Available online at www.sciencedirect.com
ScienceDirect
Journal of Psychiatric Research 42 (2008) 1010–1016
JOURNAL OF PSYCHIATRIC RESEARCH
www.elsevier.com/locate/jpsychires

Pain perception in schizophrenia: No changes in diffuse noxious inhibitory controls (DNIC) but a lack of pain sensitization

Stéphane Potvin [a,b], Emmanuel Stip [a,c], Adrien Tempier [a], Tania Pampoulova [a], Lahcen Aït Bentaleb [c], Pierre Lalonde [c], Olivier Lipp [c], Philippe Goffaux [b], Serge Marchand [b,*]

[a] *Centre de recherche Fernand-Seguin, University of Montreal, Montreal, Canada*
[b] *Department of neurosurgery, Faculty of medicine, University of Sherbrooke, Axe Douleur CRC-CHUS, 3001, 12e avenue nord, Sherbrooke J1H 5N4, Canada*
[c] *Hôpital Louis-H Lafontaine, Department of psychiatry, Faculty of medicine, University of Montreal, Montreal, Canada*

Received 16 April 2007; received in revised form 31 October 2007; accepted 2 November 2007

Abstract

Background: Pain is a dynamic phenomenon resulting from the activity of both excitatory (e.g. sensitization) and inhibitory endogenous modulation systems. Preliminary experimental studies have shown diminished pain sensitivity in schizophrenia patients. The objective of the study was to investigate the role of excitatory and inhibitory systems on pain perception in schizophrenia.
Methods: Participants were 23 patients with a schizophrenia-spectrum disorder (DSM-IV criteria) and 29 healthy volunteers, who did not differ in age, sex or ethnicity. Excitatory and inhibitory systems were elicited using a temporal summation test (Peltier thermode) administered before and after activation of the diffuse noxious inhibitory control (DNIC) by means of a cold-pressor test.
Results: Time was a significant predictor of pain scores in controls, but not in patients. That is, pain ratings increased during the tonic thermal stimulation among controls but not in schizophrenia patients. When correlation coefficients (between time and pain ratings) for patients and controls were compared, the correlation coefficient emerged as significantly weaker in the schizophrenia group ($Z = 12.04$; $p = 0.0001$), suggesting a lack of sensitization in schizophrenia. DNIC was similar in magnitude in both patients and controls.
Conclusions: Diminished pain sensitivity in schizophrenia may be related to abnormal excitatory mechanisms, but not to DNIC. More studies are needed to better characterize the neurophysiological and neurochemical mechanisms involved in the lack of sensitization in schizophrenia.

Keywords: Schizophrenia; Pain; Sensitization; Diffuse noxious inhibitory control; Negative symptoms; Cognition

1. Introduction

Diminished sensitivity to pain in schizophrenia has been reported since the early works of Bleuler (1911) and Kraepelin (1919). Since then, four series of data have provided empirical support, although inconclusive, for hypoalgesia in schizophrenia: (i) clinical case reports of schizophrenia with various painful medical conditions (ruptured appendix, perforated bowel, peritonitis, etc.) reporting little or no pain (Apter, 1981; Murthy et al., 2004; Rosenthal et al., 1990); (ii) population-based studies describing an elevated prevalence (between 37% and 91%) of diminished or absent reaction to pain in schizophrenia patients suffering from a painful medical condition (Singh et al., 2006; Torrey, 1979); (iii) population-based studies describing a very low prevalence of schizophrenia diagnosis in pain patients (Fishbain et al., 1986; Reich et al., 1983); and (iv) experimental studies showing increased pain thresholds

* Corresponding author. Tel.: +819 346 1110x15889; fax: +819 564 5424.
E-mail address: serge.marchand@usherbrooke.ca (S. Marchand).

0022-3956/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jpsychires.2007.11.001

(sensation, perception or tolerance) in schizophrenia (Blumensohn et al., 2002; Jochum et al., 2006; Kudoh et al., 2000). So far, experimental studies have been scarce, with some methodological limitations (small sample size, uncontrolled medication, diagnostic reliability, etc.) and have produced mixed results. For instance, some groups (Guieu et al., 1994; Collins and Stone, 1966) found no difference in pain perception between schizophrenia patients and healthy volunteers. Thus, the current state of science does not provide an unequivocal description of diminished pain sensitivity in schizophrenia. A satisfactory explanation for hypoalgesia in schizophrenia is also lacking. Clinically, diminished pain sensitivity in schizophrenia has been linked to key symptoms of the disorder (Singh et al., 2006), such as positive symptoms (Merskey et al., 1962), affective flattening (Dworkin, 1994; Dworkin et al., 1993), and/or attention deficits (Jochum et al., 2006). On neurobiological grounds, disturbances in dopamine, serotonin, glutamate and opioids have been proposed to account for hypoalgesia in schizophrenia (Davis et al., 1982; Dworkin, 1994; Singh et al., 2006).

Pain is a dynamic phenomenon resulting from the activity of both excitatory and inhibitory endogenous modulation systems. The temporal summation paradigm is an experimental model used in humans permitting to study excitatory mechanisms (e.g. central sensitization) the central sensitization. The temporal summation results in an amplification of pain perception following repeated or continuous administration of constant noxious stimuli (Arendt-Nielsen et al., 1994; Granot et al., 2006; Price et al., 1977). Temporal summation of pain is thought to reflect the progressive enhancement of C-fiber evoked responses of dorsal horn neurons (windup) and seems to be dependent on *N*-methyl-D-aspartate (NMDA) receptor mechanisms in both animal (Dickenson and Sullivan, 1987) and humans (Price et al., 1994). This phenomenon is potentially relevant to a variety of chronic pain conditions, including neuropathic pain (Chevlen et al., 2005).

Diffuse noxious inhibitory control (DNIC) is an endogenous modulation mechanism triggered by nociceptive stimuli. DNIC recruits serotoninergic, noradrenergic and opioidergic inhibitory neurons located in the brainstem, which project to the spinal cord and dampen the intensity of incoming afferents (Le Bars et al., 1979a,b). A deficit of endogenous pain inhibitory systems has been related to chronic pain conditions, such as fibromyalgia (Julien et al., 2005).

To our knowledge, endogenous excitatory and inhibitory systems have never been studied in schizophrenia, but functional changes of either of these systems may contribute to the diminished pain sensitivity associated with the disorder. The current experimental study pursued three objectives, namely: (i) to replicate the finding of a hyopalgesic response in schizophrenia; (ii) to relate this hypoalgesia to changes in excitatory and/or inhibitory systems; and (iii) to correlate hypoalgesic responses with schizophrenia symptoms (positive, negative, affective and cognitive).

2. Methods

2.1. Participants

Patients were diagnosed with a schizophrenia spectrum disorder, according to DSM-IV criteria. All patients signed a detailed informed consent form. The study was approved by the local scientific and ethics committee.

Exclusion criteria were the following: (i) patients suffering from chronic pain; (ii) patients with a substance use disorder; (iii) patients treated with analgesic, antidepressant (last month) or benzodiazepine (last 24 h) medications; (iv) patients suffering from cardiac, respiratory, endocrine, metabolic or neurological diseases; (v) pregnant or breast-feeding women.

Twenty-three schizophrenia-spectrum patients (21 outpatients, 2 inpatients) were included in the study. Patients suffered from schizophrenia ($n = 18$) and schizoaffective disorder ($n = 5$). Schizophrenia patients were treated with one or more of the following antipsychotics: olanzapine ($n = 7$); clozapine ($n = 7$); quetiapine ($n = 7$); risperidone ($n = 3$); haloperidol ($n = 3$) and other first-generation antipsychotics ($n = 6$). Mean lifetime hospitalizations were 5.2 ± 4.5 (SD). At the moment of testing, 2 patients were inpatients. Controls consisted of 29 healthy volunteers. Patients and controls did not differ in terms of age, sex and ethnicity (Table 1).

2.2. Clinical assessments

Psychiatric symptoms were measured with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1992). Cognitive functions were assessed using selected tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Fray et al., 1996). The tests were run on computers with touch-sensitive colour monitors. Patients completed the Motor Screening Task (MOT), an index of psychomotor speed, the "spatial working memory" (SWM) task and the "Intra-Extra Dimensional Set Shifting" (IED) task, a computerized version of the Wisconsin Card Sorting Test, which measures executive functions (for more details, see Elliott et al., 1998; Potvin et al., 2006). Patients' cognitive complaints were assessed with the Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS) (Stip et al., 2003).

2.3. Pain assessments

The temporal summation test consisted of a continuous heat pulse administered with a thermode for 2 minutes on the left forearm of participants. Experimental temperature quickly reached a fixed value that remained constant during the 2-min testing period (Time 0–Time 120). It was set at a value corresponding to a temperature individually pre-determined to induce a 50% pain rating. The tempera-