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Authors have confirmed where relevant, that experiments on animals and man were conducted in accordance with national and/or local ethical requirements.

PC79

Trafficking of potassium voltage-gated ion channels in the neuroblastoma cell line SH-SY5Y via hypoxic modulation and its relationship to Alzheimer's disease

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In Alzheimer's disease (AD) the most prevalent dementia in the western world, levels of the soluble peptide, amyloid beta (Aβ) are increased in the cerebral spinal fluid[1,2].
Elevation of this peptide has also been found in sufferers of strokes and other vascular disorders[3,4].
There is a strong positive correlate between the incidence of AD and those people who have had a prior ischemic episode[5].
To clearly define the link between these two afflictions, the human neuroblastoma cell line SH-SY5Y, was used as a neuronal model, and were either hypoxically incubated, or transfected with known AD related mutations. High-throughput planar patch clamp technique has been employed to analyse K+ channel current. Biotinylation followed by western blot, probing for Kv3.1b, was also used to detect any changes in protein localisation.
Results show that cells containing Presenlin-1 (PS-1) mutations (e.g. D385N) and hypoxically treated cells both have elevated K+ channel current density; 79 ± 16 pA/pF (n=38) and 31 ± 12 pA/pF (n=5) at 50mV respectively, versus the control group, 16.5 ± 1.8 pA/pF (n=3). This functional elevation in current can be explained by an increase in membrane localisation of voltage gated potassium channels, as indicated by the biotinylation assay. This effect is ablated when one of the enzymes key to generating Aβ (γ – secretase) is inhibited. This data indicates a mechanism for the initiation of sporadic AD as a result of ischemic episodes, and also illustrates a role for Aβ in the homeostatic control of ions in neurons.

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Authors have confirmed where relevant, that experiments on animals and man were conducted in accordance with national and/or local ethical requirements.

PC80

Failure of NMDAR activation during quantal release at cerebellar mossy fibre-granule cell synapses in adult mice

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At many excitatory synapses in the CNS, glutamate activates both AMPA- and NMDARs. Although it is commonly assumed that these receptors are co-localized in the postsynaptic membrane, the situation at adult synapses is unclear. Our studies of cerebellar granule cells (GCs) show that in immature animals NMDARs are activated during both spontaneous mEPSCs and following mossy fibre (MF) stimulation. By contrast, in mature mice, MF activity leads to activation of NMDARs (predominantly NR2C-containing; Cathala et al. 2000) but mEPSCs lack an NMDAR-mediated component (Cathala et al. 2003). Here we re-examined mEPSCs and evoked EPSCs in GCs from young and mature mice, and undertook EM immunogold localization of NMDARs, to investigate the presence and localization of NMDARs in GCs of adult mice.
Patch-clamp recordings were made from GCs in cerebellar slices from immature (P7-9) or mature (P34-55) mice, at 35C. While mEPSCs were readily detected in Mg2+ free conditions at -70mV at both ages, these events were abolished in mature GCs by CNQX (non-NMDAR blocker), suggesting that at this age GCs lack synaptic NMDARs. To determine if NMDARs are present in the synaptic membrane, but have their activity suppressed, we examined mEPSCs under conditions that increase the likelihood of activating and detecting NMDAR currents. We examined cells in extracellular Mg2+ (at +30mV) to enhance NMDAR activation, with increased glycine to maximize activation of the NMDAR glycine site, in conditions that suppress tonic H+ inhibition of NMDARs and in conditions that suppress mGluR inhibition of NMDARs. No NMDAR-mediated component was seen in any of these conditions. This was also the case when Sr2+ was used to desynchronize release and enable examination of MF-evoked quantal events, suggesting that this discrepancy does not reflect a difference between spontaneous and evoked release.
Mature GCs are thought to express mRNA for both NR2C and NR2A. Consistent with this, we found both high- (50pS) and low conductance (19 and 38pS) NMDAR channels in outside-out patches from these cells. Immunogold labeling confirmed the presence of multiple NMDAR subunit types in the extrasynaptic membrane, and revealed a high particle density at intraglomerular non-synaptic attachment plaques (between adjacent dendrites). NR1, NR2A and NR2C labeling was also detected within postsynaptic densities (PSD), but at much lower

level. Overall our data suggest that either the sparse labeling of PSD does not reflect the presence of functional receptors, or the level of synaptic NMDAR expression is below that which can be resolved during our recordings. Alternatively, NMDARs are present but not activated during the brief glutamate transient arising from the release of single quanta. Future modeling studies will address this question.

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Authors have confirmed where relevant, that experiments on animals and man were conducted in accordance with national and/or local ethical requirements.

PC81

Sheep RyR2 channel activity is regulated by an endogenous kinase other than PKA or CaMKII; an effect not mediated by S2809

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Previously we have demonstrated that PKA-dependent phosphorylation at S2809 is associated with a significant increase in RyR2 channel open probability (Po), and characteristic changes in gating[1]. To further investigate RyR2 phosphorylation, sarcoplasmic reticulum vesicles were isolated[2] from sheep hearts obtained from an abattoir and were either incorporated into artificial membranes for single-channel studies or used for Western blot[1]. In the presence of 50μM cytosolic free Ca^{2+}, 5 min incubation with 5mM Mg^{2+} and 1mM ATP, followed by wash out to control conditions, significantly increased channel Po (from 0.071±0.023 to 0.334±0.076 (SEM; *n*=17, p<0.01, Student's t-test)). The increase in Po however, was smaller than that observed when exogenous PKA was included in the incubation medium (from 0.126±0.035 to 0.574±0.106 (SEM; *n*=10). Closer examination of the individual Mg^{2+}ATP treated channels suggested the presence of two different sub-populations of RyR2. In 10 of 17 channels, Mg^{2+}ATP treatment resulted in an increase in channel Po and a change in channel gating similar to that observed after PKA-dependent phosphorylation (Po rose from 0.033±0.011 to 0.534±0.079 (SEM; *n*=10). In the remaining channels, Mg^{2+}ATP had no sustained effect (*n*=7). ATP alone, in the absence of Mg^{2+}, produced a fully reversible increase in Po in all channels treated (*n*=12). It is possible that the heterogeneous response of the channels to Mg^{2+}ATP is due to the close association of an endogenous kinase with some of the RyR2 channels reconstituted into bilayers. Use of the PKA inhibitor, PKI (10 μM), did not prevent the Mg^{2+}ATP dependent increase in channel Po although it does prevent the effects of exogenously added PKA. Similarly the Ca^{2+}/calmodulin-dependent protein kinase (CaMKII) inhibitor, autocamtide-2 related inhibitory peptide II (AIPII) (50 nM), did not prevent the increase in Po at concentrations expected to inhibit CaMKII. Increasing the concentration of AIPII to a level reported to inhibit the action of PKC (1 μM) however, prevented the irreversible Mg^{2+}ATP-induced changes. Further, use of the PKC specific inhibitor, chelerythrine chloride, also prevented the Mg^{2+}ATP related change in channel activity. In the presence of 1μM chelerythrine chloride, Po was 0.120±0.039 before and 0.044±0.021 after treatment with Mg^{2+}ATP (SEM; *n*=7). Chelerythrine chloride alone had no effect on channel Po. Although chelerythrine chloride inhibited the Mg^{2+}ATP-dependent increase in channel Po, it did not prevent phosphorylation of RyR2 at S2809. Western blot analysis demonstrated that under lipid bilayer comparable conditions, only PKI prevented Mg^{2+}ATP phosphorylation of S2809. We conclude that RyR2 channels may be associated with and phosphorylated by an endogenous kinase, possibly PKC, which does not appear to phosphorylate S2809.

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PC82

Post-natal developmental changes in ion channel and Ca^{2+} handling protein expression in the ventricle

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Transmural gradients in action potential duration (APD) and Ca^{2+} handling proteins are important for both the normal functioning of the ventricle and arrhythmogenesis. In the rabbit, the transmural gradient in APD is minimal in the neonate. During post-natal development, APD increases both in the epicardium and the endocardium, but the prolongation is more substantial in the endocardium leading to a significant transmural gradient. We have investigated changes in ion channel expression in the subepicardial and subendocardial layers of the left ventricular free wall in neonatal (2-7 days of age; n=11) and adult male (~6 months of age; n=11) New Zealand White rabbits using quantitative PCR (qPCR), *in situ* hybridisation (ISH) and immunohistochemistry. The rabbits were killed humanely in accordance with the regulations of the United Kingdom Animals (Scientific Procedures) Act 1986. qPCR revealed that in the neonate, Nav1.5 (responsible for I_{Na}), ERG (responsible for $I_{K,r}$) and minK (responsible for $I_{K,s}$) mRNAs were more abundant in the endocardium than the epicardium, whereas the reverse was true for KChIP2 (in part responsible for I_{to}) mRNA. Moreover, in the adult, Cav1.2 (responsible for $I_{Ca,L}$), SERCA2a, RyR2, ERG, KvLQT1 (responsible for $I_{K,s}$) and KChIP2 mRNAs were more abundant in the epicardium than the endocardium. Consistent with this, ISH

and mean frequency of contraction during muscle recovery between tetanic stimulation in L-carnitine supplemented-intermittent hypoxia exposed group as compared to unsupplemented and exposed group of rats. From these results it is concluded that L-carnitine delays skeletal muscle fatigue in rats by reducing free radical induced oxidative damage in intermittent hypoxic exposure.

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PC95

Power distribution in the camouflage pattern of a squid (*Loligo vulgaris*)

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Differential output of motor units during neuro-muscularly generated colour change has been assessed by comparing the expanded sizes of elements served by units that darken the skin of a squid, with their size at rest in a pale skin. The wide range of resting sizes of pigment spots (retracted into a tight sphere at rest, Fig. 1 left) is thought to correlate directly with ontogenetic age of chromatophore organ [1] – thence with the age of motor neurons supplying them. Maximum ratios of expansion (areas) subtended by individual brown (B) and red (R) spots when the skin is dark (cf. Fig. 1 right), range from c. 30:1 to c.20:1; converted to mean diameter, ratios at any moment are a measure of the shortening of chromatophore muscle and thus of firing frequency [2, 3].

Figure 2 shows the contribution that red/brown spots make to one of the common camouflage dresses worn by a squid. At medium intensity of expression, relative power falls off with increasing resting-size/age of chromatophore organ. [N.B. were the squid to have turned all-dark (maximum intensity) the curve would be nearly flat].

Evidently fine gradations of tone are achieved across a limited range of firing frequencies (data not shown) by bringing in the units of small (younger) spots first and of large (older) spots last. It recalls the way motor-unit recruitment grades the power output of vertebrate limb muscles – with here an additional developmental signature.

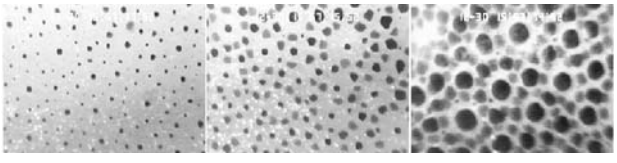

Figure 1. Frames from video-clip of natural colour change (from pale, through lightly shaded to dark) in Loligo vulgaris (captive squid, dorso-lateral mantle surface, c.1cm2).

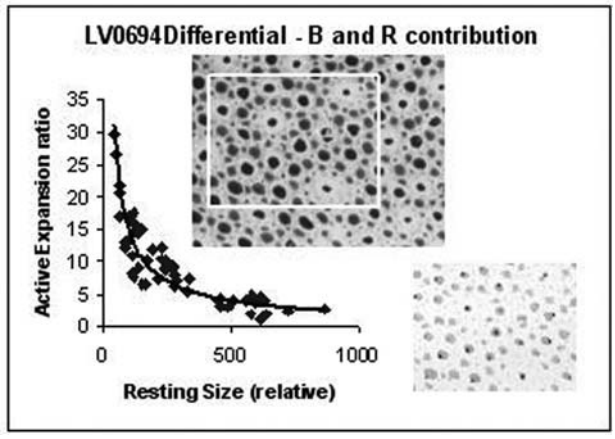

Figure 2. Differential contribution of brown and red spots to counter-shading pattern of medium intensity (detail c.1cm2). Still photograph, hand-held camera. [Right, same pattern at lower intensity overlaid by spots at resting size].

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Photoshop; U.S. National Institute of Health (NIH) freeware for ImageJ ; squid fishermen Bay of Naples.

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PC96

Optimal control predicts human performance on objects with internal degrees of freedom

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Humans regularly interact with objects with internal degrees of freedom from carrying a cup of coffee to folding a shirt. While objects with no internal degrees of freedom can be regarded as some kind of extension of our limbs, non-rigid objects pose a more complex control problem. In recent years stochastic optimal feedback control has emerged as a framework for human motor coordination. Optimal control has been used to explain average movement trajectories as well as trial-by-trial variability in a wide range of motor behaviours, such as obstacle avoidance and bimanual coordination. In this study, we investigated whether the optimal control framework can be extended to object manipulation with internal degrees of freedom and whether it can account for the complex behaviour necessary to control such objects. We used a virtual reality set-up together with a vBOT robotic interface to simulate the dynamics of a virtual object attached to the subject's hand (for

details see Körding et al., 2004). Subjects started with both hand and object aligned in the starting position and were required to move both the hand and object to the target position within a certain time window that was reduced during training down to 1 ± 0.2 s. As a prototypical object with internal degrees of freedom, the object was simulated as a damped mass, attached to the hand by a spring. However, we created six different complex dynamic objects by introducing anisotropies for the mass, viscosity and spring constant matrices (such as x-y dependencies and a velocity-dependent rotational force field applied to the mass). Subjects (n = 6) learned to control the six different mass-spring objects until they achieved 25% correct trials. Positional data and forces were recorded at 1000 Hz and the last 25 successful trials were analysed. We used an optimal control model based on the model proposed by Todorov & Jordan (2002) and included the dynamics of the different mass-spring-damper systems. Our optimal control model predicted complex hand trajectories such as loops and s-shaped curves which deviate substantially from the straight hand paths seen during normal reaching movements. Experimental performance of subjects was well predicted explaining 83 – 96% of the variance with the same parameter settings across all conditions. The results suggest that the framework of optimal control can be extended to manipulation of objects with internal degrees of freedom and underlines the generality of the optimal control framework as a theory of motor coordination.

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PC97

The role of visual motion information in the control of eye and head movement during head-free pursuit

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When human subjects move both their eyes and head to follow a target the vestibular-ocular response (VOR) is suppressed. When a target is visible, pursuit maintenance is achieved through a combination of visual feedback and internal (extra-retinal) mechanisms. If a target is extinguished, hence visual feedback is removed, the continuation of eye and head movement is under the sole control of extra-retinal mechanisms. Present experiments use very brief initial target exposures to investigate the rapid sampling of target velocity and its subsequent use by extra-retinal mechanisms. Subjects were presented with a step-ramp stimulus where a target stepped either left or right then moved in the opposite direction at 10-40deg/sec for an initial randomised period of 50-200ms. The target then continued on its trajectory but was extinguished for either 400 or 600ms before reappearing and continuing to move for 200ms. There was a randomised period of 1-3seconds between stimuli. Subjects were required to move their eyes and head to follow the target using the initial visual information to maintain pursuit when the target was extinguished. Results were compared with control conditions where the target was continuously illuminated and also to conditions where the target disappeared after its initial brief exposure and did not reappear, where subjects did not expect it to reappear but were instructed to continue their eye and head movements. Conditions were fully randomised, making it very difficult for subjects to predict events. Subjects were able to appropriately grade their eye and head responses to different target velocities, even at the briefest initial presentation. Smooth eye movements were initiated around 130ms after target onset, whereas the head movements were initiated later, around 200ms. The initial pursuit, driven by visual feedback, was sufficiently rapidly sampled to produce eye and head velocities that were sustained and even increased when the target was not visible, when there was an expectation of the target reappearing. An interesting point is that VOR was suppressed even in the absence of visual feedback, implying the extra-retinal drive in the maintenance of gaze velocity. Therefore, expectation seemed to modulate the internally generated drive for eye and head movements, which has implications that do not support an efference copy model of pursuit. Rather, the sampled velocity information output is used to facilitate continued eye and head responses.

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PC98

Climbing fibre-induced changes in Golgi cell responses to peripheral stimulation

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Golgi cells are important elements of the cerebellar cortex, controlling the flow of mossy fibre information to other cells via granule cells. There have been several reports suggesting that climbing fibres contact Golgi cells, based on anatomy, but electrophysiologically climbing fibre stimulation is reported to depress Golgi cell firing (Schulman & Bloom, 1981). We have reinvestigated this problem and, given the interest in climbing fibres as mediators of synaptic plasticity in the cerebellar cortex, we have examined the effects of conjunctive peripheral afferent and climbing fibre stimulation. Experiments were performed on adult Wistar rats (300-350g) anaesthetised with urethane (1.2 g/Kg i.p.). Golgi cells were identified by their characteristic responses in response to stimulation of peripheral afferents (Holtzman et al, 2006). Climbing fibres (CF) projecting to Purkinje cells close to the Golgi cells

(the vermis and crus II) were electrically stimulated: effective activation was confirmed by recordings of local field potentials and single Purkinje cells.
All Golgi cells tested responded to adequate CF stimulation with a reduction in firing. The onset of the depression was brief (mean latency to minimum firing rate 7.7ms, SEM ±3.1ms, n = 13) and the mean duration of inhibition was134.6ms (SEM ±21.9ms, n = 13). Golgi cell responses to peripheral stimulation were sampled before and after ~20 minutes of conjunctive stimulation of peripheral afferents and CFs (0.6Hz). In all cases a reduction in the response to peripheral stimulation was observed after the conjunctive stimulation (i.e. a decrease in the inhibition). The reduction was statistically significant ($p<0.001$, two-tailed paired T-test comparing magnitude of all responses before and after conjunctive stimulation). Control experiments in which only peripheral afferents or only CF were stimulated for 20 minutes did not produce significant changes in the Golgi cells responses. The changes to the responses to peripheral stimulation remained reduced for as long as the Golgi cells could be recorded (up to 84 minutes) after conjunctive stimulation with CFs.
These results confirm the findings of Schulman and Bloom. In addition they show that conjunctive stimulation with climbing fibres can induce long term changes in the responses of Golgi cells to peripheral afferents in vivo. At this stage the site and mechanism underlying these changes is unknown, but the results raise the possibility that changes in Golgi cell peripheral responses mediated by climbing fibres can potentially contribute to cerebellar motor learning.

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PC99

Electrophysiological identification of eyeblink-related microzones in rabbit cerebellar cortex

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One of the best understood models for behavioural motor learning is the classically-conditioned eyeblink/nictitating membrane response in the rabbit. This is known to be cerebellum-dependent; most agree that the critical region of cerebellar cortex for the acquisition and performance of conditioned responses is in Larsell's lobule HVI. There remain uncertainties about the extent of the areas involved and whether they are confined to lobule HVI. In this learning model, the instructive (unconditioned) stimulus is carried by climbing fibres activated by periocular afferents; the appropriate regions of the cerebellar cortex can therefore be identified from climbing fibre projection zones. In the cat and ferret there are several discrete 'eyeblink control' areas in lobule HVI and surrounding cortex (Hesslow, 1994; Hesslow and Ivarsson, 1994), where climbing fibres are specifically activated by stimulation of the periocular skin. However, the majority of behavioural studies have been done using rabbits, for which no definitive zonal maps exist. We addressed this problem using a combination of electrophysiological and histological mapping. Identification of specific microzones will allow mechanistic studies of the learning processes at a neuronal circuit level.
We have mapped the regions in which climbing fibres are activated by periocular stimuli within lobule HVI. We have used a linear array of seven microelectrodes (Thomas Eckhorn 7 system), to map systematically across the lobule. Climbing fibre-evoked local field potentials and complex spikes in Purkinje cells elicited by periocular stimulation were recorded within lobule HVI and surrounding areas in urethane-anaesthetised, pigmented, Murex rabbits. Electrode locations were reconstructed histologically and selected sections were immuno-stained for zebrin II (aldolase C) to correlate the responsive zones with zebrin immunoreactivity. Across all animals, large parts of the lobule were unresponsive, suggesting that the periocular microzones are discrete and occupy only a small proportion of the lobule . The most reliable locations of periocular activated areas were deep in the medial fold of lobule HVI (6/7 animals), extending to the base of the primary fissure. In zebrin-stained sections, this deep area corresponded to the P5+ band (Sanchez et al., 2002). However, in some animals periocular responses were also evident in other areas indicating heterogeneity between animals.
High resolution identification of eyeblink-controlling areas in the rabbit will allow behavioural studies to be combined with neuronal recordings targeted to the zones most likely to be involved in the learning process.

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PC100

Efferent connections in the rat from the periaqueductal grey to pre-cerebellar relays; the inferior olive and the gracile nucleus

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The dosolateral/lateral (DL/L-) and ventrolateral (VL-) columns of the periaqueductal grey (PAG) coordinate respectively 'active' versus 'passive' coping strategies, which include alterations in sensory and autonomic functions that are associated with characteristic behavioural responses (Lovick & Bandler, 2005). It is well established that descending control from the PAG acts at the level of the spinal cord to modulate sensory processing and autonomic outflow. In contrast, the pathways that control motor activity are less well understood. The aim of this study was to investigate the anatomical organisation of efferent pathways from DL/L- and VL-PAG to two key pre-cerebellar structures involved in relaying hindlimb signals to the cerebellum: the rostrolateral dorsal accessory olive (IO) and the gracile nucleus (GN).

Male Wistar rats (n=8, 275-350g) were anaesthetised (Ketamine 60mg.kg-1/Medetomidine 25μg.kg^{-1} i.p.) and injected stereotaxically into the IO (n=7) and/or GN (n=8) with mixtures of anterograde (fluoro-ruby or fluoro-emerald) and retrograde tracers (red or green fluorescent latex microspheres). In all but 1 case, successful injections were made into both sites in the same animal. After 5-7 days survival, animals were terminally anaesthetised (propofol, 30mg.kg.h^{-1} i.v.), perfusion fixed, and brains and dorsal root ganglia (DRG) removed for histological processing. In 40μm sections, injection sites in the medulla and retrogradely labelled neurones in the PAG, and in L5 DRG were mapped with a fluorescence microscope and plotted onto representative transverse sections. Anterograde terminal labelling in the cerebellum and retrogradely labelled neurones in the DRG were used to confirm the position of injection sites in IO and GN respectively.

In the same animal, injections into IO resulted in a significantly higher number of labelled cells, as compared to GN (olive=80±10; gracile=20±6; mean±SEM; t-test, p<0.0001). IO injections resulted in labelled neurones throughout the PAG with significantly more in the DL/L-PAG as opposed to VL-PAG (t-test, p<0.01). Additionally, significantly more labelled neurones were identified in caudal PAG compared to rostral PAG (caudal=108±8; rostral=53±4; mean±SEM; t-test, p<0.01).

The current data raise the possibility that neurones in the PAG may modify motor behaviour by modulating olivocerebellar (climbing fibre) pathways. That columnar (including rostrocaudal) differences in the organisation of these projections may underlie the different motor responses co-ordinated by the PAG requires further investigation.

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PC101

The role of glutamate receptor ligands in allodynia, hypersensitivity and morphine analgesia during neuropathic pain in mice

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Recent evidence have indicated that metabotropic glutamate receptor (mGluR) type 5, 2/3 and 7 are present in regions of central nervous system important for nociceptive transmission [2-4], but their involvement in neuropathic pain has not been well established. The present study was aimed to exam the influences of mGluR5 antagonist: MPEP, mGluR2/3 agonist: LY379268 and mGluR7 agonist: AMN082 on development of neuropathic pain symptoms and on morphine effects in Albino Swiss mice after sciatic nerve injury. Chronic constriction injury (CCI) to the sciatic nerve was performed under pentobarbital (36 mg/kg; I.P.) anaesthesia using the procedure described by Bennett and Xie [1]. The mechanical allodynia (von Frey test) was performed in order to evaluate sensitivity to mechanical stimulus. The cold plate test was used to assess sensitivity to cold stimulus. The experimental procedures were performed according to the Institute's Animal Research Bioethics Committee and in accordance with the NIH Guide for the Care and Use of Laboratory Animals. The data were calculated as the mean ± SEM or as a percent of maximal possible effect (%MPE) ± SEM (n=8-12 per group). Our results demonstrated that both acute and chronic administration of MPEP, LY379268, and AMN082 attenuated allodynia and hyperalgesia seven days after CCI in mice. Moreover, single administration of MPEP (30 mg/kg; I.P.) or LY379268 (10 mg/kg; I.P.) injected 30 min before morphine (20 mg/kg; I.P.) potentiated morphine analgesic effect towards mechanical allodynia and thermal hyperalgesia in the mouse CCI model. Whereas, a single administration of AMN082 (3 mg/kg; I.P.) potentiated the effects of a single morphine injection (20 mg/kg; I.P.) only in the von Frey test. Chronic administration (for seven days) of low doses of MPEP, LY379268 or AMN082 (all drugs at 3 mg/kg; I.P.) potentiated the effects of single doses of morphine (3, 10, 20 mg/kg; I.P.) administered on the last day of experiment; however, AMN082 potentiated only the effect in the cold plate test. Additionally, the same doses of MPEP and LY379268 (but not AMN082) chronically co-administered with morphine (40 mg/kg; I.P.) attenuated the development of morphine tolerance in CCI-exposed mice [5, in press, PAIN]. Our data suggests that mGluR5, mGluR2/3, and mGluR7 are involved in injury-induced plastic changes in nociceptive pathways and that mGluR5 and mGluR2/3 ligands enhanced morphine's effectiveness in neuropathy, which could have therapeutic implications.

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Serotonin-specific reuptake inhibitors (SSRI) blunt bitter taste acutely (minutes), but enhance it chronically (hours) in normal healthy humans

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Serotonin is postulated to act as either a transmitter between taste cells and gustatory neurones, and/or as an intercellular signal, modulating taste transmission within the taste bud itself