Plasma Cocaine Metabolite and Liver CYP450 3A4 Isoenzyme Levels as Indicators of Cocaine Dependence in Rats Treated with Nutritional Supplements

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ABSTRACT

The effects that chronic cocaine administration (CCA) have on craving, cocaine metabolite concentrations and cytochrome P450 3A4 isoenzyme (CYP450 3A4) activities in Sprague-Dawley rats following the administration of Salako Nutritional Supplements (SNS) were examined. Five groups of fifty rats were used to assess the effect of the SNS following CCA. Craving was analyzed for each rat using a Conditioned Place Preference protocol. Blood samples were obtained at regular intervals and used to measure cocaine plasma metabolite levels. CYP450 3A4 activity was determined in the liver. Administration of the SNS reduced craving of cocaine significantly, upon discontinuing cocaine in the rats. Blood plasma analysis showing higher benzoylecgonine equilibrium and the CYP450 3A4 levels demonstrated that the SNS possibly aided in the removal of the stored metabolites indicative of increased metabolism of cocaine, enhanced by the Supplements. Results indicate that the SNS formulation reduces craving caused by CCA by increasing the liver CYP450 3A4 activity, resulting in better plasma clearance.

Keywords: Cocaine Metabolite, Conditioned Place Preference, Drug Abuse Liver CYP450 3A4 Isoenzyme, Nutritional Supplement Formulation, Plasma, Rats

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INTRODUCTION

Cocaine (C₁₇H₂₁NO₄), classified as a stimulant, is described as being the most potent, powerfully addictive stimulant of natural origin. It is an alkaloid that is extracted from the leaves of the Coca plant (*Erythroxylum coca*), which originates in South America, and to a lesser extent, in Africa, Indonesia and India (UNODC, 2010). Cocaine is one of the oldest known psychoactive substances. Coca use has been traced as far back as around 5000 B.C. wherein the leaves of the plant were continually chewed in the mouth. Pure cocaine was isolated in the 1880’s (National Institute on Drug Abuse, 2008). In the early 1900s, pure cocaine was the main active ingredient in numerous pharmaceutical and recreational formulations due to their properties that enhanced general activity and decreased fatigue.

Cocaine use varies widely with drug users. The duration of the euphoric effects produced by cocaine is dependent on the route of administration. The faster the absorption of cocaine, the more rapid and intense the high produced, but the shorter the duration of action. Toxic amounts of cocaine can be absorbed by any route of administration, which can have a wide range of effects which can include sudden death.

Metabolism of Cocaine

Cocaine is rapidly absorbed in the blood following the snorting, smoking and intravenous administration. Cocaine is metabolized by several enzymatic and non-enzymatic pathways (Heard et al., 2008) rapidly and extensively in animals to yield benzoylecgonine and ecgonine as the principal products, along with other metabolites, particularly ecgonine methyl ester, which are all generally inactive. Norcocaine is a minor metabolite that is formed, but is active and found to be neurotoxic. Cocaine is converted to norcocaine via the cytochrome P450 3A4 isoenzyme by means of N-demethylation. Norcocaine has shown to be equal in potency to cocaine (Hawks et al., 1974; Misra et al., 1975). The pharmacology of cocaine is complex, which exhibits simultaneous effects in several organ systems in the body including the brain, cardiovascular, immune and hematological systems (Espinoza, 2012; Heard et al., 2008 and Levine et al., 1990). Cocaine has been shown to be extremely hepatotoxic (Boyer & Peterson, 2005; Kanel et al., 1989; Pasanen et al., 1995) and also results in fatty infiltration responsible for increases in lipid content of the liver (Affi et al., 1998; MachLachlan & Hodge, 1938). Developing an effective, safe and cost-effective means of treating substance abuse is of paramount importance in society.

Chronic use of cocaine results in the metabolite being present in the urine for a prolonged period following introduction of a large amount into the body. There is still a paucity of information which exists regarding the effects that cocaine has on the body as a complete system, including the toxicity that exists during chronic usage and the general basic mode of action following varying modes of administration.

Conditioned Place Preference

Conditioned place preference is one popular method of an animal model of drug dependence. The apparatus used to carry out the experiment is called a conditioned place preference box, which consists of two chambers separated by a neutral chamber. One chamber differs from the other by tactile clues such as colour and light intensity. Using a biased procedure, the non-preferred compartment is paired with the drug and the CPP is a measurement of overcoming the initial aversion for that compartment (Sanchis-Segura and Spanagel, 2006). In adult rats, place preference for cocaine is effectively established for cocaine at a dosage of 20 mg/kg (Bardo et al. 1986; and Brenhouse and Andersen, 2008).
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