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BRAIN RESEARCH

Research Report

Angiotensin II and CRF receptors in the central nucleus of the amygdala mediate hemodynamic response variability to cocaine in conscious rats

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ABSTRACT

Stress or cocaine evokes either a large increase in systemic vascular resistance (SVR) or a smaller increase in SVR accompanied by an increase in cardiac output (designated vascular and mixed responders, respectively) in Sprague–Dawley rats. We hypothesized that the central nucleus of the amygdala (CeA) mediates this variability. Conscious, freely-moving rats, instrumented for measurement of arterial pressure and cardiac output and for drug delivery into the CeA, were given cocaine (5 mg/kg, iv, 4–6 times) and characterized as vascular ($n=15$) or mixed responders ($n=10$). Subsequently, we administered cocaine after bilateral microinjections (100 nl) of saline or selective agents in the CeA. Muscimol (80 pmol), a $GABA_A$ agonist, or losartan (43.4 pmol), an AT_1 receptor antagonist, attenuated the cocaine-induced increase in SVR in vascular responders, selectively, such that vascular responders were no longer different from mixed responders. The corticotropin releasing factor (CRF) antagonist, α-helical $CRF_{9–41}$ (15.7 pmol), abolished the difference between cardiac output and SVR in mixed and vascular responders. We conclude that greater increases in SVR observed in vascular responders are dependent on AT_1 receptor activation and, to a lesser extent on CRF receptors. Therefore, AT_1 and CRF receptors in the CeA contribute to hemodynamic response variability to intravenous cocaine.

1. Introduction

The central nucleus of the amygdala (CeA) plays a critical role in integrating sympathetic and behavioral responses to stress (Bohus et al., 1996; Davis, 2000; Gray, 1993; Saha, 2005). Stimulation of the CeA produces increases in blood pressure and heart rate (Hilton and Zbrożyna, 1963; Iwata et al., 1987; Schlör et al., 1984; Stock et al., 1978). Conversely, ablation of the CeA attenuates the increase in blood pressure and heart rate to conditioned stress in rats (Iwata et al., 1987; Sananes and Campbell, 1989). The CeA is necessary for learning increased alertness to conditioned fear (Davis, 2000). There are extensive and often reciprocal projections between the CeA and nuclei in the hypothalamus and medulla that regulate autonomic and cardiac functions (Gray et al., 1989; Jhamandas et al., 1996; Pitkänen, 2000; Veening et al., 1984; Volz et al., 1990). These observations underscore the importance of the CeA in modulating the hemodynamic and behavioral responses to stress.

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Abbreviations: SVR, systemic vascular resistance; CeA, central nucleus of the amygdale; Ang, angiotensin II

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Several neurotransmitters and receptors have been localized in the CeA. The CeA contains GABA receptors (Marowsky et al., 2004) that have been shown to inhibit hemodynamic and behavioral responses to stress (Saha, 2005). The CeA also contains angiotensin II (Ang), angiotensin converting enzyme and angiotensin receptors (Brownfield et al., 1982; von Bohlen und Halbach and Albrecht, 1998). In addition, CRF-like immunoreactivity exists in the CeA (Sakanaka et al., 1986; Uryu et al., 1992). Microinjection of Ang in the CeA elicits a pressor response, whereas CRF evokes both an increase in