

Does angiotensin interact with dopaminergic mechanisms in the brain to modulate prepulse inhibition in mice?

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Abstract

Changes in the levels of angiotensin-converting enzyme (ACE) have been found in brains of schizophrenia patients, suggesting a possible involvement of angiotensin in the illness. Prepulse inhibition (PPI) is a measure of sensorimotor gating and is disrupted in patients with schizophrenia. In a previous study, a reduction of ACE activity, either in ACE knockout mice or after ACE inhibitor treatment, markedly inhibited the disruption of PPI caused by the dopamine receptor agonist, apomorphine. ACE is not specific for the angiotensin system and, therefore, in the present study we assessed pharmacological regulation of PPI in two other, more specific genetic mouse models of altered angiotensin activity. We used renin-enhancer knockout (REKO) mice, which display reduced renin activity, and neuron-specific enolase (NSE)-AT_{1A} mice, which selectively over-express angiotensin AT_{1A} receptors in the brain. Treatment of these mice with apomorphine, the dopamine releaser, amphetamine or the NMDA receptor antagonist, MK-801, significantly disrupted PPI. There was, however, no difference in these effects between the genotypes. These data suggest that genetically induced changes in the activity of the angiotensin system do not alter regulation of PPI in mice. Our previous results on the effects of reduced ACE activity could be explained by mechanisms other than angiotensin, such as effects on enkephalin or bradykinin metabolism.

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1. Introduction

There is extensive evidence for the existence of a renin–angiotensin system (RAS) in the brain. All components of the RAS, such as renin, angiotensin-converting enzyme (ACE), angiotensin I and II, and angiotensin AT₁ and AT₂ receptors, have been demonstrated in different brain regions (Mendelsohn et al., 1990). High levels of angiotensin, ACE and angiotensin receptors have been found in the striatum, substantia nigra, choroid plexus, subfornical organ, paraventricular and periventricular nuclei of the hypothalamus (Allen et al., 1998; Mendelsohn et al., 1990). An interaction of angiotensin with central

dopaminergic activity is suggested by several observations. Chronic treatment with the dopamine receptor antagonist, haloperidol, increased angiotensin AT₁ and dopamine D₂ receptor densities (Jenkins et al., 1997b). Behavioural stereotypy induced by treatment with apomorphine and amphetamine was enhanced by intracerebroventricular injection of angiotensin II (Braszko et al., 1988). Administration of the angiotensin receptor antagonist, losartan, reduced locomotor activity both at the baseline level and after stimulation with apomorphine (Raghavendra et al., 1998). Dopaminergic projections to the nucleus accumbens are also involved in the mechanism by which angiotensin II improves cognition (Winnicka, 1999). Angiotensinogen knockout mice have been reported to show both enhanced (Massiera et al., 2001) and reduced (Okuyama et al., 1999) baseline locomotor activity.

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Therefore, while there is extensive evidence for a role of the central RAS in thirst (McKinley et al., 1996), angiotensin II may have a much more widespread functional role in the brain, including in dopaminergic regulation and psychiatric illnesses (Wright and Harding, 1994, 2004). Early studies reported both a reduction or increase in ACE activity in the basal ganglia and cerebrospinal fluid of patients with schizophrenia (Arregui et al., 1979; Beckmann et al., 1984; Owen et al., 1980; Wahlbeck et al., 1993). A more recent study on polymorphisms of ACE and of catechol-O-methyltransferase (COMT) showed that patients who poorly responded to neuroleptic treatment were 10 times more likely to have a low activity COMT phenotype combined with a high activity ACE phenotype (Illi et al., 2003). The mechanism by which ACE is involved in schizophrenia could be the above-mentioned modulation of dopaminergic activity in the brain (Banks et al., 1994; Jenkins et al., 1997a,b,c; Moore et al., 2007), which is central to psychotic symptoms (Carlsson et al., 2001).

We previously studied the role of ACE in prepulse inhibition (PPI), an operational measure of sensorimotor gating, which prevents excessive extraneous sensory stimuli from disturbing integrative mental processes in the brain (Van den Buuse et al., 2005b). PPI is the attenuation of a startle response to a startle stimulus if it is immediately preceded by a weak pre-stimulus (prepulse). Patients with schizophrenia show impaired sensorimotor gating, expressed as a reduction in PPI (Braff et al., 1995). In experimental studies, PPI can be attenuated by administration of dopamine receptor agonists, such as apomorphine, dopamine releasers, such as amphetamine, and *N*-methyl-D-aspartate (NMDA) receptor antagonist, such as MK-801 (Geyer et al., 2001). Dopaminergic hyperactivity and glutamatergic hypoactivity have both been implicated in schizophrenia (Geyer et al., 2001; Van den Buuse et al., 2005c). We observed that ACE knockout mice or control mice treated with an ACE inhibitor, displayed marked attenuation of the effect of apomorphine on PPI (Van den Buuse et al., 2005b). This previous study thus showed that ACE interacts with dopaminergic mechanisms involved in PPI regulation which could be important for our understanding of a possible role of ACE in schizophrenia. However, given the relative non-specificity of ACE for the conversion of angiotensin compared to other substrates (Erdös, 1979, 1990), it is important to verify these observations in mice with other genetic alterations of the RAS.

Angiotensin production is under the control of several enzymatic steps. Renin expression is modulated by an enhancer sequence 2.5 kb upstream of the renin gene (*Ren-1^c*) which is sensitive to transcription factors as well as several second messenger systems, such as cAMP and ones responding to endothelin-1 and cytokines (Pan and Gross, 2005). REKO mice carry a targeted deletion of the renin-enhancer and consequently show marked depletion of renin (Adams et al., 2006). This genetic modification results in lower blood pressure and reduced baseline locomotor activity (Adams et al., 2006). Therefore, we used these REKO mice in our study as a genetic model of reduced activity of the RAS. The expectation was, that these mice would show similar deficiencies in

dopaminergic control of PPI as noted in ACE knockout mice and after pharmacological ACE inhibition (Van den Buuse et al., 2005b). We contrasted this by also using NSE-AT_{1A} transgenic mice, which over-expresses the AT_{1A} receptor (Lazartigues et al., 2002; Moore et al., 2007). This overexpression is specific to the brain as it is regulated by the neuron-specific enolase (NSE) promoter (Lazartigues et al., 2002). These animals show marked hypersensitivity to stimulation of the renin–angiotensin system in the brain (Lazartigues et al., 2002) and selective changes in dopaminergic modulation of alcohol intake (Moore et al., 2007). Thus, we used NSE-AT_{1A} mice as a model of enhanced angiotensinergic activity and expected these mice to show greater sensitivity to dopaminergic disruption of PPI.

Therefore, the aim of the present study was to assess if disruption of PPI with apomorphine and amphetamine was attenuated in REKO mice and enhanced in NSE-AT_{1A} transgenic mice (Van den Buuse et al., 2005a,c). For comparison, we also used MK-801 to assess if any changes in the mutant models were specific for dopaminergic regulation of PPI.

2. Methods

Male REKO mice ($n=9$) were generated as described before (Adams et al., 2006) and wildtype C57Bl/6 mice ($n=10$) were used as controls. This knockout model was established by these workers and mice were bred and genotyped by PCR there before being shipped to Melbourne, Australia, for behavioural analysis. Male NSE-AT_{1A} transgenic mice ($n=10$) and non-transgenic littermates ($n=10$) were obtained from the Howard Florey Institute, Melbourne, Australia (Moore et al., 2007). This breeding colony was originally established with animals from the University of Iowa, USA, and details of the generation and genetic background of this transgenic model have been published in detail previously (Lazartigues et al., 2002). The mice were genotyped by PCR (Lazartigues et al., 2002; Moore et al., 2007) before being transported to the Mental Health Research Institute.

All mice weighed between 25 and 35 g at the start of the experiments and were kept at the Mental Health Research Institute animal facility in standard plastic mouse boxes separately or in groups of 2–5 with free access to standard pellet food and tap water. After arrival, the mice were allowed to acclimate for one week before the start of experiments. Experimental procedures were all in accordance with Australian Code of Practice for the care and use of animals for experimental research, as published by the National Health and Medical Research Council of Australia.

For PPI experiments, we used a standard protocol where mice were treated with saline (10 ml/kg), apomorphine (5 mg/kg, Sigma), amphetamine (5 mg/kg, Sigma) or MK-801 (0.5 mg/kg, Sigma). These doses were chosen on the basis of extensive preliminary work in the laboratory and because they induce moderate disruption of PPI, thus allowing for both enhancement or inhibition of the drug effects to become apparent. All animals were treated four times, with 3–4 days interval in-between, with the sequence of treatments being pseudo-randomized and all mice receiving each treatment once, allowing within-animal comparison (Van den Buuse et al., 2005b; Wang et al., 2003). All drugs were dissolved in saline and administered intraperitoneally (IP) 5 min prior to the start of the PPI session.

The mice were tested using an eight-unit automated SRLab startle system (San Diego Instruments, San Diego, CA, USA) as previously described (Van den Buuse et al., 2005b; Wang et al., 2003). Each unit contained a transparent Plexiglas cylinder mounted on a platform and a sensitive piezoelectric sensor to detect startle responses. Throughout the session a background noise level of 70 dB was maintained. Startle stimuli were presented and startle responses measured by the SRLab software (San Diego Instruments) running on a PC in an adjacent room. Mice were put into the cylinders for a 5-min acclimation during which a 70 dB background noise was delivered. The PPI session used in these experiments consisted of ten 40 ms, 115 dB pulse-alone trials, followed

by 60 trials consisting of random delivery of 40 prepulse trials, twenty 115 dB pulse-alone trials and 10 trials during which no stimuli was delivered. The prepulse trials consisted of 20 ms, non-startling noise bursts of 74, 78 or 86 dB (PP4, PP8 and PP16, respectively) followed 100 ms later by a 115 dB pulse. The session was concluded by 10 more 115 dB pulse-alone startle stimuli.

Average startle responses were calculated from the responses to the 40 pulse-alone stimuli obtained in the first and last block of 10 stimuli and the 20 pulse-alone stimuli from the main session. PPI was calculated as the difference between responses to the prepulse trials and the pulse-alone trials, divided by responses to the pulse-alone trials, expressed as a percentage.

All data are presented as mean \pm standard error of the mean (S.E.M.). Data for startle amplitude and startle habituation were analysed using analysis of variance (ANOVA) for repeated measures. Genotype was the between-group factor and Treatment (apomorphine, amphetamine or MK-801) and Prepulse intensity were the within-group repeated measures factor. Group differences were considered significant if $P < 0.05$.

3. Results

3.1. Effect of apomorphine, amphetamine or MK-801 on startle

REKO mice tended to have reduced startle levels (main effect of genotype for all treatments combined $F(1,17) = 4.5$, $P = 0.048$) This effect did not, however, always reach significance for individual treatment comparisons (Fig. 1). Apomorphine treatment caused a significant reduction of startle (main effect of treatment $F(1,17) = 7.0$, $P = 0.017$) which was similar in both genotypes. Conversely, amphetamine treatment tended to cause an increase in startle amplitudes in both REKO mice and controls but this effect did not reach statistical significance (Fig. 1). In contrast, MK-801 treatment markedly increased startle (main effect of treatment $F(1,17) = 10.2$, $P = 0.005$) in both genotypes and in this comparison the genotype difference reached significance (main effect of genotype of saline- and MK-801 data combined $F(1,17) = 4.6$, $P = 0.046$; main effect of genotype after MK-801 treatment $F(1,17) = 4.9$, $P = 0.040$).

In NSE-AT_{1A} mice, treatment with apomorphine significantly reduced startle levels ($F(1,18) = 22.8$, $P < 0.001$). However, there was no genotype difference in the level of startle or the effect of apomorphine (Fig. 1). Treatment with amphetamine had no significant effect on startle and there was no genotype interaction either (Fig. 2). Treatment with MK-801 tended to cause an increase in startle responses in these mice but this effect did not reach statistical significance and there was no difference between the two genotypes (Fig. 1).

3.2. Effect of apomorphine, amphetamine or MK-801 on PPI in REKO mice

As expected, increasing levels of prepulses produced increases in the degree of inhibition of startle. There was no significant difference between REKO mice and their WT controls in baseline PPI, as measured after saline injection (Fig. 2).

Compared with saline treatment, injection of 5 mg/kg of apomorphine induced a significant disruption of PPI (main

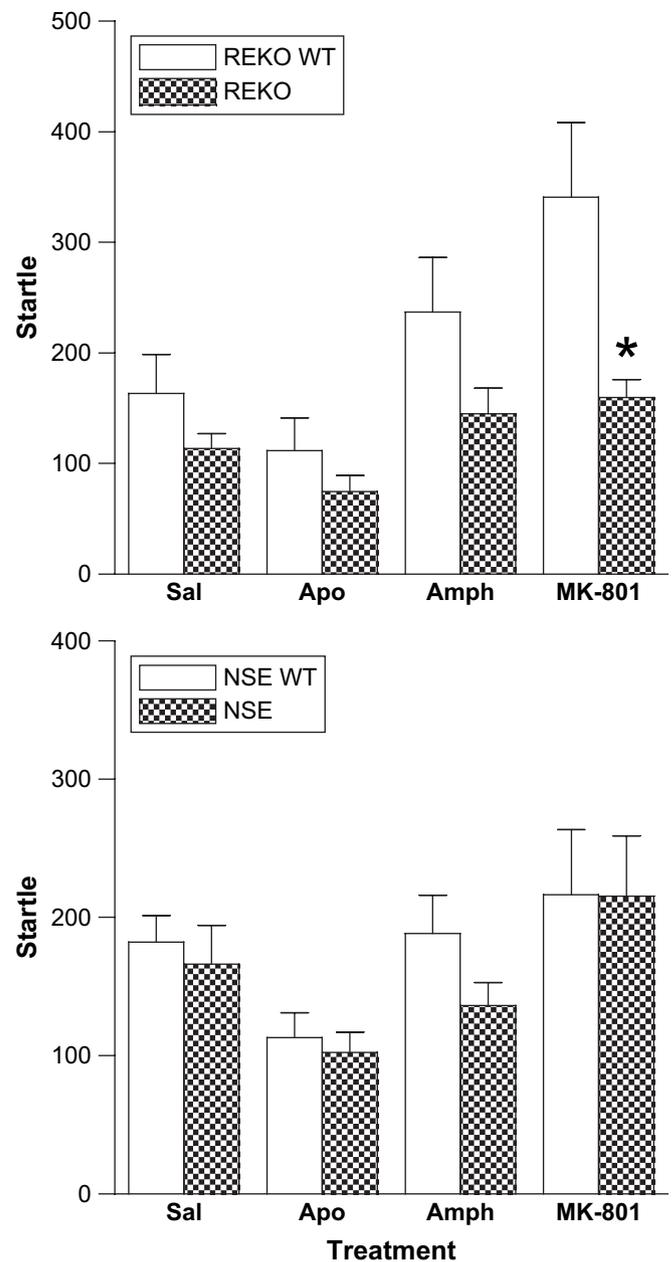


Fig. 1. Average startle amplitude in REKO mice and their wildtype controls ($n=9$ and $n=10$, respectively, top panel) and NSE mice and controls ($n=10$ each, bottom panel). The animals were treated with saline and 5 mg/kg of apomorphine (Apo), 5 mg/kg of amphetamine (Amph) or 0.5 mg/kg of MK-801. Data are mean \pm S.E.M.

effect of Treatment $F(1,17) = 23.5$, $P < 0.001$). This effect did not, however, differ between REKO and WT mice (Fig. 2). Injection of 5 mg/kg of amphetamine also significantly disrupted PPI (main effect of Treatment $F(1,17) = 14.7$, $P < 0.001$) and this effect tended to be greatest at the lower prepulse intensities ($P = 0.067$). Again, these effects were not different between the genotypes (Fig. 2). Similarly, 0.25 mg/kg MK-801 injection significantly disrupted PPI (main effect of Treatment $F(1,17) = 11.3$, $P = 0.004$) and this effect was greater at lower prepulse intensities (Treatment \times Prepulse interaction $2,34 = 4.8$, $P = 0.015$). While REKO mice tended to have a greater response to MK-801

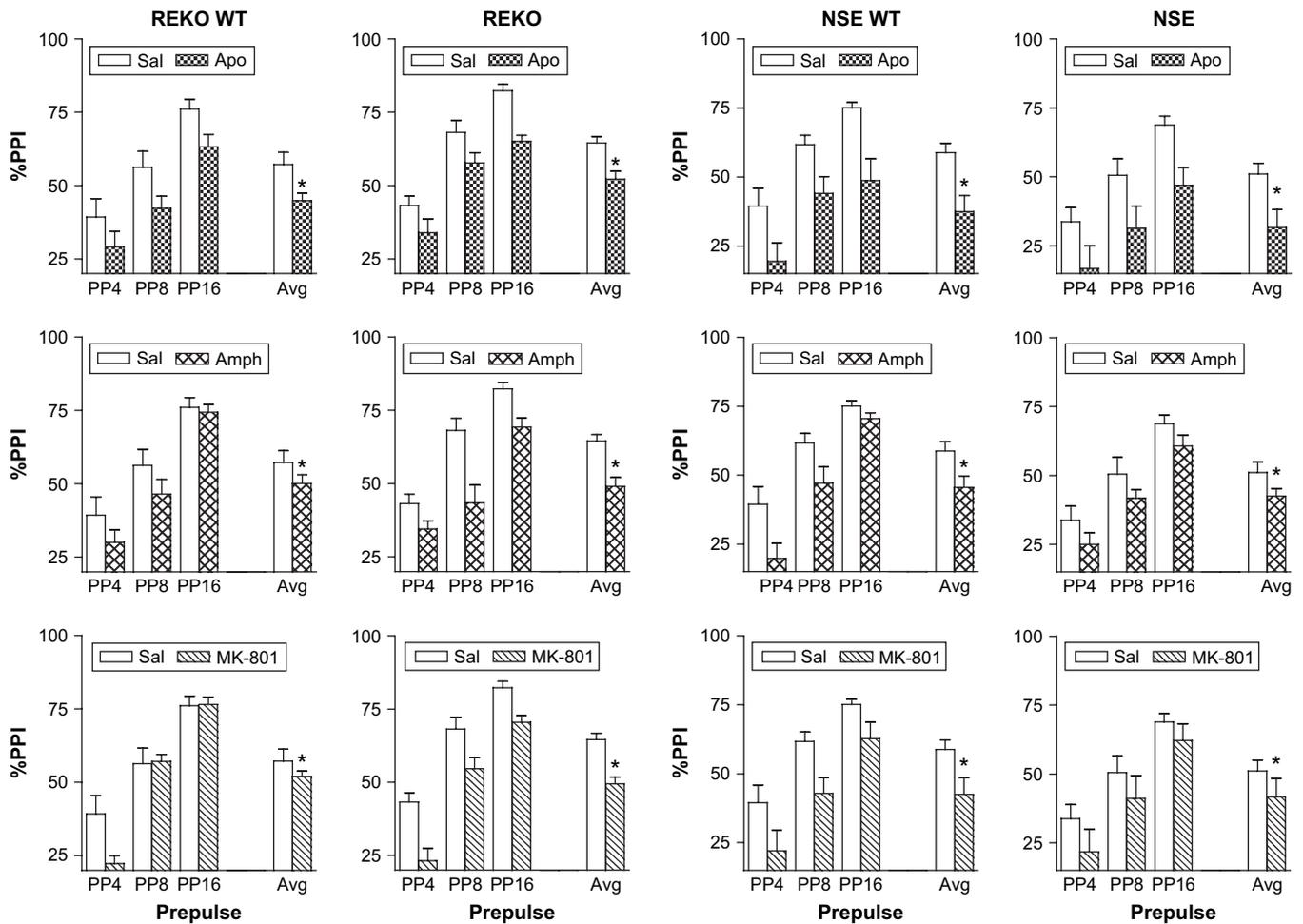


Fig. 2. Effect of treatment with 5 mg/kg of apomorphine (Apo, top panels), 5 mg/kg of amphetamine (Amph, middle panels) and 0.5 mg/kg of MK-801 (bottom panels) on PPI in REKO mice and their wildtype controls ($n = 9$ and $n = 10$, respectively) and in NSE mice and their controls ($n = 10$ each). Data are mean \pm S.E.M. All treatments significantly reduced PPI, however, there were no differences between REKO or NSE mice and their respective controls.

(Fig. 2), this effect did not reach statistical significance at the level of a genotype \times treatment interaction.

3.3. Effect of apomorphine, amphetamine or MK-801 on PPI in NSE-AT_{1A} mice

While there was the expected significant effect of prepulse level, there was no significant difference between NSE-AT_{1A} mice and non-transgenic littermates in baseline PPI, as measured after saline injection (Fig. 2).

Apomorphine treatment induced a significant disruption of PPI ($F(1,18) = 18.2$, $P < 0.0001$) which was similar in NSE-AT_{1A} mice compared to non-transgenic littermates (Fig. 2). Amphetamine treatment also induced significant disruption of PPI (main effect of Treatment $F(1,18) = 11.2$, $P = 0.004$) which again was similar in NSE-AT_{1A} mice compared to non-transgenic littermates (Fig. 2). MK-801 treatment also caused significant disruption of PPI (main effect of Treatment $F(1,18) = 6.9$, $P = 0.017$). However, there was no difference between NSE-AT_{1A} mice and their controls in the effect of MK-801 (Fig. 2).

4. Discussion

Following our previous experiments in ACE knockout mice, the aim of the present study was to further investigate the possible role of angiotensin in PPI, a measure of sensorimotor gating which is disrupted in schizophrenia and other mental illnesses. We used REKO mice, which have reduced activity of the RAS (Adams et al., 2006), and NSE-AT_{1A} mice with enhanced central activity of the RAS and exaggerated responses to endogenous angiotensin II (Lazartigues et al., 2002; Moore et al., 2007). Thus, these mice potentially represent down-regulated and up-regulated central RAS activity, respectively.

From our previous finding of an interaction of ACE with dopaminergic regulation of PPI (Van den Buuse et al., 2005b), we postulated that angiotensin could impact upon PPI by facilitating the action of dopaminergic stimulation, either by the dopamine receptor agonist, apomorphine, or the dopamine releaser, amphetamine, but not non-dopaminergic effects on PPI, such as by the NMDA receptor antagonist, MK-801. In the present experiments, treatment with apomorphine,

amphetamine, and MK-801 caused the expected disruption of PPI. However, in contrast to our previous study in ACE knockout mice, neither REKO nor NSE-AT_{1A} mice showed abnormal effects of apomorphine or amphetamine (or MK-801) on PPI. This would argue against an involvement of angiotensin in PPI and suggests that the effects of ACE knockout or ACE inhibition (Van den Buuse et al., 2005b) were mediated by mechanisms other than inhibition of angiotensin formation.

In addition to its role in converting angiotensin I to the active form, angiotensin II, ACE also acts as a kininase that catalyses the breakdown of bradykinin to its inactive form, and is involved in the processing of several other neuropeptides such as Met- and Leu-enkephalin, substance P, dynorphin and neurotensin (Skidgel and Erdos, 1987). Little is known about the potential involvement of these neuropeptides in PPI. Several have, however, been shown to affect the activity of neurotransmitter systems involved in PPI regulation. For example, substance P is a potent modulator of acetylcholine release in the striatum (Guzman et al., 1993) and of dopamine release in the nucleus accumbens (Elliott et al., 1986). Enkephalins and other opioid peptides similarly modulate mesolimbic dopaminergic activity at several sites in the brain (Spanagel et al., 1992). All of these peptidergic systems could therefore play a role in the effects observed in ACE knockout mice or after pharmacological ACE inhibition (Van den Buuse et al., 2005b) and further studies are required to determine their possible role in the central role of ACE in PPI regulation.

A number of other effects were also seen in the genetically modified animals in this study. REKO mice tended to have reduced startle responses, a difference which became significant after treatment with MK-801. The cause or significance of this startle difference remains to be clarified, but it could be caused by similar mechanisms as the locomotor hypoactivity reported in these mice (Adams et al., 2006). The relative lack of an effect of MK-801 could then point to possible deficits in NMDA receptor-mediated regulation of behaviour, although further experiments are needed to confirm this. There is also the need for larger numbers of animals per group as some drug effects on startle, for example the effect of amphetamine in REKO mice and their controls, did not reach statistical significance. It was also interesting to observe that the large increase in startle responses after MK-801 treatment observed in REKO wildtype controls was not observed in either NSE-AT_{1A} mice or their controls. This shows that control strains may not respond identically to pharmacological challenges and emphasizes the importance of proper, preferably littermate, controls when testing behavioural effects of genetic mutations. It should also be noted that, overall, the genotype differences in startle responding and the extent of drug effects on startle were moderate and unlikely to influence the PPI results.

In conclusion, REKO mice and NSE-AT_{1A} mice, which show reduced and enhanced RAS activity, respectively, did not differ from controls in the effects of apomorphine, amphetamine and MK-801 on PPI. These data suggest that genetically induced down-regulation or up-regulation of the activity of the angiotensin system in the brain do not alter regulation of PPI

in mice. This casts doubt on a significant involvement of brain angiotensin in sensorimotor gating and, possibly, in schizophrenia. Our previous results on the effects of reduced ACE activity could be explained by neuropeptide mechanisms other than angiotensin. Our results also have wider implications in that they show that the use of one genetically modified model, in this case the angiotensin-converting enzyme knockout mouse (Van den Buuse et al., 2005b), does not necessarily correctly predicts the role of a particular neuropeptide, in this case angiotensin, unless further and more specific mouse models are tested to confirm the initial results.

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