P1435 / #2201

Topic: AS09 Motor and Sensory Systems

ADRENERGIC AND SEROTONERGIC MODULATION OF COORDINATED SPONTANEOUS ACTIVITY OF DORSAL HORN NEURONS.

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The presence of spontaneous activity in spinal circuits has been reported under *in vivo* and *in vitro* conditions and may play a fundamental role in the processing of nociceptive information by adjusting the excitability of these circuits. Our aim was to investigate the modulatory role of the adrenergic and serotonergic descending systems on the ongoing activity of spinal circuits. The lumbar spinal cord of neonatal mice was excised and a single 500 µm slice preserving the superficial laminae and attached dorsal roots was obtained and maintained *in vitro*. Multielectrode arrays were used to record spontaneous activity from dorsal horn neurons. Recordings from primary afferents were obtained with micro-suction electrodes from teased dorsal rootlets to identify dorsal root reflexes and potentials in primary afferents. Drugs were bath-applied for 10-30 minutes to allow for full equilibration. Spontaneous activity in dorsal horn neurons presented different patterns and showed temporal synchronization forming population bursts. This activity is also coordinated with the activity recorded from terminal of primary afferents. The adrenergic agonists norepinephrine and A-61603 reduced spontaneous activity in a large proportion of neurons and abolished the occurrence of population bursts; these effects were accompanied by a reduction in the frequency of depolarizations recorded from the rootlets. Serotonin showed mixed effects on the activity of dorsal horn neurons and a partial reduction of coordinated firing, coinciding with a partial depression of the responses recorded from rootlets. In contrast, the application of the more selective agonist 5-carboxamidotryptamine produced mainly inhibitory actions and resembled the depressant effects of adrenergic agonists. These results suggest that the spontaneous activity in spinal cord circuits is sensitive to descending modulatory influences, which strongly affected the occurrence of synchronous activity. These effects may contribute to the depressant actions of both neurotransmitter systems on the processing of nociceptive transmission. Financial support MICINN PID2021-126330OB-I00.

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FUNCTIONAL CHARACTERIZATION OF CORTICO-SPINAL AND CORTICO-RUBRAL NEURONS DURING VOLUNTARY MOVEMENT EXECUTION IN RAT

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Motor cortex participates in the coordination of the activity of subcortical systems related to muscle control. Layer 5 pyramidal tract neurons (PTN) are canonical elements of the cerebral cortex, which connect with several subcortical structures by means of the pyramidal system contributing to various phases of the movement, such as the planning and execution. the cerebral cortex has evolved as a regulator of ancestral motor structures like the red nucleus, reticular formation, pons, and the spinal cord via the corticospinal tract (CST). To understand if PTNs projecting to different subcortical structures play distinct roles in motor control, here we characterize how two classes of L5 motor cortical neurons projecting to the red nucleus (corticorubral tract, CRT) and to the spinal cord (corticospinal tract, CST) participate in a voluntary movement. Our results indicated that both classes of neurons are different populations since they participate differentially in the control of movements. We compared selective optogenetic inhibition of motor cortex corticospinal (CST) or corticorubral (CRT) neurons during the execution of a lever movement in response to a light stimulus to analyze movement performance in rats. During the training phase movement trajectories gradually display less variability and become more stereotyped. However, the photoinhibition of CST and CRT neurons differentially modify the cinematic parameters: duration and velocity of the movement trajectories, suggesting that both classes of PTNs have different roles for sensorimotor integration.

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CELLULAR AND MOLECULAR RATIONALE OF THE VOMERONASAL ORGAN IN MALE AND FEMALE RABBITS

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Pheromones are chemosignals involved in fundamental innate socio-sexual behaviors, which are essential for animal reproduction and survival. They are mainly detected through the vomeronasal organ (VNO), which has two main types of vomeronasal receptors (V1Rs and V2Rs) linked to G-protein coupled receptors (Gαi2 and

Gα0) and the transient receptor potential channel 2 (Trpc2) to induce signal transduction. However, the molecular rationale behind pheromone perception and whether other unknown cell-types or pheromone receptors are involved in pheromone sensing remains unknown. To obtain a comprehensive view of the cell-types and receptors in the VNO, we have generated the first VNO cell atlas using single-nuclei RNAseq (snRNAseq) of the rabbit VNO –two males and two female adults–, a well-known model of chemical communication. Nuclei were processed using Chromium-10X pipeline, sequenced by Illumina, and analysed with STAR and Seurat. We identified 31 cell clusters, with no differences between sexes, consistent with our previous bulk-RNAseq data. Seven clusters were vomeronasal sensory neurons (VSNs) containing either Gαi2a or Gα0 expression. Remarkably, not all of these clusters showed V1R/V2R or Trpc2 gene expression, suggesting that other unknown species-specific receptors might also be involved in pheromone sensing and signal transduction. Five additional clusters expressing sex steroid-receptors (progesterone, prostaglandin F2α receptor, etc.) fit within the VSNs category despite not showing Gαi2/Gα0 expression. VSNs expressing VRs and sex-steroid receptors were clustered separately, raising the question of whether sex-steroid receptors act as a first screening of sensory perception in response to specific internal states followed by the activation of VRs VSNs or if instead both groups of VSNs sense pheromones independently. All in all, understanding the cellular rationale of the VNO will provide the needed framework for deciphering how pheromonal inputs are mediated by sensory neurons, potentially placing VSNs as a peripheral center that integrates internal states with external chemosignals.

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SIGMA-1 RECEPTOR AGONISM EXACERBATES IMMUNE-DRIVEN NOCICEPTION: ROLE OF TRPV1 + NOCICEPTORS

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Background: The sigma-1 receptor is a neuromodulatory chaperone protein. The antihyperalgesic effect of sigma-1 antagonists has been widely reported. Sigma-1 agonists are being developed for the treatment of neurodegenerative disorders, although their effect on pain is not well elucidated.

Material and Methods: We tested the effect of sigma-1 agonism in two experimental conditions: after injection of a low dose of prostaglandin E2 (PGE2) (an inflammatory mediator) and after superficial plantar incision.

Results: The administration of the sigma-1 agonists dextromethorphan (a broad-spectrum antitussive), PRE-084 (a standard sigma-1 ligand) and pridopidine (a selective ligand in clinical trials for the treatment of Huntington's disease and amyotrophic lateral sclerosis) were unable to induce sensitization to the mechanical stimulus (paw pressure) *per se*, but enhanced PGE2-induced mechanical hyperalgesia. Superficial plantar incision induced a transient weight bearing asymmetry at early time-points (3.5 h after surgery), but at 24 h mice were apparently recovered. Using hematoxylin-eosin staining and flow citometry, we found that in spite of the behavioral recovery, mice still maintained a noticeable edema with neutrophilic infiltration. In this condition, sigma-1 agonists induced a relapse of postincisional pain (weight bearing asymmetry), and in a manner dependent on the presence of neutrophils (a well-known cellular source of PGE2), since inhibition of neutrophil infiltration by an anti-Ly6G abolished the proalgesic effects of sigma-1 agonism. All these effects of sigma-1 agonists were reversed by administration of the sigma-1 antagonist BD-1063 in wild-type mice, and were absent in sigma-1 knockout animals. These results support the selectivity of the effects observed.

Conclusions: Sigma-1 agonism exacerbates pain-like responses in mice treated with the inflammatory mediator PGE2 and in mice with a mild inflammatory condition. The proalgesic effect of sigma-1 agonism might be a side effect that has gone unrecognized in patients treated with sigma-1 agonists in current medical practice or clinical trials.

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MAPPING THE NEURAL CIRCUITRY OF SIMPLE SOUND PERCEPTION IN AWAKE RATS: AN FMRI CONNECTOMIC STUDY

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Electrophysiological studies of sound tonotopy in the rat cortex have revealed that different frequencies of sound are processed in distinct regions of the auditory cortex, similar to what has been found in other mammalian species. Specifically, it has been shown that high-frequency sounds are processed in the anterior region of the auditory cortex, while low-frequency sounds are processed in its posterior region. This tonotopic organization is important for the brain to efficiently process different aspects of auditory information and is likely conserved across species. Nevertheless, these studies have not permitted the detection of the complete distribution of sound frequency perception across the rodent auditory system. In this study we used 7-Tesla functional magnetic resonance imaging (fMRI) in awake rats to study how different frequencies are processed and represented by the brain. Here, 4 different frequencies (7.5, 15, 38 and 46 kHz) were presented during two different recording sessions — 2 frequencies per session. In the same animal we could detect hierarchical and tonotopic organization from subcortical through cortical levels: whole-brain clusters of activity, identified auditory regions and sub-regions involved in auditory perception of pure frequencies. We show that auditory stimulation of awake rats leads to consistent and robust levels of brain activation which, opens up the possibility to use this method to examine complex auditory perception and to conduct longitudinal and translational studies, which could be used in the observation of