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Original article

Diazepam and Jacobson's progressive relaxation show similar attenuating short-term effects on stress-related brain glucose consumption

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ABSTRACT

A non-pharmacological method to reduce anxiety is "progressive relaxation" (PR). The aim of the method is to reduce mental stress and associated mental processes by means of progressive suppression of muscle tension. The study was addressed to evaluate changes in brain glucose metabolism induced by PR in patients under a stressing state generated by a diagnostic medical intervention. The effect of PR was compared to a dose of sublingual diazepam, with the prediction that both interventions would be associated with a reduction in brain metabolism. Eighty-four oncological patients were assessed with 18F-fluorodeoxyglucose-positron emission tomography. Maps of brain glucose distribution from 28 patients receiving PR were compared with maps from 28 patients receiving sublingual diazepam and with 28 patients with no treatment intervention. Compared to reference control subjects, the PR and diazepam groups showed a statistically significant, bilateral and generalized cortical hypometabolism. Regions showing the most prominent changes were the prefrontal cortex and anterior cingulate cortex. No significant differences were identified in the direct comparison between relaxation technique and sublingual diazepam. Our findings suggest that relaxation induced by a physical/psychological procedure can be as effective as a reference anxiolytic in reducing brain activity during a stressful state.

1. Introduction

Diagnostic medical exams commonly generate psychological stress, even when the interventions are minimally invasive [8]. In a previous study, we detected that 67% of oncological patients who are assessed with 18F-fluorodeoxyglucose-positron emission tomography (18F-FDG-PET) show relevant anticipatory anxiety [31]. More recently, Vogel et al. have reported comparable anxiety incidence (59%) before the performance of a FDG-PET study [38]. These data give further support to the empirical practice of administering single-dose anxiolytic medication before PET testing.

Diazepam is an anxiolytic drug classically used as premedication in medical interventions. It is a reference benzodiazepine showing a facilitating action on the inhibitory GABA system and the consequent depression of neuronal activity. Diazepam produces a dose-dependent reduction in both cerebral metabolic rate for oxygen ($CMRO_2$) and cerebral blood flow (CBF), with no net change in CBF/$CMRO_2$ index [4,28]. The effects of diazepam specifically on brain glucose utilization have previously been assessed in both animals and humans [1,6,9,12,15]. Reduction in brain metabolism and CBF associated with diazepam uses to be global [6,9,26]. Nevertheless, some studies report major effects in some areas with high benzodiazepine receptor density [9,40], and others have identified relevant anatomical differences between acute or chronic drug administrations [1,21]. Despite some differences across studies, the general consensus is that diazepam generates a wide reduction of glucose consumption notably involving the cerebral cortex.

Besides anxiolytic drugs, a variety of non-pharmacological techniques have been reported as potential instruments to reduce

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anxiety in clinical settings. Vogel et al. reported a significant relaxation effect using an "audiovisual imagery" technique to lower anxiety of patients waiting for FDG-PET examination [38]. Several studies have described functional changes in brain activity during relaxation meditation. A variety of meditation practices and imaging procedures have been used in these studies, all of them showing a combination of focal increases and decreases of brain activity, in which attention modulating systems displayed a major change [3,7,16,19,22,24,27]. Other studies have assessed plasticity effects on brain anatomy [17,23,25,37] and on intrinsic functional connectivity [18,20,36] from long-term meditation practice. This research has notably contributed to elucidate how meditation exercises modify brain function (i.e., task provocation) and the ability of practice to re-shape brain structure and functional organization. Nonetheless, treatment outcome has rarely been tested in terms of brain activity changes after its application (i.e., acute therapeutic effect). Wang et al. [39] showed focal increases of relative tissue perfusion during meditation that partially persisted after the session.

A particular non-pharmacologic method to reduce anxiety is "progressive relaxation" (PR) technique originally described by Jacobson (1938). The aim of the method is to reduce mental stress and associated mental processes by means of progressive suppression of muscle tension. The physiologist Jacobson originally described the technique at the beginning of the 20th century. However, the technique has been modified in the last years to make it more effective and simpler to perform. The basic procedure involves active muscle contraction (tension) in a body segment and posterior muscle tension release focusing attention on focally generated feelings. A rationale for the method assumes an interaction between physical and emotional relaxation, in a way that muscle relaxation may help to relief from generalized phenomena associated with psychological stress [5]. The usefulness of PR has been tested in pain [10,14], asthma [13], headache [33], tinnitus [34] and anxiety disorders [5]. However, PR action mechanisms are not well understood because few research works have been conducted to assess its physiological basis [5].

The current study was specifically addressed to evaluate changes in brain glucose metabolism induced by PR in patients under a stressing state generated by a diagnostic medical intervention. Assuming that changes in brain metabolism are coupled to changes in brain activity, we anticipated a predominant reduction of glucose utilization as a consequence of attenuating stress-related brain response. The effect of PR was compared to a single-dose of diazepam, with the prediction that both interventions would be associated with a reduction in brain metabolism, as both are putatively efficient in attenuating stress-related responses. Our interest was further centered on identifying the functional anatomy of changes for each intervention and possible regional differences across interventions. In this study, a total of 84 oncological patients were assessed with FDG-PET using standard procedures. Maps of brain glucose distribution from 28 patients receiving PR was compared with maps from 28 patients receiving sublingual diazepam. An additional group of 28 patients with no treatment intervention was examined to obtain reference data.

2. Subjects and methods

2.1. Subjects

This prospective study was approved by the institutional review board of Hospital Quiron and written consent was obtained from all patients. From 1/3/2011 to 1/10/2011, a total of 84 consecutive patients who came into the PET unit of our hospital (mean age of 56, range 19–82 years; 43 women) were included. Clinical reasons for 18F-FDG-PET exam were staging or restaging of neoplastic disease: colorectal carcinoma ($n = 7$), lymphoma non-Hodgkin ($n = 19$), Hodgkin lymphoma ($n = 7$), breast cancer ($n = 12$), lung cancer ($n = 31$), other ($n = 8$).

Patients were randomly assigned to each of the groups (pharmaceutical intervention, relaxation technique and control group) taking into account its order of citation. There were no significant differences in age, sex or reason for the visit in the nuclear medicine department.

The first group was submitted to pharmacological intervention ($n = 28$; mean age of 57.4 years, 14 women; 13 staging and 15 restaging), the second group to a relaxation technique ($n = 28$; mean age of 55.48 years, 15 women; 14 staging and 14 restaging) and the third one was the control group ($n = 28$; mean age of 49.6 years, 14 women; 13 staging and 15 restaging).

Electronic medical records of all patients were evaluated. General exclusion criteria for the three groups were: age younger than 18, lack of capacity to consent and communication difficulties, psychological disease, metastasis brain pathology or neurological disease. In the pharmacological intervention group, besides general exclusion criteria, patients with respiratory difficulties, history of myasthenia gravis, allergy to diazepam, glaucoma, benzodiazepine administration during the seven days before the test or/and those patients who had to drive after the 18F-FDG-PET scan were also excluded.

2.2. Procedure

All patients fasted for at least 6 hours before the administration of the radiopharmaceutical and abundant hydration was recommended. Upon the patients arrival at the nuclear medicine department, weight and blood glucose level were obtained. All of them laid supine in a quite area with ambient temperature and light. A venous catheter was placed in a peripheral vein, usually in the upper extremity.

2.2.1. Pharmacological intervention group

After the general procedure, a sublingual benzodiazepine was administered (diazepam 5 mg) and immediately auditory and visual stimulation were minimized. Between 10 to 15 minutes after that, weight-based dose of FDG (0.15 mCi/kg), was injected into the venous catheter. Fifty minutes after the injection of the radiopharmaceutical PET images were acquired.

2.2.2. Relaxation technique group

After the general procedure, the relaxation technique and the aim of the study were explained to the patients in order to obtain their collaboration. After that auditory and visual stimulation were minimized.

The relaxation model elected for our study consisted in three distinct phases. During the first phase the patient was told to focus on the breathing, a visualization technique was used in the second phase and the third phase was the proper progressive relaxation technique. During the first phase, the patient, with his eyes closed, had to achieve a respiratory slow and regular rhythm. This is the natural respiratory rhythm, which does not demand any effort from the person. The focus of the second phase was to get the every day life tensions out of the patient's while maintaining the patient awake and on alert. This is why we asked the patient to think on a relaxing and pleasant image. During the third phase and using the respiratory natural pattern as a guide, the different muscle groups of the body were tighten and relaxed afterwards. The method consists on tightening a group of muscles during 30 seconds and relaxing them later paying attention on the sensation that it produces. The aim of the technique was to fully relieve the muscular tension and to experience a deep relaxation feeling.