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Spinal pain in employees exposed to abusive supervision: Evidence of a sex and CRHR1 CTC haplotype interaction

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Abstract

Previous findings suggest that exposure to social stress in the form of abusive supervision may increase the risk of musculoskeletal disorders. In the present study, we examined the link between abusive supervision, the *CRHR1* genotype and spinal pain. The data were collected through a national survey drawn from the National Central Employee Register by Statistics Norway. A total of 1226 individuals returned both the questionnaire and the saliva kit. Abusive supervision was measured by a 5-item version of the Tepper's 2000 scale. Spinal pain was measured by 3 items (neck-, upper and low back pain). Genotyping with regard to CRHR1 rs242941, rs242939 and rs1876828 was carried out using Taqman assay, and Phase v.2.1.1 was used to define the CRHR1 allele combinations. The analyses revealed that abusive supervision was associated with spinal pain. In particular, we observed a strong effect of abusive supervision on spinal pain in female +CTC/+CTC carriers ($p = 0.002$). Moreover, using +CTC/+CTC as a reference, +CTC/−CTC and −CTC/−CTC both showed protective effects ($p = 0.024$, $p = 0.002$, respectively). Also, our data demonstrated a clear sex and CRHR1 CTC haplotype interaction ($p = 0.013$). No such gene-environment interaction was seen in men. Our data demonstrated that the CRHR1 CTC haplotype may exacerbate the effect of abusive supervision on spinal pain in female employees. Hence, the present study supports the theory that both gender and the CRHR1 genotype, may moderate the pain responses to social stressors.

Keywords

Social stress, spinal pain, CRHR1, glucocorticoid receptors, sex

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Introduction

In the Norwegian adult population, as many as 80% experience musculoskeletal pain.[1,2] A considerable portion of such pain states may be spinal pain, i.e. neck-, upper back- and low back pain.[3,4] The experience of pain involves activation of several brain areas such as hippocampus,[5] amygdala[6] and the prefrontal cortex.[7] These areas are also important in the response to stressful experiences. Social stress, in the form of abusive supervision in the workplace, has been recognised to be especially detrimental.[8] Thus, it seems likely that being exposed to abusive supervision also may affect the sensory processes in the brain relevant to pain.

Abusive supervision is defined as subordinates' perceptions of the supervisor engaging in sustained displays of hostile verbal and nonverbal behaviour, excluding physical contact.[9,10] Abusive supervision is a form of hindrance stressor (i.e. a constraint to a subordinate's personal achievement and goal progress), leading to various negative outcomes for exposed subordinates. As many as 10–16%[11] report being subjected to such behaviours. Experiencing abusive supervision may be linked to e.g. workplace deviance, decreased task performance and reduced creativity.[10] Evidence exists that being exposed to abusive supervision increases the risk of health complaints.[12]

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Although little is known about the mechanisms underlying the effect of abusive supervision, it seems clear that such stressors do affect the hypothalamic-pituitary-adrenal (HPA) axis. Moreover, such strong stressful experiences could influence the hypothalamic release of corticotropin-releasing hormone (CRH), disturb pituitary release of the adrenocorticotropic hormone (ACTH), which in turn control glucocorticoid synthesis of the adrenal cortex.[13] Thus, it seems likely that strong social stressors through circulating glucocorticoids,[14] may affect neuroinflammatory processes including pain.[15,16]

One of the genetic factors involved in the response to activation of the HPA axis is the gene encoding corticotropin-releasing hormone type 1 receptor (CRHR1). Located at 17q21.31, this G-protein coupled receptor binds neuropeptides of the CRH family[17] and is therefore a significant regulator of the HPA axis. In particular, this receptor may be important for the stress-induced negative feedback triggered by high cortisol levels, which in turn is crucial for the HPA deactivation and coping.[18] Additionally, CRHR1 is expressed in several of the brain areas important in cognitive function and supraspinal nociceptive processing.[19]

So far, research on the CRHR1 haplotype block comprising of SNPs rs242941, rs242939, rs1876828 has focused only on depression.[20–23] However, given the link between social stress, HPA axis activation, CRHR1 and nociceptive processing in the brain, it seems likely that this haplotype may be involved in the experience of pain. Moreover, women and men may be different regarding pain mechanisms.[24,25] Hence, our aim was to investigate associations between abusive supervision, the *CRHR1* haplotype rs242941/rs242939/rs1876828, gender and spinal pain in the general working population.

Method

Data collection

As previously described,[26] the data were based on a sample of 5000 employees randomly drawn from The Norwegian Central Employee Register collected by Statistics Norway. Briefly, inclusion criteria were adults from 18 to 60 years of age, working at least 80% of full-time employment. Questionnaires were distributed by post in 2015. A total of 1608 persons (32%) returned the questionnaire. Additionally, saliva collection kits were sent to consenting subjects (1226 returned the saliva sample kit). Ethical approval was obtained by the Regional Committee for Medical Research for Eastern Norway (REK 2014/1725).

Instruments

The respondents were asked to indicate the frequency of occurrence of several supervisor behaviours characteristic of abusive supervision. A 5-item version of the Tepper's "Abusive Supervision Scale", with response categories ranging from 0 to 4 ('never', 'rarely', 'once in a while', 'quite often' and 'very often or always'), was used.[9,27,28] Items consisted of "critiques me in front of others", "tells me my thoughts and feelings are stupid", "says I am useless", "negative remarks about me in front of others" and "ridicule me". Cronbach's alpha for abusive supervision was 0.87. Moreover, the participants were asked to answer questions indicating their level of spinal (neck-, upper and low back) pain the last 12 months. The response categories was ranged from 0 to 3 ('not bothered,' 'a little bothered,' 'considerably bothered', 'seriously bothered').

Genotyping/haplotyping

Extraction of genomic DNA from saliva was performed using OrageneRNA sample collection kit (DNA Genotech Inc. Kanata, Ontario, Canada). As previously described,[29] single nucleotide polymorphism (SNP) genotyping with regard to rs242941, rs242939 and rs1876828 were carried out using predesigned TaqMan SNP genotyping assays (Applied Biosystems, Foster City, CA, USA). In accordance with the procedure in our earlier studies,[26,29] an ABI 79000HT sequence detection system was used. Phase v.2.1.1 was used to define the CRHR1 haplotypes. The haplotyping was categorised into those individuals with two copies of CTC, those with one copy of CTC and all others. Approximately 10% of the samples were re-genotyped and the concordance rate was 100%. See Supplementary Table 1a for haplotype combinations, Supplementary Table 1b for haplotype grouping and Supplementary Table 2 for Hardy-Weinberg Equilibrium and p-value for all SNPs.

Statistical analysis

In line with previous studies,[9,27] the average of the 5 items in the questionnaire was used to score abusive supervision. An average was also calculated from the 3 questions regarding pain. The association between abusive supervision and spinal pain moderated by gender and the CRHR1 haplotype was examined using linear regression. First, the linear regression analyses were stratified by gender. In these analyses, the main effects (without any interaction term) were assessed in step 1, whereas the possible effect of the two-way interaction; abusive supervision × haplotype was assessed in step 2. Next, a linear regression analysis of the full sample with gender also included in the interaction term (three-way interaction) was conducted to assess any gender

difference revealed in the previous analysis. All statistical analyses were conducted using Stata SE 16.0. Significance was accepted at the $p < 0.05$ level.

Results

In total, 342 (46%) men and 403 (54%) women were successfully genotyped for the CRHR1 haplotype (Tables 1 and 2). The distribution within the male cohort was 86 (25.1%) with two copies of the CTC allele, 180 (52.6%) with one copy of the CTC allele and 76 (22.2%) without CTC. For females the distribution was 114 (28.3%), 208 (51.6%) and 81 (20.1%), respectively. For men the mean experienced abusive supervision and spinal pain were 0.23 (SD = 0.41) and 0.68 (SD = 0.57) for the +CTC/+CTC individuals, 0.16 (SD = 0.42) and 0.72 (SD = 0.65) for +CTC/−CTC individuals, and 0.19 (SD = 0.40) and 0.69 (SD = 0.60) for −CTC/−CTC individuals (see Table 1). The mean experienced abusive supervision and spinal pain for women were 0.18 (SD = 0.47) and 0.82 (SD = 0.67) for the +CTC/+CTC individuals, 0.18 (SD = 0.40) and 0.84 (SD = 0.70) for +CTC/−CTC individuals, and 0.15 (SD = 0.36) and 0.76 (SD = 0.63) for −CTC/−CTC individuals (see Table 2).

The analysis of the male subjects (Table 3 left, step 1) showed a significant association between abusive supervision and spinal pain (Coef = 0.274, p-value = 0.001). However, no significant association was observed between the CRHR1 haplotype and spinal pain. Further, including an interaction term (abusive supervision × CRHR1) in the model did not indicate any differences in experienced spinal pain for the different haplotypes given abusive supervision (Table 3 left, step 2 & Figure 1(a)).

In contrast to the male subjects, the female subjects (Table 3 right, step 1) did not show a significant association between abusive supervision, or the haplotype, and

Table 1. Characteristics of the male subjects by CRHR1 haplotype (rs242941, rs242939, rs1876828); +CTC/+CTC, +CTC/−CTC and −CTC/−CTC.

		+CTC/+CTC				+CTC/−CTC				−CTC/−CTC				
	Range	N	%	Mean	SEM	N	%	Mean	SEM	N	%	Mean	SEM	Sum
Subjects		86	25.1			180	52.6			76	22.2			342
Spinal pain	0 to 3			0.68	0.05			0.72	0.04			0.69	0.05	
Abusive supervision	0 to 4			0.23	0.03			0.16	0.02			0.19	0.04	
Age				45.9	0.82			45.9	0.59			45.0	0.94	
Education														
≤High school		37	43			66	37			36	47			
≥Higher education		49	57			114	63			40	53			
Smoking														
No		**54**	**62**			**137**	**76**			**54**	**71**			
Yes		**31**	**36**			**43**	**24**			**22**	**29**			

N: number of subjects, SEM: standard error of mean.

Table 2. Characteristics of the female subjects by CRHR1 haplotype (rs242941, rs242939, rs1876828); +CTC/+CTC, +CTC/−CTC and −CTC/−CTC.

		+CTC/+CTC				+CTC/−CTC				−CTC/−CTC				
	Range	N	%	Mean	SEM	N	%	Mean	SEM	N	%	Mean	SEM	Sum
Subjects		114	28.3			208	51.6			81	20.1			403
Spinal pain	0 to 3			0.82	0.05			0.84	0.04			0.76	0.06	
Abusive supervision	0 to 4			0.18	0.04				0.18	0.02		0.15	0.03	
Age				44.3	0.79				44.9	0.53		42.8	0.87	
Education														
≤High school		45	39			69	33			17	21			
≥Higher education		69	61			139	67			64	79			
Smoking														
No		**91**	**80**			**180**	**86**			**69**	**85**			
Yes		**23**	**20**			**28**	**14**			**12**	**15**			

N: number of subjects, SEM: standard error of mean.

Table 3. Hierarchical regression analysis of the effect of abusive supervision on spinal pain; main effects and two-way interaction (Abusive supervision[x]CRHR1) stratified by gender.

	Men				Women			
	B	Std. Err.	p-value	95% CI	B	Std. Err.	p-value	95% CI
Step 1								
Main effects								
Abusive supervision	**0.274**	0.081	**0.001**	(0.114, 0.433)	0.103	0.081	0.208	(−0.057, 0.263)
CRHR1 haplotype								
+CTC/−CTC	0.050	0.082	0.539	(−0.110, 0.212)	0.116	0.078	0.141	(−0.038, 0.271)
−CTC/−CTC	−0.039	0.097	0.690	(−0.231, 0.153)	0.146	0.098	0.138	(−0.047, 0.340)
Step 2								
Abusive supervision (given that CRHR1 = +CTC/+CTC)	0.344	0.188	0.069	(−0.026, 0.715)	**0.436**	0.140	**0.002**	(0.158, 0.711)
CRHR1 haplotype								
+CTC/−CTC	0.191	0.270	0.480	(−0.340, 0.722)	**0.591**	0.222	**0.008**	(0.152, 1.029)
−CTC/−CTC	−0.058	0.332	0.860	(−0.712, 0.595)	**0.997**	0.290	**0.001**	(0.427, 1.567)
Two-way interaction								
+CTC/−CTC	−0.118	0.215	0.583	(−0.542, 0.305)	**−0.409**	0.180	**0.024**	(−0.764, −0.055)
−CTC/−CTC	0.017	0.266	0.947	(−0.505, 0.541)	**−0.737**	0.236	**0.002**	(−1.202, −0.272)

The analysis were adjusted for age, education and tobacco. **Number of observations = 745**. B, beta coefficient; Std. Err., standard error; CI, confidence interval; reference group, +CTC/+CTC haplotype.

Syntax STATA:

Step 1*: by Gender, sort: regress Spinalpain Abusivesupervision i.CRHR1 Age Education Tobacco*

Step 2*: by Gender, sort: regress Spinalpain Abusivesupervision i.CRHR1 Age Education Tobacco c.Abusive supervision#i.CRHR1*

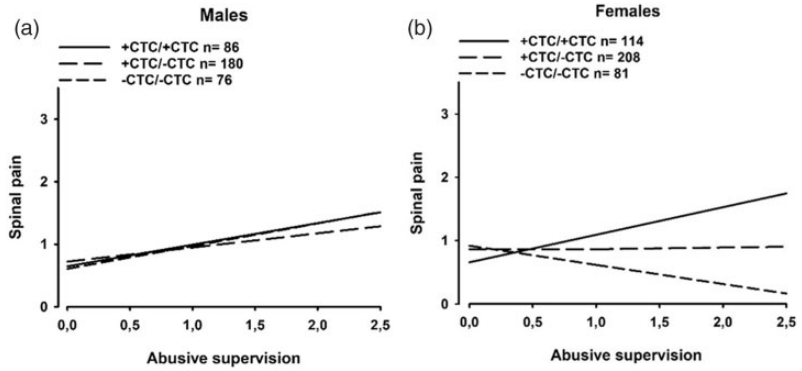

Figure 1. (a) Spinal pain in male subjects with CRHR1 +CTC/+CTC, +CTC/−CTC and −CTC/−CTC exposed to abusive supervision. Adjusted for age. (b) Spinal pain in female subjects with CRHR1 +CTC/+CTC, +CTC/−CTC and −CTC/−CTC exposed to abusive supervision. Adjusted for age.

spinal pain in the initial analysis. However, when including the interaction term (abusive supervision × CRHR1) a significant association was seen (Table 3 right, step 2 & Figure 1(b)). In women with one or no copies of the CTC allele the effect of abusive supervision was weaker (Coef = –0.409, p-value = 0.024) or much weaker (Coef = –0.737, p-value = 0.002) than in women with two copies of the allele.

Moreover, gender was included in the interaction term (abusive supervision × haplotype × gender) in a third analysis, which confirmed gender differences (Table 4). Women without the CTC allele showed significantly less spinal pain compared to men without the CTC allele (Coef = –0.668, p-value = 0.013).

Discussion

The present study showed a clear association between abusive supervision and spinal pain. Interestingly, this association was moderated by the *CRHR1* rs242941, rs242939, rs1876828 CTC haplotype in women. No such gene-environment interaction was seen in men. Thus, our data demonstrated that one or two copies of the CTC allele may reduce resilience to social stress in

Table 4. Linear regression analysis of the effect of abusive supervision on spinal pain, three-way interaction (Gender×CRHR1×Abusive supervision).

	B	Std. Err	p-value	95% CI
CRHR1 – gender difference (reference male)				
Female (+CTC/+CTC)	0.075	0.238	0.752	(−0.392, 0.542)
Female (+CTC/−CTC)	−0.197	0.153	0.200	(−0.498, 0.107)
Female (−CTC/−CTC)	−0.668	0.267	0.013	(−1.193, −0.143)

The analyses was adjusted for age, education and tobacco. B, beta coefficient; Std. Err., standard error; CI, confidence interval.
Syntax STATA: *regress Spinalpain Abusivesupervision Age Education Tobacco i.Gender i.CRHR1 i.Gender#i.CRHR1 Abusivesupervision#i.CRHR1 Abusivesupervision#i.CRHR1#i.Gender*

the form of abusive supervision, but only in women. This shows that the CRHR1 haplotype may moderate the pain responses to social stressors in employees, and adds to the existing evidence linking stress and pain.[26,30,31] Moreover, environmental stressors have long been connected to both aetiology and pathophysiology of physical health.[32]

The HPA axis is one of the primary neurobiological systems activated in response to experienced stressors. In addition to the effect circulating glucocorticoids have on the brain,[33] the precursor CRH also have neuromodulatory properties.[34] One of the extra-hypothalamic areas with high expression of CRH is the amygdala. Among other tasks, the amygdala is involved in the emotional-affective dimension of pain.[35] Especially important is the presence in the central nucleus, which serves as the amygdala output nucleus.[36] This area receives unfiltered nociceptive input as a part of the spino-parabrachio-amygdaloid pain pathway.[35,36] Earlier observations suggest that central sensitisation may enhance the excitability in the amygdala regions in musculoskeletal pain conditions.[37,38]

Previous research indicates that increased CRH in the amygdala can trigger pain-like behaviour,[36] and also links pain to the function of the opioid receptors in the amygdala.[4] Moreover, earlier data show that the opioid receptor genotype OPRM1 rs1799971 G allele increases the pain intensity in women, but have the opposite effect in men.[24] Hence, sex differences in nociceptive processing in the amygdala,[39–42] that also affect the HPA axis and subsequent emotional responses to stress including pain, seems likely. Given the central distribution of the CRHR1 receptors, it is tempting to speculate that the *CRHR1* rs242941, rs242939, rs1876828 haplotype may affect such processes.

In any case, our data suggest that spinal pain in women is associated with genetic susceptibility. In accordance with earlier observations, the present study supports the theory that women are less affected by the psychosocial work environment,[31] but more affected by genetic factors than men.[43] However, such sex differences may be dependent on choice of outcome. Although women who experience abusive supervision with two CTC alleles report more pain than men with the same genotype, these men may have other manifestations not studied in the present study. The cellular mechanism underlying the impact the CRHR1 haplotype CTC allele on spinal pain and other health outcomes remains to be investigated.

Limitations

The outcome in the present study was the average of three items regarding neck-, upper- and low back pain over the last 12 months. Thus the information given by the subjects is not immune to recall bias.[44] Additionally the level of abusive supervision is fairly low in this cohort. This may be related to the low occurrence of such behaviour in the Norwegian working population.[45] Also, due to the cross-sectional nature of this study, no information regarding cause and effect can be concluded. Further, we cannot disregard common-method bias due to self-report bias as the subjects reported both the exposure and the outcome.[46] However, as the subjects were informed that all information was treated anonymously it likely does not have any great impact.[46] Finally, the average response rate for the questionnaire was 32%. Although somewhat low, this response rate is in line with the current trends in survey research.[47] Furthermore, response rate is assumed to have little impact on the internal validity of a study and it is therefore unlikely that the response rate in this study have a major effect on the established association.[48]

Conclusion

The present data showed that the association between abusive supervision and spinal pain was moderated by the CTC allele in women. No such gene-environment interaction was observed in men. Moreover, women with CTC appeared to be less resilient than men with the same haplotype when exposed to abusive supervision. Hence, the present data emphasize that individual differences may be important in understanding how interpersonal relations between leaders and employees affect physical health. Additionally, our results may

assist in further understanding of the gender dependent responses to social stressors in the workplace. Still, as abusive supervision was associated with higher levels of spinal pain in both genders, the present data show that organizations will benefit from preventive measures that can prevent the occurrence of this kind of leadership. We conclude that both sex and the CRHR1 haplotype moderates spinal pain in response to abusive supervision.

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Author Contributions

ACS, AR, JOC, MBN and JG designed the research and analysed the data. ACS and JG wrote the manuscript with comments from AR, JOC and MBN.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

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