PC201

Propofol enhances GABAergic presynaptic Ia-inhibition in humans

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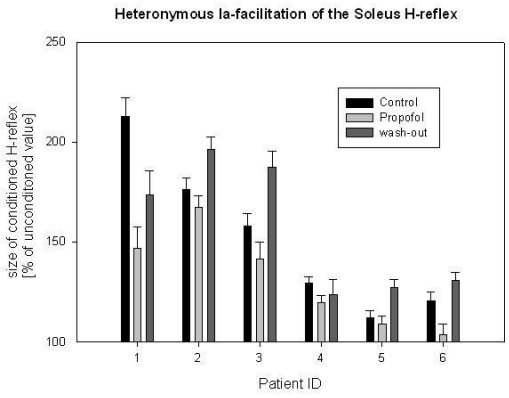
In vitro studies performed on spinal slice cultures indicate that the primary molecular targets of Propofol in the spinal cord are GABAA receptors (Grasshoff & Antkowiak, 2004). These receptors might play an important role in the suppression of movement by Propofol. However, until now the importance of GABAergic effects has not been shown in humans.

Here we used heteronymous Ia facilitation of the soleus H-reflex from the femoral nerve (Hultborn et al., 1987) as a specific pathway involving GABA to demonstrate the GABAergic effect of propofol in humans.

After approval of the local ethics committee, the study was carried out on six volunteers aged 23-32. The subjects received propofol via a target controlled infusion system yielding steady-state plasma concentrations of 2mg/l. This caused a sedative state with a sustained ability to respond to loud verbal commands. The soleus H-reflex was evoked every 6s in the popliteal fossa and was recorded with disc electrodes placed over the soleus muscle. Conditioned and unconditioned reflexes were tested in random order. The stimulation current was adjusted so that the unconditioned H-reflex amplitude was kept at 15% of Mmax, which was determined before each cycle of measurement. The femoral nerve was stimulated through a monopolar ball electrode in the femoral triangle(1.15xMT). The onset of facilitation was defined as the earliest conditioning-test interval at which the conditioned H-reflex amplitude was at least 5% higher than the test reflex (unpaired T-test $p<0.05$). Throughout the study the conditioning stimulus was applied 0.5 ms after this onset, which was determined in steps of 0.1ms. This procedure assures a facilitation caused by a pure monosynaptic EPSP. Measurements were performed under 3 conditions: a) prior to propofol administration (control) b) during steady-state propofol administration c) 35min after propofol infusion was stopped. During each condition a recruitment curve of the H-reflex amplitude was established.

The mean reduction of Hmax/Mmax by propofol yielded 25% ± 15%(mean± SD)in comparison to the control values. In all but one subject soleus H-reflex facilitation was reduced significantly by propofol (t-test, $p<0.01$, see figure). Facilitation recovered significantly in all subjects after discontinuation of propofol.

The results show that Propofol reduces heteronymous Ia facilitation of the soleus H-reflex from the femoral nerve. By adjusting the unconditioned reflex to control values before Propofol administration, this effect must be mediated by increased presynaptic inhibition on Ia afferent fibers, a specific GABAergic effect.



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Where applicable, the experiments described here conform with Physiological Society ethical requirements.

PC202

Kinematic and kinetic patterns during normal walking in subjects with chronic ankle instability and in controls subjects

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Chronic ankle instability (CAI) has not previously been investigated dynamically using 3-D motion analysis during walking. Identification of altered kinematic and kinetic patterns in CAI subjects may increase our knowledge of the causes of CAI and improve our ability to prevent and successfully rehabilitate such subjects. We hypothesised that CAI subjects would exhibit a different kinematic and kinetic pattern of movement during normal walking when compared with a control group.

Twenty five CAI subjects aged 25.5 ± 7.3 years (mean ± S.D.) and 25 age, activity, gender, and gait velocity matched controls, aged 23.61 ± 5.1 years volunteered to participate. Ethical approval was obtained locally and all subjects gave written consent. The CODA mpx30 3-D motion analysis system combined with a Bertec force plate were used to track joint motion and forces created during walking at natural self-selected velocity. Pelvic, thigh, shank, and foot 3-D segment joint angular rotation (subtracting joint angles when the subject was in their sub-talar neutral standing position), moments and powers during the period 100 ms pre-initial contact to 200 ms post-initial contact were identified for 10 trials for each subject. Average values for the above parameters were calculated for each subject and group mean profiles were derived. Independent two-sided t tests were used to analyse the data. $P<0.05$ was considered statistically significant.

The CAI subjects during 100 ms pre-initial contact, and 200 ms post-initial contact were significantly ($P<0.01$) more inverted by approximately 6-7 deg in the frontal plane compared with the controls. From initial contact to 200 ms post-initial contact the

joint moments show a significant difference (P<0.01) in the CAI subjects. The CAI subjects are controlled by an evertor moment compared with an invertor moment in the controls. The joint powers controlling CAI subjects from 10 ms to 40 ms, and 60 ms to 135 ms post-initial contact show a significant difference (P<0.03) to the controls. The CAI subjects are controlled by a concentric power generation compared with an eccentric power generation in the controls.
These findings may indicate why subjects with CAI are vulnerable to repeated sprains. Landing on a more inverted foot during early stance may reduce the shock absorption mechanism, making the ankle more vulnerable to turning over on the lateral border during early stance. The findings suggest that the motor control of the ankle changes to prevent turning over on the lateral border of the foot in subjects with CAI during this period.

Where applicable, the experiments described here conform with Physiological Society ethical requirements.

PC203

The activation of human involuntary aftercontractions responds proportionally to an increase in load

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Postural aftercontractions are involuntary contractions that occur following a strong voluntary isometric contraction (Adamson and McDonagh, 2004). The strength of these aftercontractions in m.Deltoid is proportional to the inclination of the body in the gravitational field (Lemon et al., 2003). It is greatest with the body upright and smallest with the body supine and horizontal. This effect could be due to the change in vestibular apparatus position or to the change in gravitational load on the muscle. In the present experiments head position was fixed and only load was varied. Ten subjects took part, three of whom were female (means +/- SD: age 25+/-11 years; height 172.1+/-8.3 cm; weight 73.2+/-12.5 kg).
The load on the muscle was reduced by using a first class lever to counterbalance the weight of the arm. The axis of the lever was concentric with the flexion-extension axis of the glenohumeral joint. One arm of the lever was attached to the lateral aspect of the extended upper limb and the other lever arm had a counterbalancing weight which could be moved to provide reduced loads on the arm. The subjects sat with their left arm extended forwards and downwards at an angle of 40 degrees to the vertical. They then pressed up on a force transducer for one minute with 60 % of their maximal isometric force. Following this an aftercontraction ensued which produced a flexion of the extended limb at the shoulder joint.
The activation of the aftercontraction was proportional to the loading on the arm. There was a positive linear relationship between arm load and the rectified emg amplitude (repeated measures ANOVA: p=0.001). This amplitude was expressed as a percentage of the average rectified emg signal recorded during the prior voluntary effort. The results across the 10 subjects at each load (as a fraction of the normal weight of the arm) were: means +/-SD: 0.00 load 24.8, +/-15.1%; 0.25 load 33.6, +/-17.3%; 0.50 load 46.4, +/-18.4%*; 0.75 load 57.3, +/-15.0%*; 1.00(normal) load 67.6, +/-24.8%* (data taken at a joint angle of 70 degrees, *p<0.004 pairwise comparisons of each load with 0 load condition).
In conclusion load strongly increases the activation of involuntary aftercontractions independently of vestibular changes. This mechanism may underlie the normal control of body segment position in relation to gravitational load (e.g. Dietz, 1998).

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Where applicable, the experiments described here conform with Physiological Society ethical requirements.

PC204

The inhibitory effect of intracerebroventricular morphine on a withdrawal reflex in the decerebrated rabbit does not involve spinal α_2-adrenoceptors

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Intravenous administration of the μ-opioid agonist, morphine, inhibits reflex responses in medial gastrocnemius (MG) motoneurones evoked by electrical stimulation of the sural nerve in decerebrated rabbits. This inhibition involves spinal and supraspinal sites of action as the effect of morphine is reduced, but not abolished, after complete spinal cord section (Lo et al. 2004). The inhibitory effect of i.v. morphine is also reduced by prior intrathecal (i.th.) administration of the selective α_2-adrenoceptor antagonist RX 821002 suggesting a role for noradrenergic bulbospinal pathways in this process. The present study has examined the mechanism of morphine-induced inhibition further by directly applying morphine supraspinally via the intracerebroventricular (i.c.v.) route.
Experiments were performed on 20 rabbits decerebrated under isoflurane (3-5 %)/N_2O anaesthesia, six of which were also spinalized at L1. The left sural nerve was electrically stimulated at C fibre intensity (147 times threshold using a 0.2 ms pulse width) to evoke reflex responses in the ipsilateral MG muscle nerve. Responses were averaged, integrated by computer and analysed in 3 post-stimulus time bands: 5-12 ms (phase 1); 12-100 ms (phase 2) and 100-250 ms (phase 3). After a control period ≥ 30 min, i.c.v. morphine was given at 30 min intervals in doses of 10, 20, 70, 200 and 700 μg kg^{-1} to give a total cumulative dose of 1 mg kg^{-1}. In 7 non-spinalized animals, 100 μg i.th. RX 821002 was given prior to i.c.v. morphine. Experiments were terminated by i.v. injection of saturated KCl solution.
In decerebrated animals, i.c.v. morphine significantly (Friedman's ANOVA, $p < 0.01$) inhibited all phases of the MG response so that after 1 mg kg^{-1}, median responses were 41%, 21% and 17% of pre-drug levels for phases 1, 2 and 3, respectively. In the presence of RX 821002, corresponding reductions were to 9%, 18% and 28% of pre-morphine controls and these decreases were significant (Friedman's ANOVA, $p < 0.001$). In spinalized animals the inhibitory effect of morphine was abolished, such that after the highest dose, phase 1, 2 and 3 MG responses were a median of 118%, 111% and 87% of controls, respectively. Mor-

phine-induced inhibition was significantly different between treatment groups for all three phases (Kruskal-Wallis ANOVA, $p < 0.05$) but this difference was between decerebrated versus spinalized preparations and not due to the presence of RX 821002, which in fact enhanced inhibition of short-latency responses (Dunn's multiple comparison post-test, $p < 0.05$). These data show that i.c.v. morphine inhibits MG reflexes via descending bulbospinal pathways but, in contrast to i.v. morphine, this inhibition does not involve spinal α_2-adrenoceptors. Thus any interaction between morphine and noradrenergic pathways appears to be at the spinal level.

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Where applicable, the experiments described here conform with Physiological Society ethical requirements.

PC205

Simple spike synchrony in Purkinje cell pairs located within and between cerebellar cortical zones

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A high degree of synchrony can exist in the timing of complex spikes within individual Purkinje cells located in the same parasagitally aligned strip or zone of cerebellar cortex. However, it is not known whether the simple spike activity of the same neurones can also occur synchronously and whether any observed synchrony can be modulated by peripheral inputs. Experiments in the present study were designed to explore this and related questions using multiple single unit recording techniques. In particular, we aimed to assess the degree of correlation in simple spike and complex spike firing patterns of simultaneously recorded Purkinje cells located within the same cerebellar cortical zone as compared to pairs of cells recorded within different zones. Adult Wistar rats were anaesthetised with ketamine (100mg/kg) and xylazine (5mg/kg i.p.). Percutaneous electrical stimulation of the ipsilateral forelimb and contralateral face region was used to evoke field potentials on the surface of the cerebellum in order to locate the A2 and C1 cerebellar cortical zones in the paramedian lobule. The zonal electrophysiology was used to guide the insertion of four independently controlled glass insulated tungsten microelectrodes into the cortex. Up to four Purkinje cells were recorded simultaneously within the two neighbouring zones. The simple spikes and complex spikes generated by individual Purkinje cells were discriminated independently and peri-stimulus time histograms were constructed for forelimb and face stimulation. Correlation coefficients were calculated between the occurrence of complex spikes and also between the occurrence of simple spikes for the same pairs of Purkinje cells. Preliminary findings indicate that correlation coefficients are larger in Purkinje cell pairs that are located in the same zone compared to pairs that are located in different zones. Purkinje cell pairs exhibiting a high correlation in complex spike activity exhibited a transient increase in simple spike synchrony following peripheral stimulation. The increase in simple spike correlation was not observed in the spontaneous simple spike activity of the same Purkinje cells, nor in Purkinje cell pairs that did not exhibit a high level of complex spike synchrony. These initial findings suggest that Purkinje cells with a common climbing fibre input can also have a common mossy fibre input, but that the latter is only apparent following peripheral stimulation.

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Where applicable, the experiments described here conform with Physiological Society ethical requirements.

PC206

Interhemispheric branching of pontine mossy fibres that make contact with putative Golgi cells in the rat cerebellum

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Golgi cells are inhibitory interneurones located in the granular layer of the cerebellar cortex. They occupy a unique position in the circuitry of the cerebellum, receiving direct excitatory inputs from mossy fibres, and indirectly, by way of the mossy fibre-granule cell-parallel fibre pathway. Mossy fibres are the most numerous source of inputs to the cerebellum, and can project bilaterally to the cerebellum. Such bilaterality is likely to have a significant impact on cerebellar cortical function as sensory events may directly influence the processing of information on both sides of the cerebellum. Here, we use a double retrograde axonal tracing strategy to chart the possible sources of mossy fibres with bilateral inputs to putative Golgi cells (pGCs) by injecting red and green fluorescent latex microspheres into areas on both sides of the cerebellar cortex which are functionally linked.

In adult rats anaesthetised with pentobarbitone (40mg/kg, i.p.) using stainless steel electrodes (2–3 MΩ) we have made extracellular recordings from pGCs located in the cerebellar hemisphere (Crus II) on one side. A monopolar stimulation electrode (0.1 MΩ) was used to stimulate the deep granular layers/white matter in the contralateral cerebellar hemisphere (0.5–1 mm deep). Systematic probing (0.5 mm intervals) of the contralateral cerebellar cortex with the stimulating electrode revealed areas of cortex from which single, post-synaptically evoked spikes could be observed in the recorded pGC (2–3 ms latency). The current required to evoke such spikes varied as a function of the location of the stimulating electrode and the firing rate of the recorded pGC. A microinjection of one colour of tracer material was made at the cortical site where the lowest intensity of stimulation evoked a response (10–30 μA), and a microinjection of the other colour tracer was made at the recording site on the other side of the cerebellum (~50 –100 nl of tracer in each microinjection). After 7 days survival for retrograde axonal transport of tracer to occur, the animals were anaesthetized with urethane (1000 mg/kg i.p.) and perfusion fixed. An epifluorescence microscope was used to survey various cerebellar and brainstem structures for retrogradely labelled cells (e.g. pontine nuclei, inferior olive, lateral reticular nucleus, cerebellar nuclei). Preliminary results indicate that double labelled cells are only present within the basilar pontine nucleus. This suggests that

the pons may be the principal source of mossy fibres that branch to influence Golgi cells located in both cerebellar hemispheres.

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Where applicable, the experiments described here conform with Physiological Society ethical requirements.

PC207

Predicted timing of forearm unloading influences the magnitude of the long latency stretch reflex

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Unloading of the forearm produces muscle activations in the antagonist triceps brachii as a result of stretch (Paulignan et. al. 1989). The long latency component of this stretch reflex increased in magnitude when the unloading was self-initiated and predictable in time as compared to when the unloading occurred by an external unpredictable source (McAllister & McDonagh, 2004). This study investigated whether the increase in reflex gain occurs with a time course that is related to the expected unloading onset.

Eleven subjects (9 female) were seated upright with their *right* upper arm fixed to a support. An electromagnet attached underneath their right wrist supported a 1.8-kg load. They were instructed to maintain their loaded forearm in the horizontal at an elbow angle of 105º. The subjects released the load from the electromagnet by pressing a switch with their *left* thumb. In the first ('fixed') session the time delay between the switch press and the load release remained constant whilst the subject performed 60 consecutive trials at each of the following time delays: 10, 150, 300 and 450ms. In the second ('early') session the subjects performed a total of 140 trials during which 128 trials at the 450ms delay were interspersed with 12 trials that had unexpectedly early delays; four at each of the 10, 150 and 300 ms time delays. The amplitude of the long latency reflex was calculated as the mean rectified EMG activity from the long head of the triceps brachii in the 35 to 75 ms following the load release.

The data, presented as mean ± S.E.M, was analysed using a two-way Repeated Measures ANOVA (2 session (fixed, early) x 4 delay (10, 150, 300, 450 ms)). Differences between reflex amplitudes were assessed using Tukey HSD post-hoc tests. There was a significant interaction of session and delay ($p<0.01$) indicating that the effect of time delay on the reflex gain was dependent on the expected time of unloading. During the 'fixed' session the reflex amplitudes were similar at all time delays (10 ms 11.3 ± 2.2 μV; 150 ms 12.1 ± 2.3 μV; 300 ms 15.6 ± 4.7 μV; 450 ms 13.2 ± 3.8 μV). However, during the 'early' session the reflex amplitudes at both the 0 ms (1.3 ± 0.8 μV) and 150 ms (4.3 ± 1.2 μV) delays were considerably smaller than those at either the 300 ms (13.6 ± 4.5 μV) or 450 ms (18.4 ± 6.8 μV.) delays ($p<0.05$). Furthermore, the reflex amplitudes at both the 10 ms and 150 ms delays were significantly smaller when they occurred unexpectedly during the 'early' session as opposed to when they occurred expectedly in the 'fixed' session. ($p<0.05$). The results indicate that it is not the duration of the delay per se which modulates the reflex gain but rather the predictability of any particular delay. We conclude that the long latency reflex gain increased with a time course relative to and at least 150 ms in advance of the expected unloading onset.

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Where applicable, the experiments described here conform with Physiological Society ethical requirements.

PC208

H reflexes of the serratus anterior muscle

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Serratus anterior, along with other scapulothoracic muscles such as trapezius, stabilises the scapula upon the chest wall. It is innervated by the long thoracic nerve, a nerve that exclusively supplies this muscle. The long thoracic nerve is described as being purely motor (Bizzarri et al., 2001; Schultz & Leonard, 1992). However, given that this is its sole innervation, this is at odds with the observation that the muscle contains a normal complement of muscle spindles (Voss, 1971). The long thoracic nerve is superficial, which renders it vulnerable to injury and leads to dysfunctions of clinical significance. However, it also lends itself to electrophysiological studies. We have therefore taken advantage of this to investigate the reflexes evoked by the afferents of serratus anterior.

With local ethical approval and informed consent of healthy subjects, reflexes of serratus anterior and trapezius were evoked using electrical stimuli of peripheral nerves. The effects of these stimuli were recorded electromyographically using surface electrodes placed over the ipsilateral and contralateral serratus anterior and trapezius muscle pairs. The long thoracic nerve can be located superficially at two points (i) at a proximal site, superior to the proximal end of the clavicle, and (ii) at a distal site, on the lateral surface of the chest wall along the mid-axillary line. Confirmation that the cathode was located on the long thoracic nerve was ascertained by the resulting contraction of the serratus anterior muscle. As the nerves to serratus anterior and trapezius are closely situated at the proximal site in the supra-clavicular fossa, it was also ensured that no trapezius H reflex or M response was present when stimulating at this site. Reflex activity evoked by electrical stimulation of the afferent nerve to trapezius was induced by electrical stimulation of the cervical nerve of C3/4 (see Alexander & Harrison, 2002).

Electrical stimulation of the long thoracic nerve at both sites, evoked short latency, facilitatory reflexes in the ipsilateral serratus anterior. These would appear to be H reflexes. In contrast to the short latency reflexes evoked by trapezius (a close synergist of serratus anterior) in the contralateral trapezius, no short latency reflexes were evoked by serratus anterior in the contralateral serratus anterior. Also, no synergistic responses were evoked in trapezius from stimulation of the long thoracic nerve at the distal site. These results, indicating a very restrictive pattern of reflexes from serratus anterior, are similar to those observed in the cat by Caicoya et al (1999). In addition, the pattern of short latency reflexes evoked by serratus anterior differs from that evoked by trapezius afferents. This presumably reflects differences in independent control of these muscles bilaterally.

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Where applicable, the experiments described here conform with Physiological Society ethical requirements.

PC211

GALANIN PLAYS A TROPHIC ROLE TO HIPPOCAMPUS IN ORGANOPTYPIC CULTURES

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Galanin is a 29 amino acid neuropeptide, which initiates its biological effects through specific G-protein linked receptors. It has been demonstrated that exogenous galanin or the previously described high-affinity galanin receptor 2 (GALR2)-specific agonist, reduced cell death when co-administered with glutamate or staurosporine, in both wildtype and mutant cultures and that the neuroprotective role played by galanin in the adult hippocampus is mediated at least in part by GALR2 activation (1). In addition it has been shown that adult sensory neurons are dependent, in part, on galanin for neurite extension and that this crucial physiological process is mediated by activation of the GalR2 receptor in a protein kinase C (PKC)-dependent manner (2). This study therefore aimed to investigate whether this survival role involved signalling by activation of PKC which in turn activates the ERK cascade.

Here we report that these actions are mediated by activation of the extracellular signal-regulated kinases (ERK) and protein kinase B (Akt). Further, glutamate-induced rise in activated Akt was reduced in mutant organotypic cultures at 10 and 30 min (255% of control value followed by 249% increase relative to WT control at 30 min, n=3) compared with wildtype controls (320% of control value followed by a further increase of 270% increase relative to WT control, n=3) whilst ERK activation was secondarily increased, while in transgenics overexpressing galanin, Akt and ERK were markedly higher than in WT. These results imply that a GALR2-specific agonist might have therapeutic uses in some forms of brain injury.

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Where applicable, the experiments described here conform with Physiological Society ethical requirements.

PC212

Neonatal handling impairs maternal odor preference in the pup rats: noradrenaline/CREB pathway role

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Early-life environmental events, like a disruption of the mother-pup relationship, may induce profound long-lasting changes upon several behavioral and neuroendocrine systems. A capacity that is critical for the pups in this period is identification of their mother, because she holds the vital elements for the pups' survival. Rat pups recognize their mothers through olfactory cues. This early odor learning in rats is associated with increases in noradrenaline (NA) levels and cAMP response element-binding protein (CREB) phosphorylation in the olfactory bulb (OB). The present study aimed to analyze the effects of experimental handling of rat pups on the maternal odor preference test and the NA/CREB pathway participation. Wistar pup rats were daily handled for 1 min during the first 7 days (repeated handled group) or just once on day 7 after delivery (acute handling group). The acute handling group was divided in acute handled plus mother group, in which the pup was handled and returned to the mother for 15 min before humane killing, and the acute handled no mother group, in which the pup was handled and then was kept warmed for 15 min before humane killing. A non-handled group, in which the pups were left undisturbed until day 7, was used as control. Parameters evaluated were: odor preference test, CREB, pCREB, NA and MHPG (noradrenaline metabolite) levels in the OB. Data were expressed as mean±SEM and the differences between groups ($p \leq 0.05$) were determined by Student's t-test or ANOVA followed by Newman-Keuls test as required. Neonatal repeated handled pups showed increased latency to reach the nest bedding (268.2±10.6 s, n=12) compared with nonhandled pups (223.3±12.7 s, n=15). The frequency (F) and duration (D) of locomotion in the nest bedding area of repeated handled pups were decreased (F=3.8±1.2, D=10.3±2.5 s, n=12) compared with nonhandled animals (F=6.5±0.9, D=21.0±3 s, n=15). Acute handled plus mother (1941±201.9 optic density, n=5) and acute handled no mother groups (1756±95.8 optic density, n=5) showed increased pCREB levels compared with nonhandled group (1207±127.3 optic density, n=5). CREB levels did not change in the OB. Repeated or acute neonatal handling did not alter NA content, but MHPG increased in the repeated handled (1.3±0.1 pg/mg protein, n=7), acute handled no mother (1.2±0.01 pg/mg protein, n=7) and acute handled plus mother (1.3±0.1 pg/mg protein, n=7) groups compared with nonhandled (0.9±0.06 pg/mg protein, n=7). We may conclude that neonatal handling decreases maternal odor preference in rat pups. The increased activity of NA/CREB pathway in the OB seems to be involved in this change.

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Where applicable, the experiments described here conform with Physiological Society ethical requirements.

PC213

Chromatin remodelling in rat dentate gyrus granular neurons after exposure to a novel environment

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The hippocampus is a limbic brain region that plays an important role in stress-related adaptive processes at the molecular, cellular and behavioural level. Recently, we have obtained evidence that adaptation to stress may entail chromatin remodel-

ling as a critical step in transcriptional regulation. The aim of this study was to examine whether a mild psychological stressor (i.e. exposure to a novel environment) would affect the number of (P(Ser10)-H3)$^+$ and (P(Ser10)-Ac(Lys14)-H3)$^+$ neurons in the rat dentate gyrus (DG).

Male Wistar rats were exposed to a novel environment by placing them singly in a new cage for 30 min. They were humanely killed 30 min (n=8), 2 h (n=6) or 24 h (n=10) after the start of novelty. P(Ser10)-H3 and P(Ser10)-Ac(Lys14)-H3 staining in neuronal nuclei was detected by immunohistochemistry. The numbers of P(Ser10)-H3$^+$ and P(Ser10)-Ac(Lys14)-H3$^+$ neurons were counted and expressed as number per DG per animal. In later experiments, the positive neurons were analysed with regard to localisation, i.e. closest to hilus, middle or closest to molecular layer, within the granular cell layer of the DG.

Exposure to a novel environment for 30 min induced a marked increase in P(Ser10)-H3$^+$ (control (n=6) 6.7±0.50; 30 min: 11.0±0.57 ($P<0.05$, post-hoc Dunnett's test); 2 h: 13.5±0.42 ($P<0.05$, post-hoc Dunnett's test); 24 h: 6.7±0.37) and P(Ser10)-Ac(Lys14)-H3$^+$ neurons (control: 10.1±0.74; 30 min: 17.3±0.39 ($P<0.05$, post-hoc Dunnett's test); 2 h: 19.9±0.62 ($P<0.05$, post-hoc Dunnett's test); 24 h: 10.4±0.42), an effect which was virtually restricted to the DG. Both P(Ser10)-H3 and P(Ser10)-Ac(Lys14)-H3 modifications followed similar time courses with peak levels between 30 min and 2 h, returning to baseline within 24 h. This pattern of histone modifications was evident throughout the rostro-caudal axis of the hippocampus. Furthermore, the novelty-induced rise in P(Ser10)-H3$^+$ and P(Ser10)-Ac(Lys14)-H3$^+$ neurons was exclusively found in the middle and superficial aspects of the DG granular cell layer. Previous studies have suggested that these neurons are morphologically and functionally more developed and differentiated than those in the deep part of the granular cell layer [1]. Thus, the neurons recruited in response to novelty stress are most likely mature ones.

In conclusion, the present study shows for the first time that novelty exposure evokes histone modifications in specific neurons of the hippocampal circuitry. Our data indicate that novelty enhances plasticity of DG neurons, a notion which is supported by the recent observation that this psychological challenge enhances long-term potentiation in the DG [2].

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Where applicable, the experiments described here conform with Physiological Society ethical requirements.