CORTISOL RESPONSE TO BUSPIRONE IN EXTENDED ABSTINENT ALCOHOLICS

YOUNG-HOON KIM1,2, JOO-CHEOL SHIM1,3,*, DEANNA L. KELLY5, JEONG-GOO LEE4, YOUNG-SOO SEO1 and ROBERT R. CONLEY5

1Department of Psychiatry, 2Paik Institute for Clinical Research and 3Pharmacogenomics Research Center, Inje University, Busan and 4Department of Psychiatry, Dongshu Hospital, Masan, Korea, and 5Maryland Psychiatric Research Center, University of Maryland Baltimore, MD, USA

(Received 2 January 2004; in revised form 10 February 2004; accepted 26 March 2004)

Abstract——We evaluated cortisol response to buspirone in extended abstinence alcoholic patients to determine 5-HT1A receptor sensitivity in alcoholism. Alcoholic patients were inpatients with an extended abstinent period of at least 3 months. Alcoholics had a significantly lower cortisol level than did the normal controls from 60 min through to 150 min after administration of 30 mg buspirone. Our results show that cortisol response to buspirone was significantly decreased in alcoholic patients compared to normal controls, reflecting decreased 5-HT1A receptor sensitivity.

INTRODUCTION

Serotonergic dysfunction has been implicated in the pathophysiology and treatment of alcoholism. Previous studies have reported decreased levels of the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in cerebral spinal fluid (Ballenger et al., 1979; Thomson and McMillen, 1987), blunted hormonal response to direct and indirect 5-HT agonists such as m-chlorophenylpiperazine (mCPP) (Krystal et al., 1996) and fenfluramine (Ballin et al., 1994) and reduced alcohol drinking after taking selective serotonin reuptake inhibitors in alcoholic patients (Pettinati et al., 2000). Alteration of 5-HT1A Receptor functions in alcoholics is not well known. However, several studies have supported this hypothesis. In animal studies, a mixed 5-HT1A/2A receptor drug (FG5938) suppressed alcohol drinking (Piercy et al., 1996), a 5-HT1A receptor antagonist (WAY-100635) reduced alcohol consumption in the rat (Zhou et al., 1998) and the 5-HT1A receptor antagonist (pindobind-5-HT1A) was found to block ethanol reward (Risinger and Boyle, 2002). Few clinical studies have been performed in this area. In a post mortem study, 5-HT1A receptor binding was decreased in the cortical and hippocampal region of alcoholics (Dillon et al., 1991). Decreased cortisol response to flesinoxan, a highly potent and selective 5-HT1A agonist, has also been reported (Pinto et al., 2002).

Cortisol response to buspirone, 5-HT1A Partial agonist, has been used for the evaluation of 5-HT1A receptor sensitivity in many psychiatric disorders (Meltzer and Maes, 1994). In the present study, we evaluated cortisol response to buspirone in extended abstinent alcoholic patients to determine if 5-HT1A receptor sensitivity is related with pathophysiology of alcoholism.

MATERIALS AND METHODS

Thirty-three male subjects participated in this study; 22 alcoholic patients and 15 normal controls. Alcoholic patients were inpatients who had been admitted to the Alcoholism Unit of Dongshu Hospital, Masan, Korea, who met DSM-IV criteria for alcohol dependence, with no other axis I or axis II diagnosis. They were chronic, multiply relapsed patients, but with an extended abstinent period of at least 3 months at that time of the study. Data on the alcohol history of patients are as follows. First psychiatric treatment for alcohol drinking, 17.73 ± 6.42 years ago; number of previous inpatient hospitalizations for alcohol detoxification, 3.73 ± 1.20; duration of recent admission, 3.82 ± 0.91 months. Alcohol subjects were clinically stable with no overt depressive nor anxiety symptoms. Mean scores for the Hamilton depression rating scale (HDRS) and the Hamilton anxiety rating scale (HADS) were 6.00 ± 1.38 and 4.23 ± 1.38, respectively. Controls were healthy volunteers with no history of a psychiatric disorder nor family history for a major psychiatric disorder in first-degree relatives. Subjects gave informed consent to the study, which was approved by the local ethics committee. No subject had taken any form of medication for more than 1 week prior to the study. Blood was collected at 0, 30, 60, 90, 120 and 150 min after oral administration of 30 mg buspirone hydrochloride at 09:00 hours. Serum concentrations of cortisol were determined by radioimmunoassay (RIA) using a commercial kit (DiaSorin). Inter- and intra-assay coefficient of variation were 4.1 and 2.6%, respectively. Two-tailed Student’s t-test, repeated measure analysis of covariance (ANCOVA) and ANOVA were used to analyse the data. An alpha level of 0.05 was considered to be statistically significant and all tests were two-tailed.

RESULTS

The mean age of alcoholic patients (44.10 ± 5.49 years) was significantly higher than that of the normal controls (39.93 ± 4.80 years) (t = 2.51; P = 0.01). Baseline cortisol levels were not significantly different between the two groups (8.61 ± 2.95 μg/l for patients; 10.00 ± 2.50 μg/l for controls). Cortisol levels in alcoholic patients compared to normal controls revealed a significant time effect (F = 8.95, P < 0.001); time × group (F = 3.59, F = 0.008) and time × baseline (F = 5.21, P = 0.006) on repeated measures ANCOVA, indicating the two groups had different response profiles. ANCOVA, controlling for baseline differences, showed that alcoholics had...
a significantly lower cortisol level than the normal controls from 60 through to 150 min (60 min: $F = 12.43$, $P = 0.001$; 90 min: $F = 9.00$, $P = 0.005$; 120 min: $F = 4.52$, $P = 0.041$; 150 min: $F = 4.48$, $P = 0.042$) (Fig. 1). ANCOVA, controlling for age differences, showed cortisol levels were not significantly different between groups.

**DISCUSSION**

The major finding of this present study is that cortisol response to buspirone was significantly decreased in extended alcoholic patients compared to normal controls, reflecting decreased 5-HT$_{1A}$ receptor sensitivity. Little is known about the role of 5-HT$_{1A}$ receptors in alcoholic patients. Recently Pinto et al. (2002) reported decreased cortisol response to flesinoxan, a 5-HT$_{1A}$ agonist, in alcoholic with abstinence of more than 3 weeks, suggesting a decreased sensitivity of post synaptic 5-HT$_{1A}$ receptor. Our finding is consistent with their results. Serotonin dysfunction can be different depending on the stage of alcoholism. For example, the withdrawal from chronic alcohol intake induced the supersensitivity of 5-HT$_{1A}$ receptors in animal studies (Esteban et al., 2002), whereas recently detoxified patients showed blunted cortisol responses to m-chlorophenylpiperazine. In comparison with those studies, the subjects of our study were abstinent more than 3 months at that time of study. Thus, our results suggest that the decreased 5-HT$_{1A}$ receptor sensitivity is a persistent finding after abstinence from alcohol in some alcoholic patients.

Little is known about serotonin dysfunction in regards to relapse of alcoholic patients. It has been reported that high concentrations of the 5-HT metabolite, 5-hydroxyindoleacetic acid, in cerebrospinal fluid was related to relapse (George et al., 1999) but this finding has not been replicated. Thus far, several serotonergic drugs have been tried in alcoholic patients, of which none have shown specific effectiveness in relapse prevention of alcohol dependents. We suggest the possibility that decreased 5-HT$_{1A}$ receptor sensitivity could be a predictive factor for poor clinical outcome, as the patients in our study were chronic patients with a history of multiple relapse who had abstained from alcohol for more than 3 months. To test this, however, comparison of alcoholic patients with persistently decreased 5-HT1A sensitivity with a sample of alcoholics with normalized 5-HT1A receptor sensitivity after the cessation of alcohol would need to be performed.

Our results should be interpreted with caution because of several limitations of our study. First, the effect of buspirone on the cortisol response may not directly reflect 5-HT$_{1A}$ receptor sensitivity. Second, we cannot exclude the possibility that blunted cortisol response to buspirone is due to hyporeactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Although many studies have reported that the chronic alcohol assumption can lead to disturbance of HPA axis and hormonal stress response (Nolan et al., 1991; Lee and Rivier, 1995; Ehrenreich et al., 1997), it is not a consistent finding. For example, Umhau et al. (2001) reported that long-term abstinent alcoholics did not have an exaggerated corticotrophin and cortisol response after 2-deoxy-d-glucose (2-DG) compared to normal controls. Adinoff et al. (1990) reported that corticotrophin response to Corticotropin releasing hormone (CRH) was significantly attenuated in the alcoholics within 3 weeks of abstinence, compared with controls; however, it was not significantly different after 3 weeks of abstinence. Moreover, in our study the baseline level of cortisol, which can be used as an index of the activity of the HPA-axis, was not significantly different between two groups. Thus we suggest our results may reflect the 5-HT$_{1A}$ dysfunction in the extended abstinent alcoholics. Third, our study was not a placebo-controlled neuroendocrine challenge. Fourth, serotonergic function in patients could be different according to their clinical characteristics, such as subtypes of alcoholism and comorbid psychopathology. In our study, we excluded any subjects with comorbid anxiety and depression or any other Axis I disorders, but not necessarily other symptoms such as aggression, and did not analyse separately cortisol response according to subtype of alcoholic. Also all subjects were male and fairly young, limiting the generalizability of our result. Also, the mean age of the alcoholic patients was higher than that of the controls, although age effect on cortisol response to buspirone was not found in our study, and it is not clearly determined yet whether the age influences cortisol response to buspirone.

Further work is needed to understand whether or not 5-HT$_{1A}$ receptor sensitivity changes are related to relapse in alcoholic patients. However, our results provide useful information and aid understanding of the role of the 5-HT$_{1A}$ receptor in the pathophysiology and clinical outcome of alcoholism.

**Acknowledgements** — This study is supported by a program grant to Y.-H.K. and J.-C.S. from the Department of Psychiatry, Inje University, Korea and an Intervention Research Center Grant (MH-40279). We thank Jeong-Ik Kim, Seong-Hwan Yoon and Tae-Min Kang for referring patients to our study. We also thank Yang Yu for assistance with data analysis.

**REFERENCES**


