The Thermal Grill as a Tool to Investigate Analgesic Clinical Pharmacology

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Abstract

Human experimental pain models are important aids in the study of pain mechanisms, and have been extensively used in clinical drug development to demonstrate the analgesic potential of new compounds. However, the peripheral nature of such pain models makes it difficult to separate the peripheral and central mechanisms of pain. Whilst peripheral mechanisms underlie acute pain, central mechanisms are believed to underlie chronic pain conditions; therefore using an illusion to trick the brain into believing it is experiencing pain may allow investigation of these central mechanisms. One such illusion is the thermal grill illusion, where interlaced innocuous warm and cool temperature bars (thermal grill) produce a paradoxical burning pain sensation. Considering the uniqueness of the thermal grill illusion and the thermal grills' potential ability to investigate the interaction between the nociceptive and thermoreceptive pathways, the objective of this thesis was to investigate whether the response to the thermal grill was tolerable in patients with chronic pain to determine whether the thermal grill illusion could be used to screen for novel centrally acting analgesics in the future. Previously the response to the thermal grill had not been systematically investigated in patients with chronic pain. In order to address this objective, the response to the thermal grill illusion was characterised in pain-free participants, in patients with heterogeneous chronic pain conditions and also in patients with homogenous chronic pain conditions to determine 1) whether the response to the thermal grill differs between pain-free participants and patients with chronic pain, 2) whether the response to the thermal grill differs between body location and body side and 3) whether the thermal grill can differentiate chronic pain phenotypes. In addition, the response to the thermal grill was longitudinally

investigated in patients with chronic medication overuse (MOH) and chronic tension-type headache (CTTH) whom were receiving a novel pharmacological and non-pharmacological therapy for their headaches respectively. Initial studies demonstrated a reduced response to the thermal grill illusion in patients with heterogeneous chronic pain compared to pain-free participants. Although not significant, subsequent studies revealed a similar pattern of reduced response in patients with chronic sciatica pain and CTTH, suggesting that any real differences observed in the previous study were not robust or that the true effect size was small. Amongst all populations, the average intensity of pain experienced from the thermal grill illusion was quite low, thus questioning the utility of the thermal grill as a model to assess the efficacy of analgesics, given the inability of the thermal grill test to reach the clinically relevant substantial pain threshold. Additionally, the test-retest reliability of the thermal grill response over time in patients with MOH and CTTH was poor, further questioning the thermal grills' ability to longitudinally assess the efficacy of analgesics. Although the thermal grill is unlikely to be a suitable tool to assess the efficacy of analgesics, the thermal grill may still be a useful tool to better understand the physiology of pain, given the paradoxical reduced pain observed in patients with certain types of chronic pain.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Nicole M. Sumracki Date

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Abbreviations

5-HT	Serotonin
5-HTT	Serotonin transporter
ACC	Anterior cingulate cortex
AIDS	Acquired immunodeficiency syndrome
AMHs	A-δ mechano-heat nociceptive afferents
ANOVA	Analysis of variance
ASI	Anxiety severity index
BAC	Breath alcohol concentration
BDI-II®	Beck Depression Inventory®-II
BMI	Body mass index
C-warm	C-fibres responsive to warm
C2	C-fibres responsive to cold, warmth and heat
CAP	Capsaicin
CH	C-fibres responsive to noxious heat
CI	Confidence interval
CMH	C-fibres responsive to noxious mechanical and heat stimuli
CMHC	C-fibres responsive to noxious mechanical, heat and noxious cold stimuli
COLD	Lamina I thermoreceptive specific cells
CPT	Cold pain threshold
CRPSI	Chronic regional pain syndrome type I
CTTH	Chronic tension-type headache
CU	Clinical unit
CWC	Warm stimulus flanked by two cool stimuli
EEG	Electroencephalography
EPT	Electrical pain threshold
F	Female
fMRI	Functional magnetic resonance imaging
GFR	Glomerular filtration rate
HADS	Hospital anxiety and depression scale
HADS-A	Hospital anxiety and depression scale (anxiety)
HADS-D	Hospital anxiety and depression scale (depression)
Hep B	Hepatitis B
Hep C	Hepatitis C

HIV	Human immunodeficiency virus
HPA	Hypothalamo-pituitary-adrenal
HPC	Lamina I multimodal cells
HPT	Heat pain threshold
i.d.	Intradermal
IQR	Interquartile range
LFTs	Liver functions tests
M	Male
mA	Milliampere
MDD	Major depressive disorder
MDvc	Ventral caudal medial dorsal nucleus
MOH	Medication overuse headache
MS	Multiple sclerosis
NNT	Number needed to treat
NRS	Numerical rating scale
NS	Nociceptive specific cells
NSAIDs	Non-steroidal anti-inflammatory drugs
^{o}C	Degrees celcius
OIH	Opioid induced hyperalgesia
P	Pearson
PARC	Pain and anaesthesia research clinic
PET	Positron emission tomography
QST	Quantitative sensory testing
S	Spearman
S1	Primary somatosensory cortex
S2	Secondary somatosensory cortex
SCL-90-R®	Symptom checklist-90-R
SD	Standard deviation
SEM	Standard error of the mean
SMT	Spinomesencephalic
SRT	Spinoreticular tract
STAI	State trait anxiety index
STAI-T	State trait anxiety index (trait)
STT	Spinothalamic tract
tDCS	Transcranial direct current stimulation
TG	Thermal grill

TGI	Thermal grill illusion
TLR-4	Toll-like receptor 4
TLRs	Toll-like receptors
TMS	Transcranial magnetic stimulation
TRPA1	Transient receptor potential ankyrin 1
TRPM8	Transient receptor potential melastatin 8
TRPV1	Transient receptor potential vanilloid 1
TRPV2	Transient receptor potential vanilloid 2
TRPV3	Transient receptor potential vanilloid 3
TRPV4	Transient receptor potential vanilloid 4
VAS	Visual analogue scale
VMpo	Posterior aspects of ventral medial nucleus
VP	Ventral posterior nucleus
VPI	Ventro-posterior-inferior nuclei
VPL	Ventro-posterior-medial thalamic nuclei
WARM	Lamina I warm cells
WCW	Cool stimulus flanked by two warm stimuli
β-CD	Hydroxypropyl-β-cyclodextrin