Neuropsychopharmacology (2009) 34, 2585–2600

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H_3 Receptor Antagonism Enhances NCAM PSA-Mediated Plasticity and Improves Memory Consolidation in Odor Discrimination and Delayed Match-to-Position Paradigms

Andrew G Foley[1], Alison Prendergast[1], Claire Barry[1], Darren Scully[1], Neil Upton[2], Andrew D Medhurst[2] and Ciaran M Regan*[,3]

[1]Berand Neuropharmacology, NovaUCD, Belfield Innovation Park, University College Dublin, Dublin, Ireland; [2]Neurosciences Centre of Excellence for Drug Discovery, GlaxoSmithKline, Harlow, UK; [3]School of Biomolecular and Biomedical Science, UCD Conway Institute, University College Dublin, Belfield, Dublin, Ireland

To further understand the procognitive actions of GSK189254, a histamine H_3 receptor antagonist, we determined its influence on the modulation of hippocampal neural cell adhesion molecule (NCAM) polysialylation (PSA) state, a necessary neuroplastic mechanism for learning and memory consolidation. A 4-day treatment with GSK189254 significantly increased basal expression of dentate polysialylated cells in rats with the maximal effect being observed at 0.03–0.3 mg/kg. At the optimal dose (0.3 mg/kg), GSK189254 enhanced water maze learning and the associated transient increase in NCAM-polysialylated cells. The increase in dentate polysialylated cell frequency induced by GSK189254 was not attributable to enhanced neurogenesis, although it did induce a small, but significant, increase in the survival of these newborn cells. GSK189254 (0.3 mg/kg) was without effect on polysialylated cell frequency in the entorhinal and perirhinal cortex, but significantly increased the diffuse PSA staining observed in the anterior, ventromedial, and dorsomedial aspects of the hypothalamus. Consistent with its ability to enhance the learning-associated, post-training increases in NCAM PSA state, GSK189254 (0.3 mg/kg) reversed the amnesia induced by scopolamine given in the 6-h post-training period after training in an odor discrimination paradigm. Moreover, GSK189254 significantly improved the performance accuracy of a delayed match-to-position paradigm, a task dependent on the prefrontal cortex and degree of cortical arousal, the latter may be related to enhanced NCAM PSA-associated plasticity in the hypothalamus. The procognitive actions of H3 antagonism combined with increased NCAM PSA expression may exert a disease-modifying action in conditions harboring fundamental deficits in NCAM-mediated neuroplasticity, such as schizophrenia and Alzheimer's disease.

Neuropsychopharmacology (2009) **34,** 2585–2600; doi:10.1038/npp.2009.89; published online 5 August 2009

Keywords: GSK189254; odor discrimination paradigm; delayed match-to-position paradigm; spatial learning; NCAM PSA; neurogenesis

INTRODUCTION

Histamine mediates diverse biological effects through the histamine H_1, H_2, H_3, and H_4 receptor subtypes (Hough, 2001). The H_3 receptor is widely expressed in the mammalian brain, particularly in regions associated with cognition and arousal, such as the cerebral cortex, hippocampus, and hypothalamus (Martinez-Mir *et al*, 1990; Pollard *et al*, 1993; Pillot *et al*, 2002). Activation of H_3 autoreceptors inhibits histamine synthesis and release, whereas activation of H_3 heteroreceptors inhibits the release of transmitters such as acetylcholine, noradrenaline, dopamine, and 5-HT from non-histaminergic neurons (Schlicker *et al*, 1994; Schlicker and Kathmann, 1998; Brown *et al*, 2001). As a consequence, several strategies are being pursued for the development of selective histamine H_3 receptor antagonists that increase the release of neurotransmitters involved in cognitive processes, such as acetylcholine (Johnson *et al*, 2004; Witkin and Nelson, 2004). The first generation of imidazole-based molecules, including thioperamide (Arrang *et al*, 1987), have recently been superseded with the second generation of non-imidazole H_3 receptor antagonists (Hancock, 2003; Stark, 2003; Celanire *et al*, 2005; Leurs *et al*, 2005) and many of these exert significant cognition-enhancing actions in a variety of rodent models, including object recognition, olfactory recognition, water maze, radial maze, and passive avoidance conditioning paradigms (Esbenshade *et al*, 2003, 2004, 2005; Fox *et al*, 2003, 2005; Medhurst *et al*, 2007).

H_3 receptor antagonists, such as GSK189254 (6-((3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy)-*N*-methyl-3-pyridinecarboxamide hydrochloride), ABT-239 (4-(2-(2-((2*R*)-2-methylpyrrolidinyl)ethyl)-benzofuran-5-yl)

*Correspondence: Professor CM Regan, School of Biomolecular and Biomedical Science, UCD Conway Institute, University College Dublin, Belfield, Dublin 4, Ireland, Tel: +353 1 7166775, Fax: +353 1 7166920, E-mail: Ciaran.Regan@ucd.ie
Received 3 April 2009; revised 27 May 2009; accepted 20 June 2009

benzonitrile) and ciproxifan, have also been shown to induce *c-fos* activation in cortical, hippocampal, and hypothalamic brain regions (Hancock *et al*, 2006; Medhurst *et al*, 2007), a neuroplastic event associated with processes of memory consolidation (Guzowski, 2002; Kaczmarek *et al*, 2002). GSK189254 can also reverse amnesia induced by scopolamine administered at 6 h after passive avoidance conditioning (Medhurst *et al*, 2007), a period associated with extensive synaptic remodeling during consolidation of avoidance conditioning and spatial learning paradigms within the rodent hippocampal dentate gyrus (O'Malley *et al*, 1998, 2000; Eyre *et al*, 2003). Such synaptic remodeling is accompanied by the activation of neural cell adhesion molecule (NCAM) polysialylation (PSA) state, a mechanism supporting structural plasticity in the adult nervous system (Bonfanti, 2006; Gascon *et al*, 2007; Rutishauser, 2008). Interestingly, NCAM PSA is significantly enhanced by chronic administration ($\sim$40 days) of cognition-enhancing drugs such cholinesterase inhibitors (Murphy *et al*, 2006) and 5-HT6 receptor antagonists (Foley *et al*, 2008).

In the adult brain, NCAM PSA is primarily associated with regions that undergo structural reorganization in response to physiological and/or behavioral stimuli, such as the hypothalamus and hippocampal formation (Bonfanti *et al*, 1992). The consolidation of many behavioral tasks is now known to require a transient increase in the frequency of polysialylated neurons, notably at the 12 h post-training time, in the hippocampal dentate gyrus (Fox *et al*, 1995 [84]Murphy *et al*, 1996; Foley *et al*, 2003a; Sandi *et al*, 2003, 2004) and associated entorhinal and perirhinal cortex (O'Connell *et al*, 1997; Fox *et al*, 2000). Moreover, disruption of PSA function, by intraventricular infusion endoneuraminidase-N or anti-PSA, impairs task consolidation (Becker *et al*, 1996; Muller *et al*, 1996; Venero *et al*, 2006; Lopez-Fernandez *et al*, 2007; Seymour *et al*, 2008). Many of the NCAM PSA-immunopositive cells located at the infragranular zone of the dentate gyrus have been identified as newly generated granule cells that remain available for integration into the neuronal architecture and before their natural loss by apoptosis (Ge *et al*, 2007; Dupret *et al*, 2007; Toni *et al*, 2008). Similarly, the activity-dependent modifications to hypothalamic synapse and astrocytic coverage of oxytocinergic neurons, which occur in response to physiological stimuli arising during parturition, lactation, or chronic dehydration, are dependent on NCAM PSA, as these are prevented by infusions of endoneuraminidase-N (Hoyk *et al*, 2001; Monlezun *et al*, 2005; Catheline *et al*, 2006; Theodosis *et al*, 2006).

To further explore the influence of H_3 antagonism on the processes of memory consolidation, we investigated the effects of GSK189254 and thioperamide on the modulation of NCAM PSA state, as this has been shown to underpin learning-associated synaptic remodeling, and is a necessary neuroplastic mechanism for memory and learning.

METHODS

Animal Maintenance

Naive male Wistar rats (postnatal day 80, $\sim$350 gm) were employed in all studies. The animals were purpose bred at the Biomedical Facility, University College Dublin, and maintained in standard laboratory conditions until the time of use. Animals were introduced to the experimental holding rooms 5 days before the commencement of the study, housed in pairs during this period, and maintained at 22–24°C on a standard 12-h light/dark cycle, with food and water available *ad libitum*. Food-restricted animals were maintained at approximately 90% of their free-feeding weight ($\sim$20 g/rat/day) with *ad libitum* access to water. For 2 days preceding the commencement of behavioral studies, the animals were handled, and weighed and assessed in an open field arena for locomotor activity, rearing, and general behavior over a 5-min period. All experimental procedures were approved by the Animal Research Ethics Committee of University College Dublin, conformed to EU Council Directive 86–609-EEC, and were carried out by individuals retaining the appropriate license issued by the Irish Department of Health.

Odor–Reward Association Paradigm

The training protocol employed has been described previously (Roullet *et al*, 1997; Foley *et al*, 2003a). Each individual animal was assigned a specific target odor that was always associated with the sponge that contained the food reward and the sponges were interchanged between the three corners of the training apparatus between trials to prevent spatial bias. Training was carried out in a single session of five trials. An inter-trial interval of 5 min was allowed between trials, and latency (s) was defined as the time taken to correctly identify the correct target odor and obtain the associated food reward. Animals were tested for recall in a single trial 24 and 72 h after training. Statistical analysis of the behavioral data employed two-way ANOVA and the Mann–Whitney *U*-test for non-parametric data. In each case, *p*-values less than 0.05 were considered to be significant.

Water Maze Spatial Learning Paradigm

The training protocol employed has been described previously (Murphy *et al*, 1996; Foley *et al*, 2004). Water maze training was initiated at 4 h after the final drug administration. During testing, the platform was hidden in the same quadrant 30 cm from the sidewall. Animals were trained in a single training session consisting of 5 trials, each separated by an inter-trial test interval of 300 s. Computerized tracking software (Watermaze 3.1, Labview written by Matthias Grossmann, Dresden, Germany) was used to track the swim path for each animal. The time taken by the rat to find the hidden platform within a 90-s criterion period was defined as the escape latency time. Escape latencies were measured over five trials in each training session. The effect of drug treatment and trial number on escape latency from the water maze was assessed by repeated measures ANOVA. Specific trials and probe differences were analyzed using Mann–Whitney *U*-test for non-parametric data. In all cases, *p*-values less than 0.05 were considered to be significant.

Delayed Match-to-Position Paradigm

The training paradigm employed was based on a modification of those previously described (Dunnett, 1985, 1993;

Kirkby *et al*, 1995; Sahgal, 1987). Postnatal day 80 Wistar rats were housed in pairs and autoshaped for lever pressing over a period of 40 days. Animals were required to remember which of two levers had previously been presented and select (press) this lever following a random delay period to record a correct response and receive food reinforcement. Animals were considered to have completed the autoshaping training once they had achieved a stable level of daily performance ($>85\%$ successful trials) over a period of 3 consecutive days. During training, a single lever was presented and, after defined delay periods of 4–32 s, two levers were introduced and selection of the correct lever resulted in a food reward. Animals were trained each day in 72 trials, 12 of each delay period pseudorandomly presented, over a period of 4 days using a block design that ensured each animal was administered each dose of the test compound and, thereby, served as its own control. Performance of the animals in the delayed match-to-position (DMTP) paradigm was expressed as percent correct lever press at increasing delay periods, and values significantly different between the vehicle- and drug-treated groups were analyzed by two-way ANOVA and the Mann–Whitney *U*-test for non-parametric data. In each case, *p*-values less than 0.05 were considered to be significant.

Quantitative Analysis of BrdU and NCAM PSA Expression

BrdU immunolabeling. After transcardial perfusion with a 4% paraformaldehyde solution (pH 7.4), brains were removed and snap-frozen. For the analysis of bromodeoxyuridine (BrdU)-immunopositive hippocampal dentate granule cells, horizontal sections (50 μm) were taken at 500-μm intervals between level 4.1 and 7.6 mm below bregma (Paxinos and Watson, 1986). The sections were then washed in 0.1 M phosphate-buffered saline (PBS) containing 5 mM MgCl2 and 1 mM CaCl2, and denatured at 37°C for 1 h in DNAse (1000 U/ml). The sections were again washed and blocked with 10% (v/v) normal goat serum (NGS) for 30 min, then incubated for 20 h with the primary antibody (anti-rat IgG BrdU; Harlan, Bicester, UK) diluted 1 : 100 in PBS containing 10% (v/v) NGS. Subsequently, the sections were washed and incubated at room temperature for 1 h with the secondary antibody (Alexa488 or Alexa647 goat anti-rat IgG; Molecular Probes, Paisley, UK) diluted 1 : 200 again in PBS containing 10% NGS. The sections were again washed and mounted in Citifluor© (Agar, Essex, UK).

The total number of immunopositive cells within the entire granule cell layer of each section was determined by the Cavalieri method, as previously described (Mirescu *et al*, 2004). The average density of BrdU-labeled cells per granule cell layer at each bregma level was established and used to estimate the total number of BrdU-immunopositive cells in the hippocampus of each treatment group by multiplying the density of immunopositive cells by the estimated volume. Statistical analysis employed ANOVA followed by Bonferroni *post hoc* test and analysis by Student's *t*-test. For qualitative purposes, some sections from 4% paraformaldehyde-perfused brains were employed for double immunolabeling of NCAM PSA and BrdU in the hippocampal formation at a level −5.6 mm from bregma. The same immunohistochemistry staining protocols were employed but without 70% ethanol post-fixation.

NCAM PSA immunolabeling. The immunohistochemical procedures employed to detect NCAM PSA have been described in greater detail previously (Fox *et al*, 1995). Cryosections were thaw-mounted onto glass slides, fixed for 30 min with 70% ethanol, and incubated overnight with anti-PSA ascitic fluid (generous gift of Prof G Rougon; Rougon *et al*, 1986) diluted 1 : 500 in 1 M PBS containing 1% (w/v) BSA and 1% (v/v) NGS. The sections were exposed for 1 h to Alexa488- or Alexa647-conjugated goat anti-mouse IgM (Molecular Probes) diluted 1 : 200 in PBS containing 1% BSA and 1% NGS, and mounted in Citifluor© (Agar). For the analysis of the NCAM PSA-positive hippocampal dentate granule cell layer/hilus border cells, 10 alternate sections were taken at a level equivalent to 5.6 mm below bregma, at which level this cell population was found to be maximal. The frequency of polysialylated neurons in the rat medial temporal lobe was examined in layer II of the entorhinal and perirhinal cortices at bregma levels −7.1, −7.6, −8.1, and −8.6 mm.

The total number of NCAM PSA-immunoreactive neurons on the right dentate granule cell layer/hilar border was counted in seven alternate 12-μm sections, commencing −5.6 mm from bregma, to preclude double counting of the 5–10 μm perikarya ($n=6$). Cell counts were standardized to unit area of the granule cell layer, $0.15 \pm 0.01\,mm^2$ at this level, and expressed as mean ± SEM values. In the cortex, cell counts were standardized to unit length of the layer II band taken to be 10 mm ($n=3$). Hypothalamic NCAM PSA immunostaining was evaluated in coronal cryostat sections (12 μm), which were cut in the rostro-caudal plane at the level of 1.8 mm, 2.56, and 3.3 mm caudal to bregma. The average gray level intensity of PSA-immunopositive neurons was determined and standardized with respect to nonspecific background staining measured in the corpus callosum, and these values were used to generate mean ± SEM values for each treatment group. Statistical analysis employed the Student's *t*-test and a significance level of $p<0.05$ was employed in all cases.

Drug Administration Protocols

All studies were conducted using thioperamide and the hydrochloride salt of GSK189254 (6-((3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy)-*N*-methyl-3-pyridinecarboxamide hydrochloride. Studies addressing the influence of GSK189254 (0.1–3 mg/kg) and thioperamide (10 mg/kg) on NCAM PSA expression employed animals that had received drug or vehicle (1% methylcellulose solution in dH_2O) by oral gavage once daily for a period of 4 days and were drug free at time of analysis 24 h after the final drug treatment. This 4-day dosing regime was selected as an intermediate protocol based on efficacy observed in cognition models after 1–8 days dosing. Analysis of repeat drug administration on spatial learning was carried out 2 h after the final dose, and the animals were culled for NCAM PSA expression 12 h later. In the protocol employed in analyzing the drug influence on neurogenesis and apoptosis, BrdU (50 mg/kg) was administered by the intraperitoneal route and GSK189254 (0.3 mg/kg) by oral gavage, and

these were separated by 1 h. A second BrdU injection was given 12 h later. One cohort was killed 24 h after the final injections, whereas another cohort was maintained drug free for a further 14 days to evaluate the effects on cell survival. In both the odor discrimination and DMTP tasks, GSK189254 or vehicle was administered acutely by oral gavage 2 h before training. In the odor discrimination task, scopolamine (0.8 mg/kg) was administered by intraperitoneal injection at 20 min before training.

RESULTS

NCAM PSA in the Hippocampal Dentate Gyrus is Enhanced by Repeat Administration of GSK189254

NCAM PSA expression in the adult dentate gyrus was found to be primarily associated with granule cell bodies located at the infragranular zone and their dendritic arbor that extended through the granular cell layer and into the molecular layer (Figure 1a). A 4-day treatment with GSK189254 significantly increased the frequency of these NCAM-polysialylated cells in a dose-dependent manner ($F(4,25) = 6.39$; $p < 0.05$; one-way ANOVA) (Figure 1b). The maximal effect of GSK189254 was observed at doses of 0.03–0.3 mg/kg ($p < 0.05$; Bonferroni *post hoc* analysis) as compared with the vehicle-treated groups, and the higher doses of 1 and 3 mg/kg were without significant effect on polysialylated cell frequency, indicating the drug effect to exhibit a bell-shaped response. Repeat administration of the H_3 receptor antagonist thioperamide for 4 days also significantly increased the frequency of polysialylated neurons (Figure 1c). The thioperamide and GSK189254 studies were carried out at different times and the small variation in baseline NCAM PSA-labeled cell frequency can be found under these circumstances. The effect of GSK189254 on NCAM PSA expression was dependent on repeat drug treatment, as a single administration of GSK189254 at the optimal dose (0.3 mg/kg) was without effect on dentate polysialylated cell frequency (vehicle: 169 ± 6.1; drug-treated: 174.0 ± 12.3 cells/unit area).

Spatial Learning-Induced Activation NCAM PSA State in the Dentate Gyrus is Augmented After Repeat Administration of GSK189254

Given that the frequency of dentate polysialylated neurons transiently increase at the 12 h post-training time during the consolidation of a variety of learning paradigms (Fox *et al*, 1995; Murphy *et al*, 1996; Foley *et al*, 2003a; Sandi *et al*, 2003), and that the extent of this increase is commensurate with complexity experienced in consolidating the task (Sandi *et al*, 2004; Murphy *et al*, 2006), we determined whether GSK189254-induced increases in basal polysialylated cell expression could be further enhanced at the 12 h post-training time after water maze training. Separate cohorts of animals were treated with either vehicle or GSK189254 (0.3 mg/kg) for 4 days and trained in the water maze paradigm at 2 h after the final drug treatment. All animals acquired the spatial learning task as indicated by the gradual reduction in latency to reach the hidden platform over the five trials of the single training session ($F(4,65) = 16.47$; $p < 0.0001$; 2-way ANOVA) (Figure 2a). Moreover, a further 2-way ANOVA indicated that a 4-day treatment with GSK189254 induced a significant improvement in the acquisition of the water maze task compared with vehicle-treated controls ($F(1,65) = 5.02$; $P = 0.0285$). Analysis of the hippocampal dentate gyrus in brain tissue collected from the vehicle-treated animals at 12 h after task acquisition revealed the expected increase in polysialylated cell frequency as compared with that in the tissue taken immediately after training ($p < 0.05$; Student's *t*-test) (Figure 2b). Similarly, sections taken from the GSK189254-treated cohort revealed a significant increase in dentate NCAM PSA immunoreactivity between animals killed immediately after training (0 h) and those killed at the 12 h post-training time ($p < 0.05$; Student's *t*-test). However, comparison of vehicle- and drug-treated groups at the 12 h post-training time also showed a significant increase in dentate polysialylated cell frequency ($p < 0.05$; Student's *t*-test), indicating that this learning-induced increase was not saturated and could be further increased during consolidation after administration of GSK189254.

Dentate Neurogenic Rate is Unaffected by GSK189254 but Cell Survival is Enhanced

Many of the NCAM PSA-immunopositive cells located at the infragranular zone of the dentate gyrus have been identified as newly generated granule cells (Gage, 2000; Seki, 2002). These newborn granule cell neurons in the dentate gyrus remain available for integration into the neuronal architecture for 1–2 months after their birth (Ge *et al*, 2007; Kee *et al*, 2007) and before their natural loss by the process of apoptosis (Dupret *et al*, 2007). As this process of cell generation and loss has been argued to provide a substrate for the synaptic remodeling associated with memory consolidation (Lledo *et al*, 2006), we determined whether GSK189254 influenced neurogenic rate in the hippocampal dentate gyrus. Neurogenic rate in the infragranular zone of the dentate gyrus was determined by estimating the number of BrdU-immunolabeled cells immediately after a 4-day treatment with BrdU, and the survival of labeled cells was similarly determined 2 weeks later. BrdU immunoreactivity was located to the cell nucleus and was clearly differentiated from the cell surface labeling of anti-NCAM PSA; however, not all BrdU-immunopositive cells were immunoreactive for NCAM PSA (Figure 3a). BrdU-immunopositive cells were quantified throughout the hippocampal dentate gyrus granule cell layer from a level -4.1 to -7.6 mm with respect to bregma and expressed as total cell number, as previously documented (Foley *et al*, 2008), and showed that no drug-induced modulation of BrdU-positive cell frequency was observed after 4-day administration of GSK 189254 (vehicle: 1325 ± 98.3; GSK189254: 1366.7 ± 69.8) (Figure 3b). However, after a 14-day period, during which animals received no additional drug treatments, the number of surviving BrdU-immunopositive cells was significantly increased in the hippocampal dentate gyrus of animals that had been treated with GSK189254 (vehicle: 265 ± 33.3; GSK189254: 491.7 ± 69.9; $p < 0.05$; Student's *t*-test) (Figure 3c).

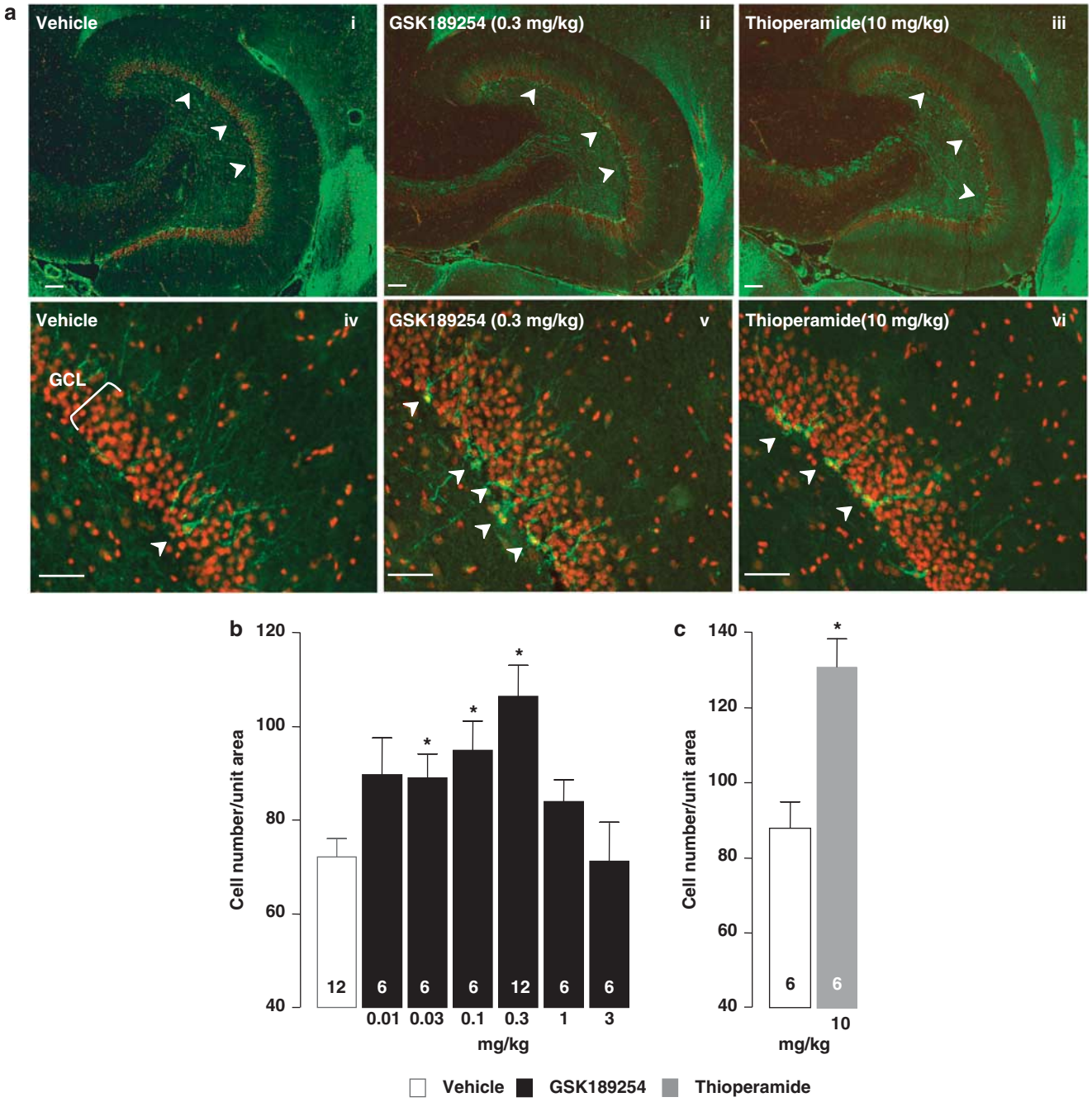

Figure 1 The effect of GSK189254 on polysialylated cell frequency in the dentate gyrus of adult Wistar rats. The animals received GSK189254 (0.3 mg/kg, p.o.), thioperamide (10 mg/kg), or vehicle (1% methylcellulose (w/v)) for 4 days and were drug free at the time of killing 24 h after the final treatment. (a) Illustrates qualitative images of PSA immunoreactivity at low- (i–iii) and high-resolution (iv–vi) in the dentate granule cell layer (GCL) at −5.6 mm with respect to bregma. The arrowheads indicate the position of the immunostained cells at the infragranular zone and the scale bars represent 100 μm. The quantitative, dose-dependent effects of repeat dosing with GSK189254 are shown in (b), and the effects of repeat dosing with thioperamide in (c). Data points represent the mean ± SEM and group sizes are indicted within the columns. Values significantly different ($p < 0.05$) from the vehicle control are indicated with an asterisk.

NCAM PSA Expression in the Hippocampal Entorhinal and Perirhinal Cortex and Hypothalamus After Treatment with GSK189254

We also investigated the influence of GSK189254 on the expression of NCAM PSA state in brain regions other than the hippocampal dentate gyrus. The entorhinal cortex of the hippocampal formation was selected because previous studies had indicated the cognition-enhancing effects of 5-HT6 antagonists to be associated with a substantial increase in NCAM PSA expression in layer II of the entorhinal and perirhinal cortex (Foley *et al*, 2008) As reported previously (O'Connell *et al*, 1997; Fox *et al*, 2000), a band of PSA-immunopositive neurons was observed in the entorhinal and perirhinal cortex at 7.1 mm below bregma (Figure 4a), and their numerical density significantly increased at each descending level from 7.1 to 8.6 mm below bregma (Figure 4b). However, a 4-day treatment with GSK189254

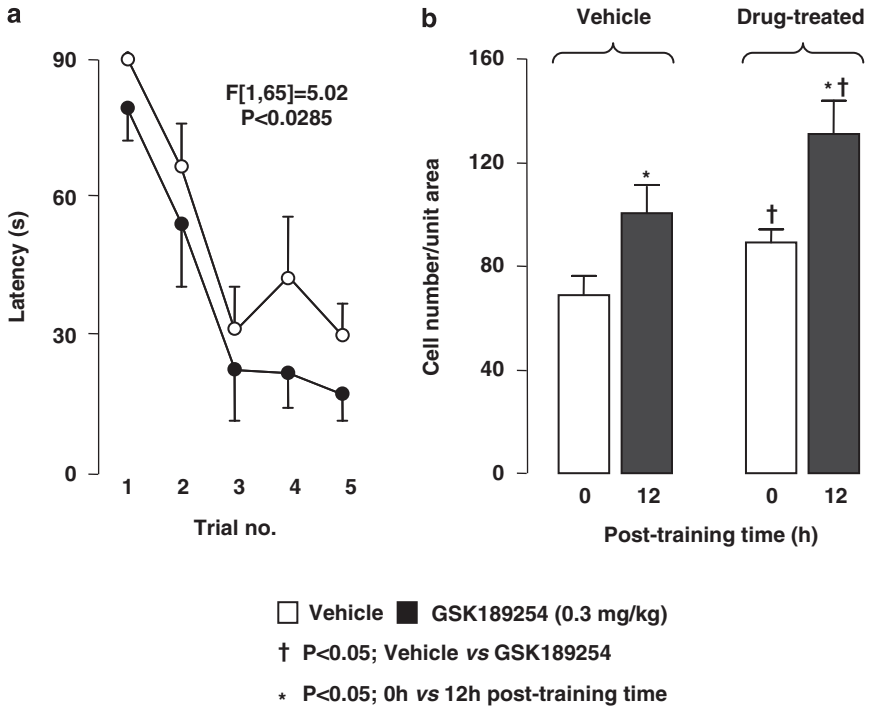

Figure 2 Influence of repeat administration of GSK189254 on learning-induced activation of dentate polysialylated cell frequency in adult Wistar rats after spatial learning in the water maze paradigm. The animals received GSK189254 (0.3 mg/kg, p.o.) or vehicle (1% methylcellulose (w/v)), for 4 days before training and trained 2 h after the final drug treatment; NCAM PSA expression was analyzed 12 h post-training. (a) GSK189254 to induce a significant improvement of task acquisition in a single trial of five sessions ($n = 3$–4). The significant ($p < 0.05$), learning-induced increase in dentate polysialylated cell frequency between the 0 and 12 h post-training times in these animals is shown by the asterisks in (b). The cross indicates the significant difference in polysialylated cell frequency that exists between the vehicle- and drug-treated animals at the 0 and 12 h time.

(0.3 mg/kg), the dose found to optimally increase dentate polysialylated frequency, or thioperamide (10 mg/kg), had no effect on the dorso-ventral density and distribution of immunostained cells within each treatment group ($F(3,24) = 34.34$; $p < 0.0001$; two-way ANOVA) (Figure 4b).

Given that the pro-vigilant actions of H_3 antagonists could contribute, in part, to their procognitive actions (Le *et al*, 2008), we also analyzed the effect of GSK189254 treatment on NCAM PSA expression in the hypothalamus. Within this brain region, PSA immunoreactivity was diffuse in nature, as would be expected given its dominant association with glia (Theodosis *et al*, 1999). The areas examined for NCAM PSA immunoreactivity in the coronal sections, cut in the rostro-caudal direction at bregma levels 1.8, 2.56, and 3.3 mm, and their relationship to the same region in the rat stereological atlas (Paxinos and Watson, 1986), are shown in Figure 5. The absence of discrete immunostained cell bodies in the areas encompassing the anterior, ventromedial, and dorsomedial aspects of the hypothalamus necessitated the use of gray level analysis to quantify the effect of drug treatment on NCAM PSA expression. Using this procedure, 4-day administration of GSK189254 (0.3 mg/kg) was found to induce a significant and uniform increase in NCAM PSA immunoreactivity (Student's *t*-test, $p < 0.05$) (Figure 6).

GSK189254 Enhances Consolidation of an Odor Discrimination Paradigm

The finding that H_3 antagonism exerted a significant effect on dentate NCAM PSA state supports our previous study in which GSK189254 was found to reverse the amnesia for avoidance conditioning task when induced by scopolamine administered at the 6 h post-training period of consolidation (Medhurst *et al*, 2007). Given that the training stimulus employed in such tasks is based on the avoidance of stressful experience (Merino *et al*, 2000), we further determined whether GSK189254 (0.3 mg/kg) exerted a similar effect in an odor discrimination paradigm in which the conditioning stimulus is stress free. Animals readily learned to acquire the odor discrimination paradigm, as the latency to locate the correct target odor became significantly reduced over the five trials of the training session. The latency to nose-poke in the sponge with the target odor decreased markedly from trial 1 to trial 2 and remained stable thereafter (Figure 7a). Acute administration of scopolamine alone, or in combination with GSK189254, had no significant effect on task acquisition, as judged by a two-way ANOVA analysis of the individual treatment groups in terms of escape latency times ($F(2,60) = 0.29$, $p = 0.75$). However, a similar analysis revealed all treatment groups to significantly decrease their latencies to locate the sponge containing the correct target odor over the five acquisition trials employed in the paradigm ($F(4,60) = 16.53$, $p < 0.0001$), indicating a rapid and robust acquisition of the task in all treatment cohorts.

Rats treated with vehicle alone showed good task recall at both the 24 and 72 h recall times. By contrast, acute scopolamine treatment alone was found to significantly impair task consolidation, as was evident by the significant increase in latency to locate the correct target odor at the 24 h recall time ($p < 0.05$; Mann–Whitney *U*-test)

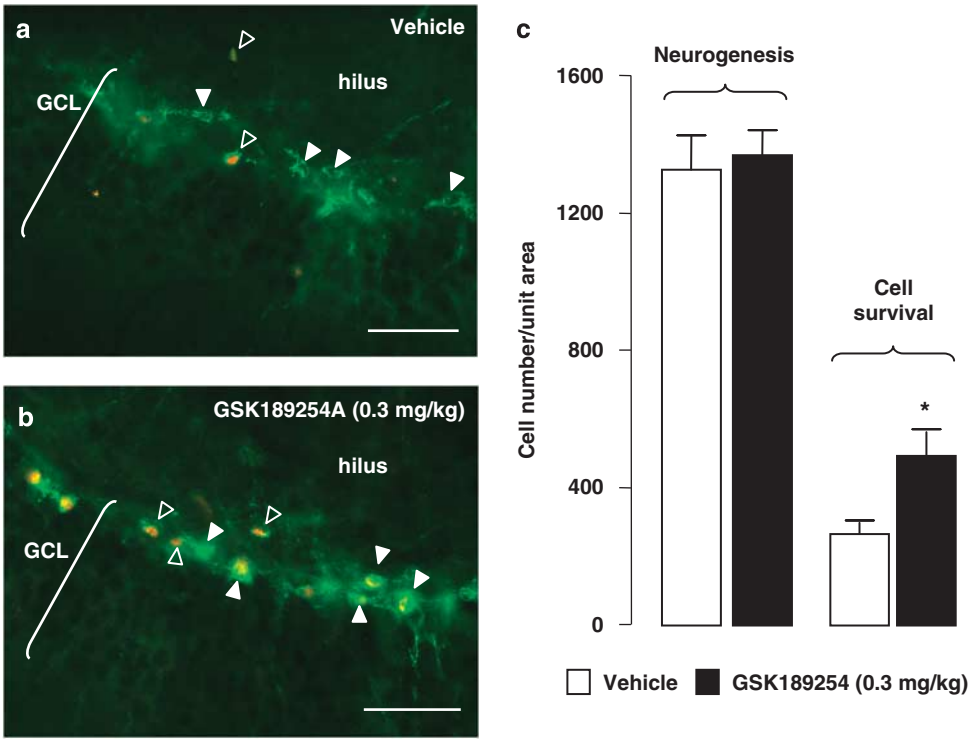

Figure 3 Influence of repeat administration of GSK189254 on neurogenesis and cell survival in the adult dentate gyrus of the Wistar rat. BrdU- (red) and NCAM PSA-immunolabeled cells (green) at −5.6 mm to bregma in the dentate granule cell layer (GCL) of animals treated with vehicle (1% methylcellulose (w/v)) and GSK189254 (0.3 mg/kg, p.o.) are shown in (a) and (b), respectively. The animals were treated for 4 days and were drug free at the time of killing 24 h after final drug treatment. The BrdU-positive cells are indicated by the arrowheads and the NCAM PSA-positive cells by asterisks. The scale bar represents 100 μm. (c) Illustrates the quantitative effect of the drug treatment on the frequency of BrdU- and NCAM PSA-labeled cells at postnatal day 80 (neurogenesis) and postnatal day 94 (cell survival). Data points represent the mean ± SEM ($n = 3$) and values significantly different ($p < 0.05$) from the vehicle control are indicated with an asterisk.

(Figure 7b). A similar, but not statistically significant, trend to increased latency was also observed with scopolamine at the 72 h recall time. Acute administration of GSK189254 (0.3 mg/kg) significantly reversed the scopolamine-induced recall deficits observed at both the 24 and 72 h recall times ($p < 0.05$; Mann–Whitney *U*-test) (Figure 7b). These results suggested that the primary action of scopolamine in the odor discrimination paradigm emerges in the period of consolidation, as has been observed previously for an avoidance conditioning paradigm (Doyle and Regan, 1993), and that repeat administration of cognition-enhancing drugs, including H_3 antagonists, ameliorate this amnesic action of scopolamine (Foley *et al*, 2004, 2008; Medhurst *et al*, 2007).

Influence of Acute GSK189254 Administration on the DMTP Paradigm

All animals were trained in the DMTP paradigm for a period of 40 days and had achieved a stable level of performance at the chosen delays of 0, 4, 8, 16, 24, and 32 s. During training, baseline performance accuracy was approximately 80% in all groups at the shortest delay periods (0–8 s) but decreased as the delay period was lengthened to 32 s. Analysis of the vehicle-treated group revealed that choice accuracy decreased in a delay-dependent manner ($F(5,216) = 26.31$, $p < 0.0001$; 2-way ANOVA). Acute administration of GSK189254 (0.3 mg/kg) significantly improved task performance accuracy ($F(1,108) = 6.04$, $p = 0.01$; 2-way ANOVA) (Figure 8); however, this was not observed after administration of the higher doses of 1 and 3 mg/kg, suggesting that the effect of H_3 antagonism on the DMTP task exhibited a bell-shaped response.

DISCUSSION

A major finding in this study was that a 4-day treatment with the H_3 receptor antagonist GSK189254 resulted in a dose-dependent increase in the frequency of polysialylated neurons in the infragranular zone of the hippocampal dentate gyrus. GSK189254 is a highly selective H_3 receptor antagonist that improves cognitive performance in a diverse range of cognition paradigms in rats (Medhurst *et al*, 2007). Our current data show for the first time that, amongst other transmitter systems, regulation of histaminergic function through H_3 receptor blockade can augment neuroplasticity mechanisms necessary for the effective consolidation of memory. Previous studies have shown other cognition-enhancing drugs, such as nefiracetam and tacrine, to increase NCAM PSA expression in the dentate gyrus (Murphy *et al*, 2006); however, their magnitude of effect was much less than that observed with GSK189254. Indeed, the ability of GSK189254 to increase the basal frequency of dentate polysialylated cells was more akin to that observed with a chronic 40-day administration of 5-HT_6 antagonists

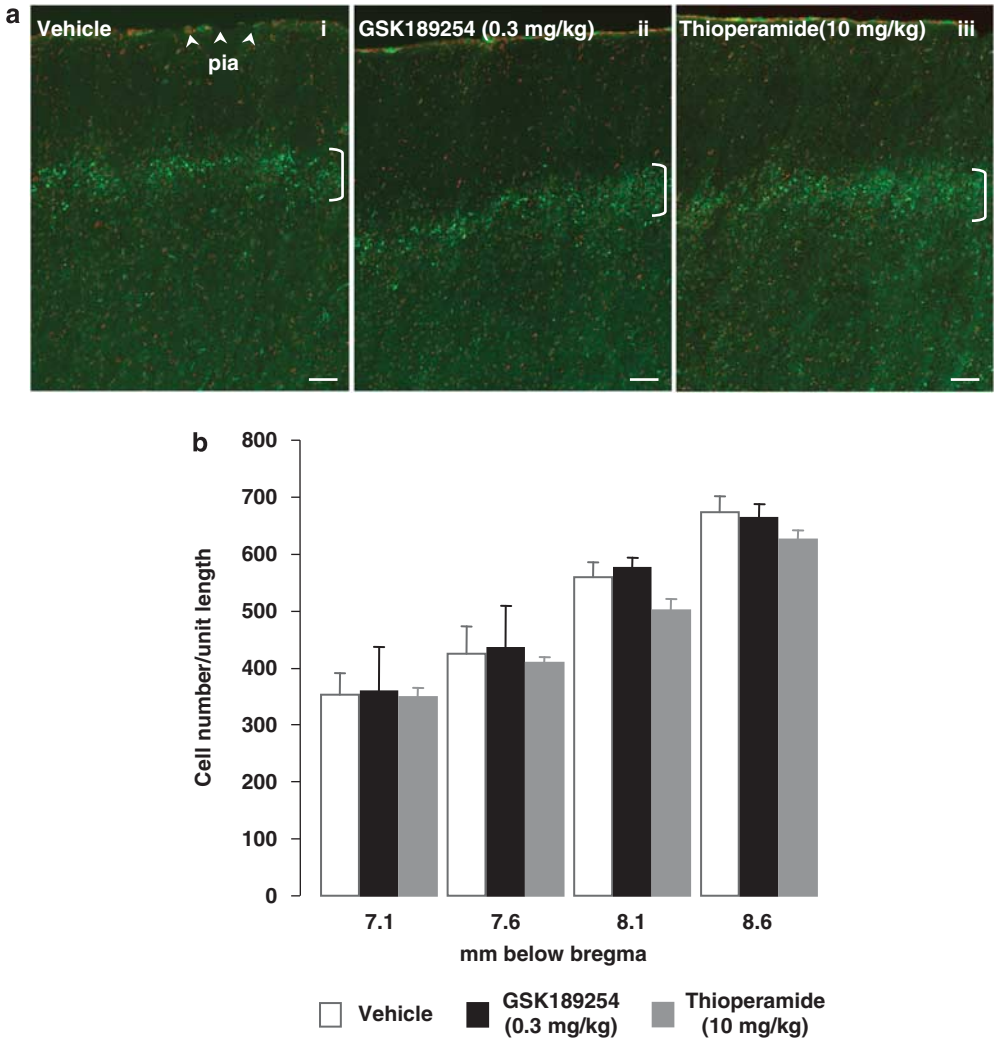

Figure 4 Influence of repeat administration of GSK189254 and thioperamide on basal polysialylated cell frequency in layer II of the entorhinal cortex of adult Wistar rats. The animals received GSK189254 (0.3 mg/kg, p.o.), thioperamide (10 mg/kg, p.o.), or vehicle (1% methylcellulose (w/v)) for 4 days before training and were drug free at the time of killing 24 h after final drug treatment. (a) Qualitative images of PSA immunoreactivity after treatment with vehicle (i), GSK189254 (ii), and thioperamide (iii) in layer II of the entorhinal cortex (indicated with bracket). The arrowheads indicate the position of the pia and the scale bar represents 200 μm. (b) Illustrates the quantitative effect of drug treatment on polysialylated cell frequency at increasing levels below bregma. Data points represent the mean ± SEM ($n = 3$).

such as SB-271046 and SB-399885 (Foley *et al*, 2008), which suggests that the more recently developed procognitive agents tend to exert a more substantial impact on the neuroplastic mechanisms associated with memory consolidation.

The common ability of agents with differing primary modes of action to enhance NCAM PSA-mediated neuroplasticity remains, however, a complex issue. Glutamatergic excitation, driven by the NMDA receptor, is known to be necessary for the rapid decrease in NCAM PSA expression in the adult vagal complex after stimulation of its afferents (Bouzioukh *et al*, 2001), which suggests that post-translational glycosylation of NCAM is associated with periods of enhanced inhibition and/or neuronal quiescence. This is consistent with the marked downregulation of transcripts associated with neurotransmission, ion channel conductance, and signal transduction that is observed at the 12 h post-training period of memory consolidation when a transient increase in NCAM PSA expression is required for memory consolidation (O'Sullivan *et al*, 2007). In contrast, however, the potent procognitive actions of NNC-711 (1-(2-((diphenylmethylene) amino) oxy) ethyl)-1,2,4,6-tetrahydro-3-pyridinecarboxylic acid hydrochloride), a GABA reuptake inhibitor with anticonvulsant activity (Suzdak *et al*, 1992), fails to influence polysialylated cell frequency, as does phenytoin, which lacks a procognitive action but dampens neural activity by slowing reactivation of voltage-dependent sodium channels (Rogawski and Porter, 1990; Murphy *et al*, 2006).

In general, the molecular events associated with regulation of the adult form of polysialyltransferase (ST8SiaIV/PST) remains to be fully elucidated; however, it would seem to be to regulated by protein kinase Cδ (PKCδ; Gallagher *et al*, 2000, 2001), which, in turn, is influenced by complex cell-signaling mechanisms (Steinberg, 2004). Agents, such as curcumin and α-tocopherol, which induce the degradation of PKCδ, enhance PST activity and PSA of neurons in the infragranular zone of the dentate gyrus and the synaptic

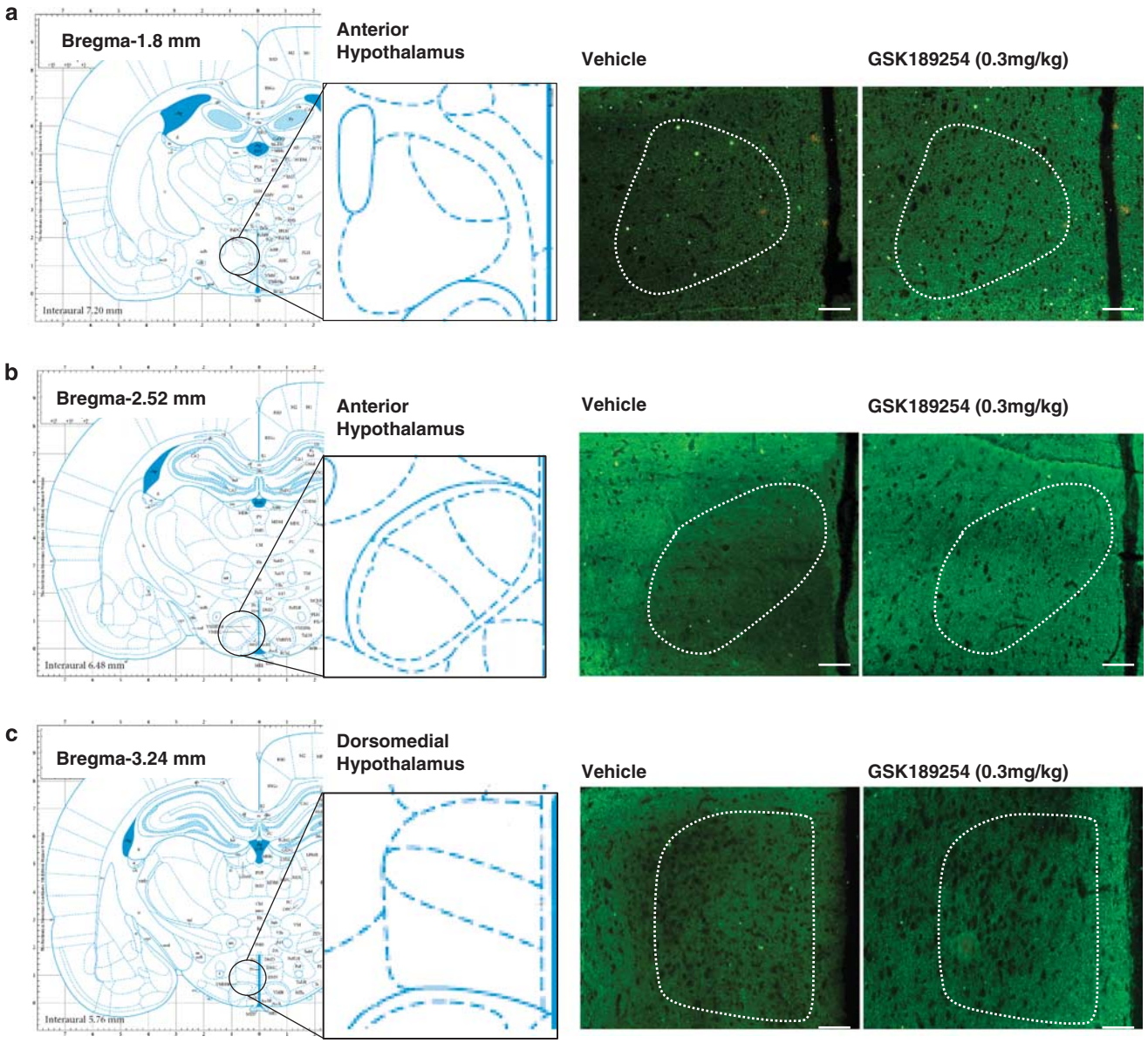

Figure 5 Influence of repeat administration of GSK189254 on NCAM PSA expression in the hypothalamus of adult Wistar rats. PSA immunoreactivity in coronal sections, at an increasing rostro-caudal distance, containing the anterior, ventromedial, and dorsomedial areas of the hypothalamus is shown in (a), (b), and (c), respectively. The animals were treated with vehicle (1% methylcellulose (w/v)) or GSK189254 for 4 days and were drug free at the time of killing 24 h after final drug treatment. The panels show the precise brain region, located by reference to a rat brain atlas (Paxinos and Watson, 1986), and the delineated area used to determine gray level in the vehicle- and drug-treated animals.

remodeling of their dendritic arbor (Conboy *et al*, 2009; Ferri *et al*, 2006; Zingg and Azzi, 2004). The ability of GSK189254 to increase dentate polysialylated cell frequency may, however, be related to its ability to augment the outflow of acetylcholine, as two other cholinergic agents, tacrine and nefiracetam, similarly increase cholinergic drive (Nishizaki *et al*, 2000; Irizarry and Hyman, 2001; Medhurst *et al*, 2007) and all three agents enhance NCAM PSA in a bell-shaped dose-dependent manner (Murphy *et al*, 2006). By contrast, 5-HT_6 antagonists increase polysialylated cell frequency in a linear, dose-dependent manner over the range in which they elicit procognitive actions, but can increase not only acetylcholine release (Rogers and Hagan, 2001; Shirazi-Southall *et al*, 2002; Foley *et al*, 2008) but also modulate excitatory amino acid neurotransmission (Dawson *et al*, 2001). The cause of the bell-shaped curve observed with GSK189254 on NCAM PSA is unclear. It may reflect the fact that H_3 antagonists can increase the release of multiple neurotransmitters in addition to acetylcholine, such as histamine, dopamine, and noradrenaline (Arrang *et al*, 1988; Fox *et al*, 2005; Medhurst *et al*, 2007), or it may be a consequence of the existence of numerous H_3 receptor splice variants (Hancock *et al*, 2003). The non-overlapping nature of the NCAM PSA bell-shaped dose–response curve with the effective doses in the passive avoidance and aged water maze paradigms may relate to a higher dose requirement be necessary to ameliorate memory loss in these deficit models (Medhurst *et al*, 2007).

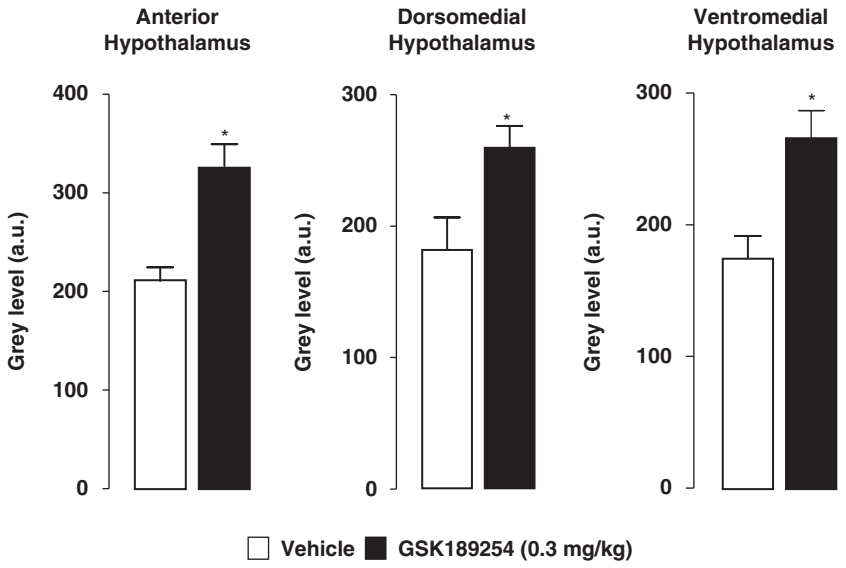

Figure 6 Quantitative gray level analysis of NCAM PSA expression in the hypothalamus of adult Wistar rats after repeat administration of GSK189254. The animals were treated with vehicle (1% methylcellulose (w/v)) or GSK189254 (0.3 mg/kg, p.o.) for 4 days and were drug free at the time of killing 24 h after final drug treatment. Data points represent the mean ± SEM ($n = 4$) and values significantly different ($P < 0.05$) from the vehicle control are indicated with an asterisk.

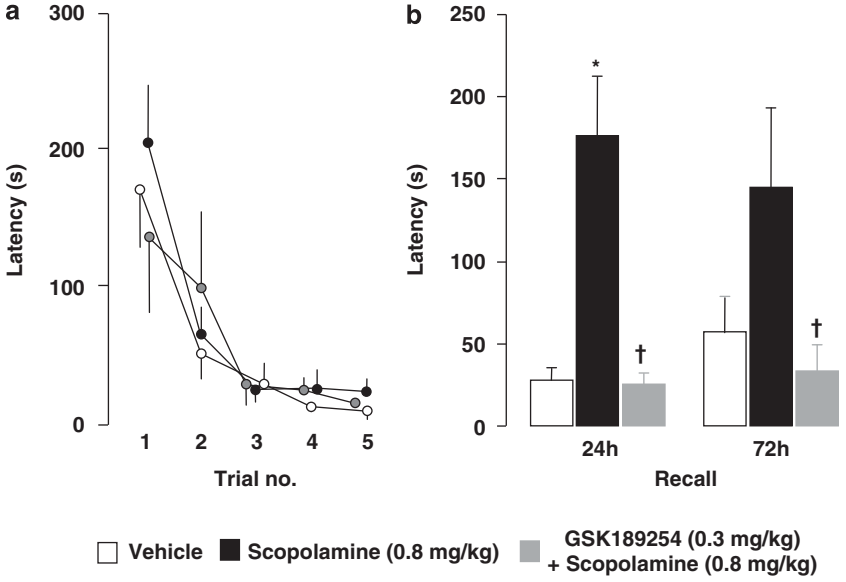

Figure 7 Influence of acute GSK189254 administration on the reversal of a scopolamine-induced learning impairment in the acquisition and retention phases of an odor discrimination paradigm in adult Wistar rats. The animals received GSK189254 (0.3 mg/kg, p.o.), or vehicle (1% methylcellulose (w/v)) at 2 h before training. The scopolamine (0.8 mg/kg, i.p.) was administered 20 min before the training. The influence of drug treatment on task acquisition and retention (recall) is shown in (a) and (b), respectively. Data points represent the mean ± SEM ($n = 6$), and values significantly different ($p < 0.05$; two-way ANOVA and the Mann–Whitney *U*-test) from the vehicle control are indicated with an asterisk. Values significantly different between cohorts treated with scopolamine alone and scopolamine co-administered with GSK189254 are indicated with a cross ($p < 0.05$; two-way ANOVA and the Mann–Whitney *U*-test).

The ability of GSK189254 to increase the basal frequency of dentate polysialylated neurons not only improved performance in the acquisition of a water spatial learning paradigm but also resulted in a significant enhancement of the transient increase in NCAM PSA expression at the 12 h post-training time. This has also been observed after separate treatments with tacrine and nefiracetam (Murphy *et al*, 2006), and the 5-HT_6 antagonists SB-271046 and SB-399885 (Foley *et al*, 2008). The improved learning associated with increased NCAM PSA expression is not surprising given that the numerical frequency of polysialylated dentate neurons is directly correlated with task performance (Sandi *et al*, 2004; Murphy *et al*, 2006). The majority of newly synthesized PSA seems to be associated with the synapse-specific NCAM 180-kDa isoform (Doyle *et al*, 1992), and this would serve to reduce cell–cell signaling and facilitate synapse remodeling (Rutishauser, 2008), a suggestion reinforced by the learning deficits

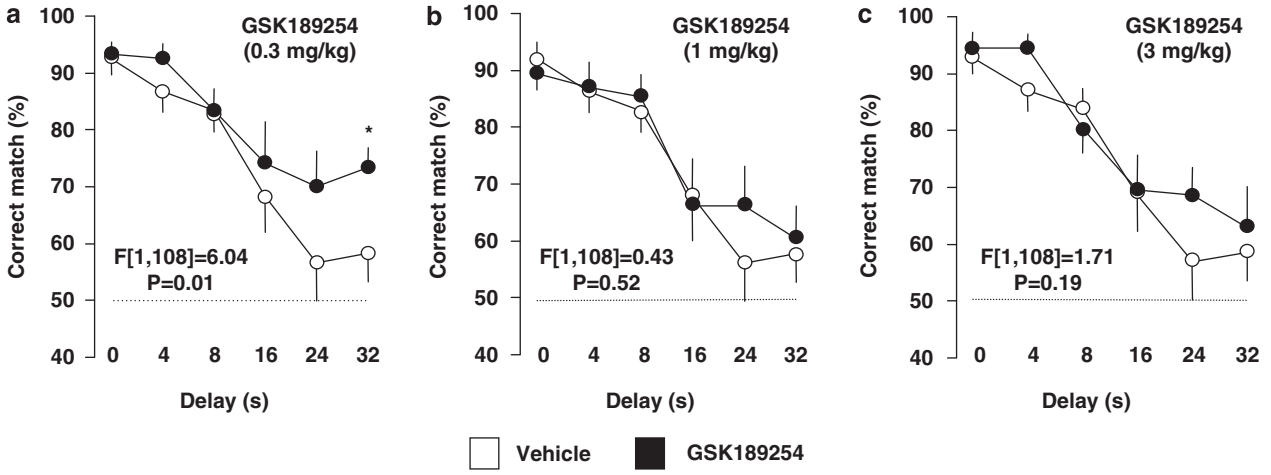

Figure 8 Influence of acute GSK189254 administration on the delayed match-to-position paradigm in adult Wistar rats. The animals received acute GSK189254 by gavage, at doses of 0.3 mg/kg (a), 1 mg/kg (b), and 3 mg/kg (c) 2 h before training and compared with those receiving vehicle (1% methylcellulose (w/v)) alone. Data points represent the mean ± SEM ($n = 10$) and values significantly different ($p < 0.05$; two-way ANOVA and the Mann–Whitney *U*-test) from the vehicle control are indicated with an asterisk.

observed in mice that are deficient for the adult form of polysialyltransferase (ST8SiaIV/PST-1) (Markram *et al*, 2007) and the enhanced consolidation of this paradigm by post-training infusions of a cyclic oligopeptide that acts as a non-competitive agonist of PSA (Torregrossa *et al*, 2004; Florian *et al*, 2006). Moreover, facilitation of PSA activation by cognition-enhancing drugs, such as the H_3 receptor antagonist GSK189254, may have implications for the treatment of neurodegenerative conditions as, in Alzheimer's disease, the natural autoprotective response to age-related cognitive deficits is a small, but significant, activation of dentate polysialylated cell frequency (Mikkonen *et al*, 1999).

Many, but not all, of the NCAM PSA-immunopositive cells located at the infragranular zone of the dentate gyrus are newly generated granule cells (Gage, 2000; Seki, 2002) that are proposed to be involved in memory and learning (Gould *et al*, 1999; Shors *et al*, 2001; Dupret *et al*, 2007), and that their rate of production may be modulated by change in neurotransmitter status (Brezun and Daszuta, 2000; Malberg *et al*, 2000). However, in this study, GSK189254 was found to be without effect on neurogenic rate, despite producing marked increases in basal and learning-induced polysialylated cell frequency. This finding was not completely unexpected, as previous studies have consistently failed to implicate increased NCAM PSA-mediated plasticity with neurogenesis (Fox *et al*, 1995; Pham *et al*, 2005; Lopez-Fernandez *et al*, 2007; Duveau *et al*, 2007). Moreover, in a previous study, we have failed to associate chronic treatment with 5-HT_6 antagonists, with any alteration in hippocampal neurogenesis despite the significant increase in polysialylated cell frequency in both the hippocampal dentate gyrus and layer II of the medial temporal lobe (Foley *et al*, 2008), the latter being a brain region that does not sustain neurogenesis into adulthood (Ehninger and Kempermann, 2003). It is likely, however, that the activation of NCAM PSA state facilitates the integration of newborn cells into the dentate neuronal architecture over the 1- to 2-month period that follows their birth (Ge *et al*, 2007; Kee *et al*, 2007; Toni *et al*, 2008). In this respect, it was interesting to observe that a 4-day treatment with GSK189254 increased the survival time of the newly formed dentate granule cells, as evidence by the significant increase in BrdU-labeled cells remaining at 2 weeks after the final BrdU injection. This would have the consequence of increasing the availability of newly formed cells for incorporation into the structure of the hippocampal formation in response to the neuroplastic demands necessary for information processing. Increased neural activity enhances cell survival (Bruel-Jungerman *et al*, 2006) and their incorporation into the neural architecture is a complex multistep process that is associated with NCAM PSA expression (Schmidt-Hieber *et al*, 2004; Zhao *et al*, 2006; Toni *et al*, 2008). The ability of GSK189254 to prolong the half-life of these neuronal precursors, by reducing apoptosis, may also explain the general ability of H_3 receptor antagonists to protect against NMDA-induced cell death (Dai *et al*, 2007). PSA acts as a competitive antagonist of the extrasynaptic NR2B glutamate receptor subunit (Hammond *et al*, 2006), and its enhanced expression induced by GSK189254 administration may confer a neuroprotective quality by improving cell survival.

Unlike the hippocampus, we found no evidence for an effect of a 4-day treatment with GSK189254 on the frequency of polysialylated neurons in the rat entorhinal or perirhinal cortex, despite H_3 receptors being widely distributed in brain cortical regions (Pillot *et al*, 2002). This finding was surprising, as H_3 antagonists including GSK189254 are known to activate the intermediate early gene c-*fos* in both the prefrontal and somatosensory cortex (Medhurst *et al*, 2007; Southam *et al*, 2009), and cortical reorganization of sensory information is accompanied by increased glutamatergic drive and c-*fos* activation (Benali *et al*, 2008). In contrast, chronic treatment (40 days) with the 5-HT_6 receptor antagonists SB-271046 and SB-399885 markedly increase NCAM PSA expression in the entorhinal and perirhinal cortex (Foley *et al*, 2008), an effect that may relate to their ability to increase glutamate outflow (Dawson *et al*, 2001), as a similar action is not observed with GSK189254 (Medhurst *et al*, 2007). However, H_3 receptor

antagonism is also known to enhance c-*fos* mRNA expression in the supraoptic and paraventricular nuclei of the hypothalamus (Vizuete *et al*, 1995) and, in this brain region, we found GSK189254 to induce a widespread, uniform, and substantial increase in NCAM PSA expression. Modulation of vasopressin and oxytocin neurons in the hypothalamus is associated with an array of homeostatic functions (Hass *et al*, 2008), which are dependent on the activation of c-*fos* expression (Kjaer *et al*, 1994; Ma *et al*, 2008) and the NCAM PSA-mediated morphological plasticity that modifies astrocytic coverage of oxytocinergic neurons and their synaptic inputs in response to homeostatic functioning of the hypothalamic axis (Theodosis *et al*, 1999, 2006). Histamine acting on the hypothalamus affects the release of many hormones from the pituitary gland (Eriksson *et al*, 2001) that mediate the reaction to stress in the hypothalamic–pituitary axis, which may, in part, support the suggestion that H_3 receptor antagonists have some efficacy as antidepressants (Pérez-García *et al*, 1999). It is currently unclear why GSK189254 increased NCAM PSA in the hippocampus and hypothalamus, but not in cortical areas. This may be due to the involvement of different H_3 receptor splice variants in distinct brain areas (Hancock *et al*, 2003) or the potential heterogeneity of histaminergic nerve projections from the hypothalamus to different brain structures (Giannoni *et al*, 2007).

Given that H_3 antagonism has been associated with an increase in c-*fos* expression in the prefrontal cortex (Medhurst *et al*, 2007; Southam *et al*, 2009) and that modulation of NCAM PSA expression in this brain region is associated with learning-induced neuroplasticity (ter Horst *et al*, 2008), we determined whether GSK189254 influenced the DMTP task, as this paradigm specifically requires activation of the prefrontal cortex and not the hippocampus (Sloan *et al*, 2006). As the delay-dependent deficits increased in parallel with the load on working memory, GSK189254 was found to produce a significant improvement on task accuracy. This finding is of particular interest, as deficits in similar tasks in human subjects have been linked to psychiatric conditions, such as schizophrenia (Goldberg *et al*, 1987; Berman and Weinberger, 1990; Owen *et al*, 1995). Moreover, the ability of GSK189254 to increase cortical outflow of acetylcholine (Medhurst *et al*, 2007) along with the requirement of the cholinergic system in the DMTP task (Herremans *et al*, 1995) and the increase in acetylcholine release induced by atypical antipsychotics (Ichikawa *et al*, 2002) further implicates the role of the histaminergic system in schizophrenia (Arrang, 2007) and the potential of H_3 antagonists as novel antipsychotic agents (Southam *et al*, 2009). It is worth noting that a potential bell-shaped dose–response relationship occurred in the DMTP task similar to that observed in the NCAM PSA studies. However, this is not consistent with efficacy data in several other rodent cognition models with GSK189254 (Medhurst *et al*, 2007), and therefore may be specific to the DMTP paradigm.

Finally, the apparent importance of GSK189254 in the modulation of acetylcholine release and its relationship to NCAM PSA expression in learning was further underscored by its ability to reverse scopolamine-induced deficits in the odor discrimination paradigm, a task involving an increase in hippocampal NCAM PSA-mediated neuroplasticity (Foley *et al*, 2003a; Knafo *et al*, 2005). The cholinergic projection neurons from the medial septum, which innervate the dentate granule cells, are extensively polysialylated (Foley *et al*, 2003b) and disruption of this pathway by lesions to the septal nuclei or fornix leads to impairments in rodent tasks of learning and memory (Everitt and Robbins, 1997). Moreover, rats trained in an odor discrimination paradigm exhibit a significant increase in c-*fos* expression in the CA1 and CA3 regions of the hippocampus but not in the dentate (Hess *et al*, 1995), suggesting that modulation in the PSA status of the mossy fiber afferents may induce c-*fos* expression in the trisynaptic pathway of the hippocampus.

These studies are the first to show the procognitive actions of an H_3 receptor antagonist to be associated with a profound activation of NCAM PSA state, a neuroplastic mechanism intimately associated with the synaptic remodeling that accompanies memory and learning. Improved expression of NCAM PSA, whether through the direct action of a PSA peptidomimetic (Florian *et al*, 2006) or indirectly by a receptor-mediated mechanism, not only exerts a profound effect on cognitive competence but is also associated with neuroprotective actions (Foley *et al*, 2005; Murphy *et al*, 2006; Duveau *et al*, 2007) that have the potential to provide a disease-modifying action in conditions that harbor fundamental deficits in NCAM PSA-mediated neuroplasticity, such as schizophrenia and Alzheimer's disease (Barbeau *et al*, 1995; Mikkonen *et al*, 1999).

DISCLOSURE/CONFLICT OF INTEREST

This work was supported by funding from GlaxoSmith-Kline. The authors NP and ADM are current employees of GlaxoSmithKline

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