



Doxapram-induced panic attacks and cortisol elevation

David A. Gutman^{a,*}, Jeremy Coplan^b, Laszlo Papp^c, Jose Martinez^d, Jack Gorman^{d,e}

^a*Department of Psychiatry, Columbia University School of Medicine, 1051 Riverside Drive, New York, NY 10032, USA*

^b*Department of Psychiatry, State University of New York, Downstate, Brooklyn, NY, USA*

^c*New York State Psychiatric Institute, New York, NY, USA*

^d*Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, USA*

^e*Department of Neuroscience, Mount Sinai School of Medicine, New York, NY, USA*

Received 29 August 2004; accepted 26 October 2004

Abstract

Numerous agents with differing biological properties and central nervous system (CNS) effects can induce panic attacks in predisposed individuals. A potential explanation of this finding is that panic disorder patients are more likely to panic than normal control subjects when given a panicogen due to an excessive fear response to somatic arousal. We test this hypothesis by using doxapram, a panicogen with minimal CNS effects, to induce panic in patients and control subjects. Doxapram was given to six subjects with panic disorder with or without agoraphobia and four healthy volunteers. Measures comprised the Acute Panic Inventory, the Borg Exertion scale, the 10-point Anxiety Scale, the 10-point Apprehension Scale, cortisol, prolactin, and MHPG, all obtained at baseline and multiple time points after the doxapram infusion. All panic disorder patients panicked with doxapram, whereas no control subjects had a panic attack. Panic patients had similar levels of breathlessness with doxapram compared with control subjects. Although panic patients had higher levels of anxiety and apprehension, these did not change significantly with doxapram compared with control levels. Doxapram led to similar increases in cortisol and prolactin in both groups, and MHPG was consistently elevated in panic patients, but unaffected by doxapram. These results show that doxapram is a useful panicogen in the study of panic disorder. Since the panic patients and control subjects had similar levels of physiological and psychological arousal, but the panic patients were more likely to have a panic attack, this lends support to the concept of a sensitized fear network in panic disorder patients.

© 2004 Elsevier Ireland Ltd. All rights reserved.

Keywords: Doxapram; Panic attacks; Ventilatory stimulant; Cortisol

1. Introduction

A number of agents with varying biological properties and central nervous system (CNS) effects have been shown to produce panic attacks in predisposed individuals. These “panicogens” include

* Corresponding author. Tel.: +1 212 342 1101; fax: +1 419 730 3208.

E-mail address: dg170@columbia.edu (D.A. Gutman).

compounds that produce osmotic stress (sodium lactate and hyperosmotic sodium chloride); stimulate neurotransmitter systems (yohimbine and m-CPP); stimulate brain peptide systems (cholecystokinin); and stimulate breathing (carbon dioxide and doxapram). Although many theories have been suggested to explain the mechanism of action of these panicogens, what they have in common is the capacity to produce significant somatic distress. We have proposed the hypothesis that panic disorder patients are more likely to panic when given a panicogen because they develop a greater fear response when somatic systems are aroused (Gorman et al., 2000). This is consistent with the catastrophic misinterpretation hypothesis of panic disorder that has been articulated by cognitive theorists (Austin and Richards, 2001). Animal models of conditioned fear have demonstrated a coordinated brain circuitry, with the amygdala at its core, that can be linked to the excessive fear in panic disorder patients.

A test of this hypothesis is to administer an agent that produces somatic symptoms but does not have an appreciable CNS action at panicogenic doses. Doxapram is one such substance. The Ann Arbor, Michigan group has done interesting and significant work in exploring the properties of doxapram as a panicogen. Doxapram does not directly affect vascular flow, appears not to activate centrally mediated neurohormonal systems and minimally stimulates a noradrenergic response (Folgering et al., 1981; Calverley et al., 1983; Winnie, 1973; Burki, 1984; Abelson et al., 1995, 1996a). It induces panic attacks quickly in 75–80% of subjects and only 12.5–20% of controls (Lee et al., 1993; Abelson et al., 1996a,b). We hypothesize that doxapram will produce equivalent physiological changes in patients with panic disorder and control subjects, but that the former will experience more fear and therefore be more prone to panic. In this study, we will evaluate this hypothesis as well as validate the effectiveness of doxapram as an efficient precipitant of panic attacks in panic patients by measuring the anxiety and physiological responses to doxapram.

We propose doxapram as an effective agent for precipitating panic attacks for imaging purposes, based on work by Abelson and Lee (Lee et al., 1993; Abelson et al., 1996a,b). As mentioned previously, doxapram does not directly affect vascular

flow, appears not to activate centrally mediated neurohormonal systems, minimally stimulates a noradrenergic response, is sensitive and specific for inducing panic in panic disorder subjects versus control subjects, and has a rapid and predictable onset (Lee et al., 1993; Abelson et al., 1996a,b). In this study, we examine whether doxapram will produce increases in systems linked to the fear response during panic attacks by measuring MHPG (noradrenergic systems), cortisol, and prolactin (neuroendocrine systems). Furthermore, we will validate the effectiveness of doxapram as a precipitant of panic attacks in patients with panic disorder and not in control subjects by replicating the work of Abelson and Lee (Lee et al., 1993; Abelson et al., 1996a,b).

2. Methods

2.1. Subjects

Six subjects with panic disorder with or without agoraphobia (DSM-III-R; 1987) and four healthy volunteers participated in the study. The normal controls consisted of two males and two females, with a mean age of 29.75 ± 10.94 . The patients consisted of five males and one female, with a mean age of 37.33 ± 7.74 . The age was not significantly different ($t = -1.30$; $df = 8$; $P < 0.23$). Subjects signed informed consent after a thorough description of the study.

Psychiatric diagnoses were made by a psychiatric interview by a psychiatrist, and the Structured Clinical Interview for DSM-III-R (Spitzer et al., 1990) was performed by a trained rater. A medical history, physical examination, EKG, blood and urine tests including a thyroid function test, pregnancy test, and toxicology screen were performed. All subjects were required to be medically healthy, without a history of hypertension, cerebrovascular or cardiac disease, nonsubstance abusing, and medication-free for 2 weeks prior to the study. Any medication known to affect neuroendocrine function (e.g., phenytoin, phenobarbital, oral contraceptives, thyroid replacement, or other hormones) had to be discontinued at least 3 months prior to the study. A current or past diagnosis of an affective disorder, eating disorder, suicidal or homicidal ideation, schizophrenia, or other psychotic

متن کامل مقاله

دریافت فوری ←

ISIArticles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات