediates PPI involves an inhibitory projection from the PPTg to the PnC (Fendt et al., 2001) but this pathway is probably only recruited for the mediation of PPI at intermediate ISIs, but not at very short or very long gaps between prepulse and pulse (Fendt et al., 2001). Brain systems responsible for PPI at short (<30 ms) and long (>520 ms) are so far unknown. The present data suggest that some of the PPI-regulating effects of the different drugs used in this study are mediated by other brain substrates connected with these hitherto unknown pathways. This might be trivial on the one hand, but on the other hand clearly underscores the notion that drugs that have been used in this paradigm in order to model some aspects of neuropsychiatric disorders (e.g. dopamine, cannabinoid and serotonin receptor agonists or glutamate NMDA receptor antagonists) do not act via a common final pathway.

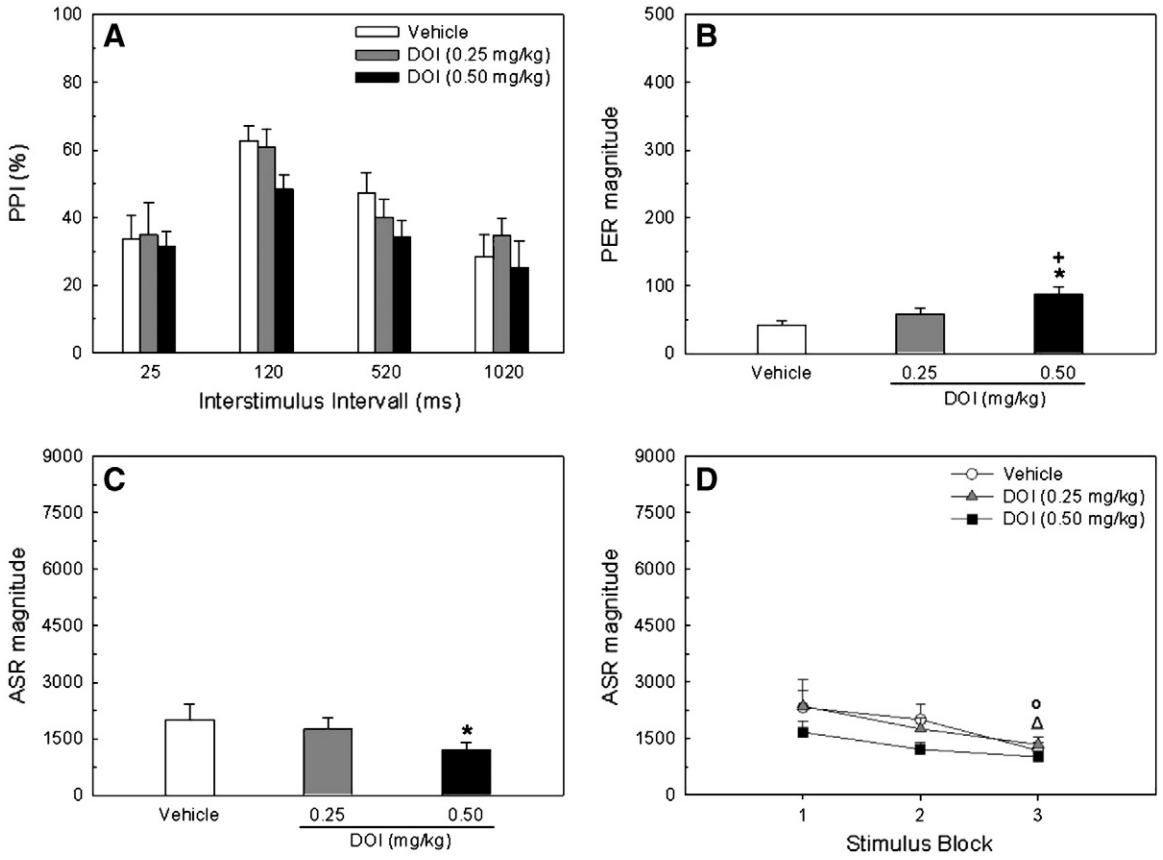

Fig. 6. Effect of variations of interstimulus interval (ISI) and systemic DOI treatment (0.25 or 0.50 mg/kg; s.c.) on the rats' PPI, ASR and PER magnitudes (n = 10). DOI had no effect on PPI at different ISIs (A). The high dose of DOI increased the rats' PER (B) whilst decreasing the ASR (C). Habituation was blocked by 0.50 mg/kg of DOI (D). Data are mean ± SEM. For PER and ASR, *asterisks* or *cross* indicates a difference compared to the vehicle group or low dose treatment, respectively. For habituation, *triangle* or *circle* indicates a difference to stimulus block 1 for the vehicle or DOI 0.25 mg/kg group, respectively. Data were analysed by one- or two way RM ANOVAs followed by Duncan's test ($p<0.05$).

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