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BRIEF REPORT

Haloperidol alters circadian clock gene product expression in the mouse brain

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Abstract

Objectives. Circadian rhythms are patterns in behavioural and physiological measures that recur on a daily basis and are driven by an endogenous circadian timekeeping system whose molecular machinery consists of a number of clock genes. The typical anti-psychotic haloperidol has previously been shown to induce significant deficiencies in circadian timing in patients. In this study we examined the impact of haloperidol treatment on molecular components of the circadian clock in the mouse brain. *Methods.* We examined how haloperidol treatment, either acute (both at day and night) or chronically over 14 days, alters the expression of three clock gene protein products (PER1, PER2, BMAL1) across the mouse brain by means of immunohistochemistry. *Results.* Chronic haloperidol treatment significantly decreases the expression levels of PER1 in a number of brain areas, including the hippocampus, the prefrontal and cingulate cerebral cortex and the paraventricular nucleus of the hypothalamus. PER2 expression was only altered in the dentate gyrus and the CA3, and BMAL1 expression was only altered in the paraventricular nucleus of the hypothalamus. *Conclusion.* These data indicate that haloperidol has the potential to alter circadian rhythms via modulation of circadian clock gene expression.

Key words: *Circadian, haloperidol, clock gene, anti-psychotic, PER1*

Introduction

The temporal regulation of physiological and behavioural processes with near 24 periods is driven by the circadian timekeeping system consisting of a master pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus, with other brain and peripheral sites also possessing circadian clocks with varying abilities to maintain circadian time in an autonomous fashion (Hastings et al. 2008). The molecular basis for circadian rhythm generation depends on a panel of clock genes, which regulate their own expression as well as driving the expression of clock controlled outputs. These clock genes include *Per1, Per2, Bmal1, Clock, Cry1* and *Cry2*, amongst others. Recent studies have reported rhythmic expression of clock genes in various parts of the mammalian brain such as the hippocampus, amygdala and the dopaminergic midbrain (Guilding and Piggins 2007).

Circadian rhythm disturbance has been described in many psychiatric disorders (Benca et al. 2009). There are a number studies reporting that patients with schizophrenia display markedly abnormal circadian rhythms (e.g., Martin et al. 2005). However, it has been postulated that in patients treated with typical anti-psychotics, such as haloperidol, this circadian disturbance may be, at least in part, treatment-related, perhaps due to lowering arousal and activity levels (Wirz-Justice et al. 1997, 2001). Interestingly, similar circadian rhythm disturbance has been reported in patients with Gilles de la Tourette syndrome (Ayalon et al. 2002) and Alzheimer's disease (Wirz-Justice

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et al. 2000) treated with haloperidol. Further, in the limited number of studies where such interventions were possible, switching from typical to atypical (e.g., clozapine) antipsychotics ameliorated the deterioration in circadian rhythmicity (Wirz-Justice et al. 1997, 2000).

A possible mechanism via which haloperidol and other typical antipsychotics disrupt circadian rhythms involves perturbation of the molecular components of the circadian clock. A number of psychoactive drugs have been described to modulate clock gene expression in various brain regions (Manev and Uz 2006). In the mouse SCN haloperidol leads to a phase-independent upregulation of *Per1* across the diurnal cycle following a single treatment (Viyoch et al. 2005). In the present study we have examined whether haloperidol, administered in either an acute or a chronic manner, alters the expression of three clock gene products (PER1, PER2 and BMAL1) in a number of sites in the mouse brain. While haloperidol is no longer widely used in the clinic except for severe cases (Joy et al. 2006) it remains an important tool to investigate effects of antidopaminergic substances. This is important since some of the modern atypicals (such as risperidone and amisulpride) still exhibit considerable antidopaminergic properties (e.g., Moller 2005). Thus, in the current study we set out to examine if there were molecular correlates in mice of the circadian rhythm disruption observed in patients treated with haloperidol.

Methods

Animals

Two- to three-month-old male C57/Bl6 mice, maintained under a 12/12-h light/dark cycle with water and food available ad libitum in constant temperature and humidity were used. Upon sampling, brains were removed rapidly and frozen, prior to being fixed in 4% paraformaldehyde. Animals received intraperitoneal injection of haloperidol (5 mg/kg) at Zeitgeber Time (ZT) 3 (where ZT0 is lights on) and were sampled 6 h later (ZT9). Acutely treated animals received a single dose of haloperidol, chronically treated animals received a daily dose for 14 days, and were sampled 6 h following the final treatment (ZT9). Control animals either received a single dose of 0.9% saline or a daily injection of saline for 14 days. There were a further two treatment groups, which either received saline or haloperidol 2 h after lights out (ZT14) and were sampled 6 h later (ZT20). Group size for each of the six treatments was six to seven. Night-time sampling was conducted under dim red light. The experimental protocols were in compliance with the European Communities Council Directive (86/609/EEC).

Immunohistochemistry

Brains underwent an antigen-unmasking procedure by overnight incubation in 0.1 M citrate buffer (pH 4.5) followed by 2.5 min heating in a microwave oven at 700 W followed by cryoprotected in sucrose (30%) for a further 24 h, and then sectioned at 30 μm (four sets of serial sections) on a freezing stage microtome. Free-floating sections were processed via a standard avidin-biotin complex/nickel-DAB immunohistochemical protocol. Primary antibodies used in this study were polyclonal antibodies raised in rabbit against PER1, PER2 and BMAL1 (all Santa Cruz Biotechnology, Germany) and were all used at a dilution of 1:500. The use and specificity of these antibodies in immunohistochemistry in the mouse brain has previously been described (Koyanagi and Ohdo 2002; Borgs et al. 2009; Wyse and Coogan 2010). Further to this, for the PER1 and PER2 antibodies, the immunising peptides were used for adsorbtion control, resulting in blocking of immunostaining (data not shown; the immunising peptide for the BMAL1 antibody was not available). Sections for each antigen were reacted for standardized lengths of time to allow for uniform intensity of staining across experimental groups. Sections were then mounted onto gelatin-coated slides, dried, dehydrated, cleared in Histoclear (National Diagnostics, UK), and coverslipped using Entellan (Merck, UK).

Image analysis and statistics

Levels of immunostaining were densitometricaly assessed using the Scion Image 4.2 software (Scion Corporation, Frederick, MD). Photographs of the regions of interest were taken using a digital camera mounted on an Olympus BX-51 microscope. Regions of interest were defined as by the mouse brain atlas of Paxinos and Franklin (2004). Background levels of staining in non-specifically stained adjoining regions were subtracted for each region of interest, and stain density within a user-defined region of the unilateral area of interest was analysed by measurement of optical density. At least five photographs per animal were quantitated for each brain region. Statistical analysis was carried out on SPSS (www.spss.com) on a PC using two-way ANOVAs (with treatment (six levels) and brain area (12 levels) as the factors) as well as with one-way ANOVAs with a priori testing (the haloperidol treated groups compared to their respective saline controls for each specific brain region, as well as day acute control saline vs. night acute control saline): $P < 0.05$

was considered statistically significant. The areas examined in this study were: hippocampus – CA1, CA3 and dentate gyrus (DG); cerebral cortex: prefrontal infralimbic (ILC), prefrontal perlimbic (PLC) and medial cingulate (CC); amygdala: central nucles (CEA) and basolateral nucleus (BLA); hypothalamus: suprachiasmatic nucleus (SCN) and paraventricular nucleus (PVN); ventral tegmental area (VTA), caudate putamen (CPu).

Results

There was expression of PER1, PER2 and BMAL1 in all of the brain areas examined, and the nature of the staining was predominantly nuclear (Figure 1).

Two-way ANOVA revealed significant main effects of treatment, region and significant region × treatment interactions for PER1 and PER2 ($P < 0.001$ in all cases), whilst there was a significant main effect of region (but not treatment) for BMAL1, and a significant region × treatment interaction ($P < 0.001$). Upon further region by region analysis we found that PER1 was the most reactive antigen to haloperidol treatment (Figure 2A) and that the most common effects were suppression of PER1 expression following chronic haloperidol treatment. The PVN ($P < 0.05$), PFC-IL ($P < 0.005$), PFC-PL ($P < 0.05$), CA1 ($P < 0.01$), CA3 ($P < 0.001$), DG ($P < 0.05$) and CC ($P < 0.01$) all showed significantly reduced levels compared to controls following chronic haloperidol treatment. In contrast to this, the effects of acute haloperidol treatment were more modest on PER1: day-time treatment elicited a significant suppression only in the CC, whilst night-time treatment enhanced expression significantly in the PFC-PL and the CC. The SCN did not show any significant change in PER1 expression following any of the haloperidol treatment schedules. There were significant day/night differences between the acute saline control groups in the SCN, the CC, the VTA, the CPu and the CeA.

For PER2 immunoreactivity, the effects of haloperidol treatment were less marked. Chronic treatment resulted in significant upregulation of PER2 in the CA3 ($P < 0.05$) and the DG ($P < 0.01$), whilst daytime acute treatment did not significantly alter the expression of PER2 in any of the regions examined (Figure 2B). Night-time acute treatment resulted in an upregulation of PER2 immunoreactivity solely in the BLA ($P < 0.05$). There were no significant effects observed in the SCN. There were significant day/night differences between the acute control groups in the SCN, PVN, CA3, DG and CPu. BMAL-1 immunoreactivity was only significantly altered in the PVN ($P < 0.05$) following chronic haloperidol treatment (Figure 2C), with acute treatments in either day or night phases ineffective at altering its expression. There were significant day/night differences in BMAL-1 levels in the PFC-IL, DG, VTA, CPu, CeA and BLA.

Discussion

This is the first study to examine the effects of haloperidol expression on clock gene product

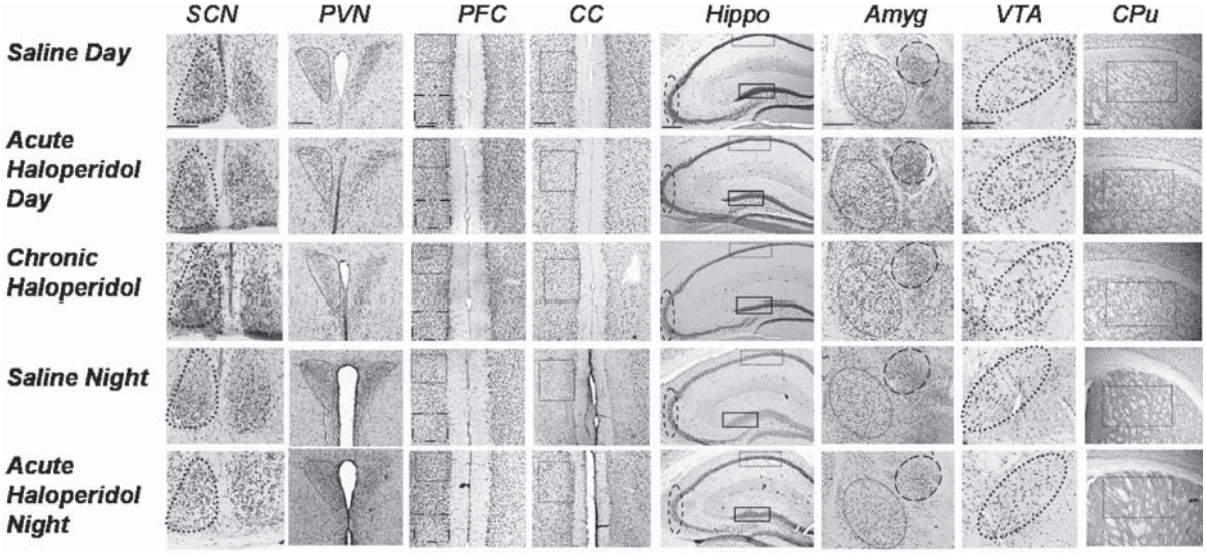

Figure 1. Sample photomicrographs of PER1 expression in the areas of interest and treatments examined in this study. For each are the area delineated for analysis is outlined. For the prefrontal cortex (PFC) the dotted box represent the area of prelimbic cortex examined and the dashed box the area of infralimbic cortex. For the hippocampus (Hippo), the dotted box is in the CA1, the dashed ellipse the CA3 and the solid-outline box the dentate gyrus. For the amygdala (Amyg) the dotted oval represents the basolateral amygdala and the dashed circle the central nucleus. The scale bar = 200 μm.

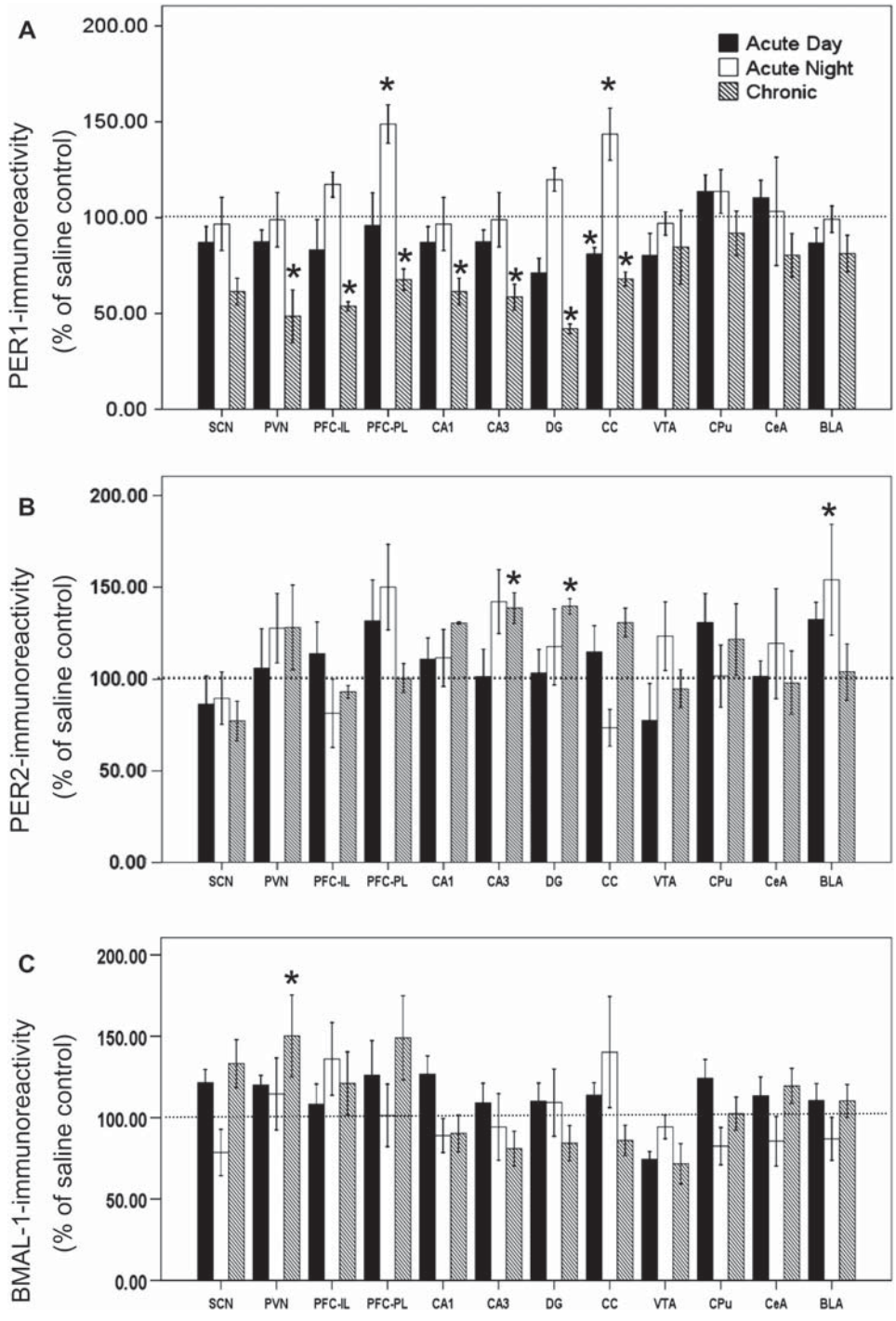

Figure 2. Semi-quantitation of photomicrographs for regulation of (A) PER1, (B) PER2 and (C) BMAL1 expression by haloperidol treatment. Each group (acute haloperidol day (black bars), acute haloperidol night (white bars), chronic haloperidol (hatched bars)) is expressed as a percentage of its respective saline group mean value. Significant effects of drug treatment compared to the appropriate saline control group is denoted by*. The regions examined were: cerebral cortex: hypothalamus: suprachiasmatic nucleus (SCN) and paraventricular nucleus (PVN); prefrontal infralimbic (PFC-IL), prefrontal perlimbic (PFC-PL) and medial cingulate (CC); Hippocampus – CA1, CA3 and dentate gyrus (DG); amygdala: central nucles (CEA) and basolateral nucleus (BLA); ventral tegmental area (VTA), caudate putamen (CPu).

expression in a number of brain areas. The results from this study, that PER1 and to a much lesser extent PER2 and BMAL-1, expression is altered in a number of these areas, provides molecular evidence that haloperidol may alter circadian time across the brain.

A number of studies have implicated circadian processes in schizophrenia (Wirz-Justice et al. 2001;

Mansour et al. 2006), although candidate clock gene association studies are equivocal (e.g,. Kishi et al. 2009b; Mansour et al. 2009). Previous studies have indicated interplay between the circadian system and typical antipsychotics. Circadian processes are known to influence haloperidol's actions, with circadian rhythms described in haloperidol-induced catalepsy (Campbell and Baldessarini 1982), a principle that is also found for other psychoactive medications (Kishi et al. 2009a). Conversely, Viyoch et al. (2005) reported that acute haloperidol treatment increases the expression of *per1* in the SCN across the diurnal cycle, an effect that was independent of the time of day of the treatment and was blocked by the NMDA-channel blocker MK801 and involved the transcription factor CREB. The effects of haloperidol, along with clozapine and anxiolytics, was examined on the expression of *per1*and *per2* in the mouse cerebellum in study by Akiyama et al. (1999), with no effects of haloperidol treatment on either of these clock genes reported. In the present study we did not demonstrate any significant effect of haloperidol treatment on SCN expression of PER1, PER2 and BMAL1. Viyoch et al. (2005) report that *per1* is upregulated in the SCN with treatments administered across the diurnal cycle, and therefore it seems unlikely that we fail to show SCN effects by treating at an unresponsive circadian phase. A possibility is that neither of our sampling times (ZT9, ZT20) include the early-night peak of SCN PER1 and PER2, therefore raising the possibility that a suppression of maximal SCN PER1/2 levels might be missed. The results of Honma and Honma's study (1995) of SCN lesioned rats showing that haloperidol can alter behavioural circadian rhythms mediated outside of the SCN is in broad agreement with our results, indicting that haloperidol elicits circadian effects by, in part at least, acting outside of the SCN. Further, the lack of effect on SCN clock gene product expression is in line with the observation that halopediol does not entrain rat behavioural circadian rhythms (Gillman et al. 2009). Other factors, such as the time between treatment and sampling for acutely treated animals (e.g., is 6 h sufficient time to see alterations in levels of PER1 protein?), a disconnect between mRNA and protein expression and the effects of repeated doses for chronic treatment, may be responsible for the differences observed between our results in the SCN and those of Viyoch et al. (2005).

Since many brain areas are now believed to possess at least the molecular machinery required to act as circadian oscillators (Guilding and Piggins 2007), it is of particular interest to investigate the effects of psychoactive substances across a number of brain sites, including those previously shown to respond to a particular drug (e.g., by c-Fos expression, Roberstson and Fibiger 1992). The functional significance of clock gene expression in many brain sites is incompletely understood, partly due to the complexity of delineating their circadian functions from any non-circadian functions, and partly in teasing apart the autonomous role of a circadian clock in a particular structure apart from the functioning of the brain's distributed circadian system as a whole. However, evidence is now emerging regarding important roles for circadian clocks in the functioning of extra-SCN sites: for example, the hippocampus expresses rhythmic patterns of clock genes, and disruption of these by gene knockout affects memory task performance and synaptic plasticity (Gerstner and Yin 2010). If haloperidol alters the hippocampal circadian clock, which in turn contributes to memory function, one might speculate that this effect could contribute to the deleterious effects of haloperidol in hippocampal-dependent memory (e.g., Hou et al. 2006). For a number of the regions examined in the present study, it is still somewhat speculative as to what the functional consequence of rhythmic clock gene expression is, although one might imagine for example roles for the circadian clock in the prefrontal cortex in the temporal regulation of executive function and working memory, as has been described in humans (Schmidt et al. 2007). Further, alteration of the normal prefrontal circadian processes by haloperidol could contribute to haloperidol-induced deficits in working memory (Castner et al. 2000). Therefore, it is conceivable that the poor profile of haloperidol in ameliorating, or even worsening, neurocognitive deficits may be mediated partly through effects on circadian processes.

Broader dopaminergic regulation of clock gene expression is evidenced by Imbesi et al. (2009) who report that in cultured primary striatal neurons the D2 class agonist quinpirole suppresses expression of *clock* and *per1*, whilst the D1 agonist SKF38393 enhances *clock*, *per1*, *bmal1* and *npas2* expression, with quinpirole also phase-shifting of PER1 expression in the striatum *in vivo*. Acute exposure to cocaine leads to increased *per1* but not *per2* and *bmal1* expression in the hippocampus, whereas chronic cocaine administration increases *per1* and *per2* levels (Uz et al. 2005). The same study shows that acute cocaine does not affect *per1*, *per2* or *bmal1* in the caudate putamen, but chronic cocaine does upregulate *per1* and downregulates *per2* and *bmal1*. Whilst it is difficult to compare these results with those presented in this paper (haloperidol vs. cocaine, protein vs. mRNA expression), it is interesting to note the differential regulation of *per1*, *per2* an *bmal1*, the regional specificities of the effects and the fact that chronic treatment is more efficacious at producing alterations in

clock gene expression than acute treatments, all facets that are reported in the current study with regards to haloperidol. The molecular mode of action by which oppossing regulation of PER1 and PER2 may be brought about by dopaminergic agents is not clear and warrants further study. One possibility is that the rhythmic expression of PER1 and PER2 may have somewhat different phasing in any given brain area (Feillet et al. 2008) and haloperidol-induced phase-shifts of these rhythms may appear to have opposing actions (e.g., PER1 may be shifted away from its peak, PER2 may be shifted towards its peak).

Our current study indicates that haloperidol can alter expression of circadian clock genes in various sites across the brain. This potentially disruptive effect on the molecular mechanisms of circadian timekeeping might in part explain the disruptive effects of haloperidol on behavioural rhythms reported in patient studies (Wirz-Justice et al. 1997, 2000, 2001; Ayalon 2002), effects that are seen to persist throughout haloperidol monotherapy (Wirz-Justice et al. 2001). Our results highlight the deleterious consequences typical anti-psychotics may have for patients' circadian rhtyhms. However, it is worth considering such negative effects in the light of improved sleep measures also reported for haloperidol in schizophrenics (Monti and Monti 2004), indicating possible divergent regulation of sleep homeostatic and circadian processes. Given the partial antidopaminergic properties of widely used atypical anti-psychotics (reported to improve circadian rhythms in demented or schizophrenic patients), examining their effects on circadian clock gene expression will be of considerable future interest. Studies of rhythmic clock gene expression in patients treated with antipsychotics (both typical and atypical) would also be most revealing.

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Statement of Interest

The authors have no conflicts of interest.

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