The link between chronic musculoskeletal pain and sperm quality in overweight orthopedic patients

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Aims: The association between low fertility potential and an overweight is well recognized. In addition, a link between pain and overweight condition has been identified. However, it is not known whether overweight pain patients present any alterations in fertility potentials. Hence, the current study provided a profounder vision into the possible relation between an overweight condition, chronic musculoskeletal pain, and fertility potential in overweight male patients.

Methods: This "observational study" was based on 10 overweight chronic pain patients (OP and 10 healthy matched controls (OC) from the referrals to the orthopedic department at Aalborg University Hospital, Aalborg, Denmark. The study was approved by the regional Ethics Committee of the Northern Jutland, Denmark and conducted from June 2014 to December 2015. Semen samples were obtained from all participants and assessed for sperm concentration, motility, and kinematic parameters with the Sperm Class Analyzer (SCA®, Spain). Pressure pain thresholds (PPT) were also measured by a handheld pressure algometer in 16 pre-defined points of the subjects in both groups.

Results: The OP group demonstrated a decline in PPT values compared to the (OC); however, difference between the two was insignificant. But, the OP group showed a lower percentage of static and non-progressive motile sperm ($P < 0.05$). The sperm kinematic parameters (progressive motility, VCL, VSL, VAP and BCF) also demonstrated a lower trend in OP group in comparison with the controls.

Conclusions: This study presented that sperm quality declines in overweight chronic pain patients. Since the control group consisted of pain free overweight individuals, we propose that chronic musculoskeletal pain could potentially affect sperm quality, distinct from what an overweight alone does to the male fertility potential. However, further investigation in overweight chronic pain patients of different types is required before a general conclusion can be made. In addition, mechanisms underlying such effects need further clarification.

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Several days of muscle hyperalgesia facilitates cortical somatosensory excitability

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Background and aims: Maladaptive plasticity in neural circuits has been proposed in chronic musculoskeletal pain and has been discussed as a key component of the transition from acute to chronic pain. The induction of delayed onset muscle soreness (DOMS) in healthy individuals is one method that can be used to investigate the adaptations of neural circuits in response to several days of muscle hyperalgesia. The aim of this study was to determine the adaptations of the sensory cortex in response to muscle hyperalgesia induced by eccentric exercise of the wrist extensor muscles. It was hypothesized that muscle hyperalgesia would result in a facilitation of cortical somatosensory excitability, based on sensory evoked potentials evoked by electrical stimulation of the radial nerve.

Methods: Twelve healthy subjects performed eccentric exercise of the wrist extensors. Muscle soreness, pressure pain thresholds (PPTs) on the extensor carpi radialis (ECR) muscle, somatosensory evoked potentials (SEPs) based on 10 channel EEG recorded during electrical stimulation of the radial nerve were recorded before (Day0Pre), 2 h (Day0Post), 2 days (Day2), and 6 days (Day6) after exercise.

Results: Compared to Day0Pre: (i) Muscle soreness increased at Day0Post and increased further at Day2 (both $P < 0.05$). (ii) Pressure pain thresholds decreased at Day2 ($P < 0.05$), (iii) the peak-to-peak N30-P45 and P45-N60 amplitude of the sensory evoked potential from the central-parietal recording sites were increased at Day2 (both $P < 0.05$); (iv) reduction in ECR PPTs was correlated with an increase of the post-central P45 wave.

Conclusions: These data demonstrate that hyperalgesia developing across several days is accompanied by an increase in sensory cortical excitability. In addition, sensory cortical adaptation followed a similar temporal profile to increased sensitivity to pressure (PPTs). This model may be relevant for further understanding neural adaptation in the transition from acute to chronic pain.

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Social stress, epigenetic changes and pain

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Aims: Bullying is a prevalent issue in society, with adverse effects ranging from psychological symptoms to somatic ailments like chronic pain. The purpose of this study was to generate new knowledge about the underlying mechanisms behind this association. Using an animal model, we investigated the changes in microRNA expression in plasma, in the pituitary gland and the adrenal gland following social stress.

Methods: A resident-intruder paradigm where male Sprague Dawley rats (intruders) were exposed to male Long Evans rats

(resident) 1 h daily for a week was used. Bodyweight was measured and blood samples were collected throughout the experiment. Changes in plasma microRNA expression was determined by qPCR.

Results: Rats exposed to social stress showed reduced weight gain compared to controls. Preliminary results suggested that social stress increased the plasma expression of miR-146a-5p, miR-30c-5p and miR-223-3p.

Conclusions: The data showed that social stress gives reduced weight gain and increased expression of several circulating microRNAs. How this affects the development of persistent pain remains to be investigated.

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Characterization of released exosomes from satellite glial cells under normal and inflammatory conditions

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Aims: Satellite glial cells (SGCs) are non-neuronal cells that entirely surround neurons within sensory ganglia. This unique structure allows SGC-neuron interactions. Altered cross-talk following nerve injury or inflammation is thought to contribute to pathogenesis of chronic pain. Release of extracellular vesicles in form of exosomes has been found to play a key role in cell-cell communication. However, release of exosomes from SGCs and their potential role in modulating pain remain unknown. Hence, this study aimed at identifying and characterizing shed exosomes from SGCs under normal and inflammatory conditions.

Methods: Fresh primary cultures of rat trigeminal ganglia (TG) were prepared from adult male Sprague–Dawley rats. Danish Animal Inspectorate approved the study protocol. Primary SGCs were kept in culture up to 21 days and were characterized by morphology and immunohistochemistry. Cultured SGCs were monitored under normal and LPS (50 ng/mL) treatment. Collection of conditioned media was performed over time and exosomes were isolated. Particle size distribution and total protein were determined by NTA and LC–MS/MS, respectively.

Results: SGCs formed small clusters, spread outwards to areas devoid of cells but remained spindle-like in appearance with larger cell bodies. The primary cultures of SGCs were clearly GS positive with a low expression of GFAP. LPS treatment led to higher GFAP expression. Particle size distribution showed that two third of the particles were in the exosomal size range. Upon LPS-stimulation, four proteins (histone H2B, ubiquitin-60S ribosomal, myosin-9, elongation factor 1-alpha) were found exclusively expressed compared to normal treated SGCs.

Conclusions: For the first time it was demonstrated that SGCs shed extracellular vesicles in exosomal size range. Mysoin-9 was identified as a possible novel marker of SGCs activation under inflammatory conditions. This protein plays a role in cell-cell adhesion and possibly contributes to SGC-SGC cross-talk upon inflammation which may consequently influence the excitability of nearby neurons.

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Cell-based platform for studying trigeminal satellite glial cells under normal and inflammatory conditions

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Aims: Satellite glial cells (SGCs) in sensory ganglia contribute to the pathogenesis of chronic pain. *In vitro*, providing enough fresh primary SGCs poses some practical limitations; hence, frozen stocks of primary cells for culture could be an attractive alternative for cell-based studies or drug screening. This study was designed to investigate the morphology and marker expression of frozen and freshly isolated trigeminal SGCs under normal and inflammatory conditions.

Methods: SGCs from trigeminal ganglia of three male Sprague–Dawley rats and three frozen (sub cultured and passaged) batches of stored primary SGCs were cultured. Their morphology was observed by phase microscopy and the phenotype was characterized by immunocytochemistry of glutamine synthetase (GS) and glial fibrillary acidic protein (GFAP). Lipopolysaccharide (LPS) was used to simulate a state of neurogenic inflammation *in vivo*. A pilot test was performed to determine the optimal concentration of LPS to activate SGCs based on GFAP expression. A long-term activation of the SGCs with 50 ng/mL LPS was chosen for further characterization.

Results: The fresh and frozen primary SGCs elicited similar phenotypes based on GS marker expression. However, frozen primary SGCs differed in terms of size and morphology. GFAP was constantly expressed in frozen primary SGCs regardless of LPS stimulation. Activation of primary fresh SGCs with LPS spread the GFAP expression from around the cell body throughout the longer processes and activation was only seen in the LPS treatment.

Conclusions: The phenotypic marker, GS was independent of culture conditions. There was no difference in upregulation of GFAP in thawed SGCs regardless of LPS stimulation. This indicates that freeze-thawing might activate SGCs and therefore frozen and passaged cells cannot be suitable for use in cell-based models for inflammation. Fresh primary cells are therefore optimal for studying SGCs under normal and inflammatory conditions.

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Tramadol in postoperative pain – 1 mg/ml IV gave no pain reduction but more side effects in third molar surgery

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Aims: Does pre-emptive single dose intravenous tramadol produce a safe and effective postoperative analgesia?

Methods: Randomized, placebo controlled, single blinded clinical trial of pre-emptive intravenous tramadol 1 mg/kg in combination with IV midazolam in patients with dental fear. A "Pain diary" evaluates the efficacy. The safety is evaluated perioperative monitoring (SpO_2 and BP).

Results: Pain scored by VAS showed no differences between the groups. It took longer time to first rescue pill in tramadol vs. control group (157 vs. 110 min, $p = 0.049$). Desaturation ($SpO_2 < 90\%$) was more commonly found in tramadol vs. placebo and control