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Review

Cocaine and mitochondria-related signaling in the brain: A mechanistic view and future directions

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ABSTRACT

Cocaine is extensively used as a psychostimulant among subjects at different ages worldwide. Cocaine causes neuronal dysfunction and, consequently, negatively affects human behavior and decreases life quality severely. Cocaine acts through diverse mechanisms, including mitochondrial impairment and activation of cell signaling pathways associated to stress response. There is some controversy regarding the effect of cocaine in inducing cell death through apoptosis in different experimental models. The aim of the present work is to discuss data associated to the mitochondrial consequences of cocaine exposure of mammalian cells in several experimental models from *in vitro* to *in vivo*, including *postmortem* human tissue analyses. Furthermore, future directions are proposed in order to serve as a suggestive guide in relation to the next steps towards the complete elucidation of the mechanisms of toxicity elicited by cocaine upon mitochondria of neuronal cells.

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1. Introduction

Cocaine ($C_{17}H_{21}NO_4$, MW 303.35294 g/mol), an alkaloid ester, is a psychostimulant extracted from coca (*Erythroxylum coca*) widely utilized among humans at different ages (Roy et al., 2015). Cocaine activates the brain reward centers, which mediates, at least in part, the processes of addiction (Ritz et al., 1987; McCreary et al., 2015). Cocaine also suppresses dopamine uptake through interacting with the dopamine transporter and causing its inhibition (Ritz et al., 1987). Thus, cocaine is able to maintain the extracellular levels of dopamine higher than normal, leading to an enhancement in the dopamine-related signaling and hyperactivation of neurons responsive to dopamine. Moreover, cocaine stimulates heart rate, causing an augment in the blood pressure (Costa et al., 2013a,b). Either powder or solid crystal (the so called "crack", which may be smoked and is more potent than cocaine) forms of cocaine are consumed by users (Dinis-Oliveira et al., 2012; Dinis-Oliveira, 2015). Plasma levels of cocaine vary from 1 to 91 ng/mL (after intranasal use), from 9 to 348 ng/mL (after intravenous use), and from 2 to 306 ng/mL (after smoke cocaine) depending on the individual and time of exposure (Cone, 1995). Psychiatric disturbances among cocaine users include depression (leading to increase suicide ideation), anxiety, and paranoia (Nazıroglu and Demirdas, 2015; Roy et al., 2015). Cocaine causes neuronal damage through diverse mechanisms, including mitochondrial dysfunction. Actually, cocaine interacts with mitochondria and enters the organelle by a still unknown mechanism, since research involving the evaluation of specific targets of cocaine in mitochondria is still being performed (Heard et al., 2008). Additionally, it remains to be determined how much cocaine enters mitochondria impairing their activity. Hence, further research is necessary in order to examine the exact way by which cocaine impairs mammalian mitochondria and the specific consequences that may rise from such interaction, as alterations in signaling pathways that are associated to mitochondrial (dys)function.

Mitochondria are responsible for the maintenance of energetic status of mammalian cells by producing ATP as a result of the mitochondrial electron transfer chain (METC, complex I – complex IV) and complex V (ATP synthase) reactions (Melser et al., 2015; Mailloux, 2015). METC is a physiological major source of cellular reactive oxygen species (ROS) due to electron leakage and partial reduction of some of the components of that intricate system, as ubiquinone, for example (Scheibye-Knudsen et al., 2015). Moreover, mitochondria are a central piece during the intrinsic apoptotic pathway (an active process that serves as a organized cell death route) releasing pro-apoptotic factors, as for instance cytochrome c and Smac/DIABLO, to the cytosol, consequently activating the apoptotic machinery known as apoptosome (Galluzzi et al., 2014). After activation of caspases (cysteine-aspartate proteases), several components of the dying cell are cleaved, leading to the formation of the apoptotic bodies and posterior consumption of the cell parts by other members of the tissue where apoptosis occurred, as phagocytic cells and even cells at the neighborhood (Green et al., 2014). On the other hand, excessive damage to mitochondria, release of cytochrome c in an oxidized form (that does not activate the apoptosome, Pan et al., 1999; Brown and Borutaite, 2008), bioenergetics disturbances (reduced ATP production), and excessive production of free radicals and ROS production, culminating in cell death through necrosis, a passive process by which cells release its cytosolic contents in the environment causing damage to neighborhood cells and tissue inflammation (Karch and Molkentin, 2015; Orrenius et al., 2015). Loss of mitochondrial membrane potential (MMP) is also observed during apoptosis and necrosis (Green et al., 2014). Moreover, mitochondria may release apoptosis-inducing factor (AIF), which may induce apoptosis without activating the apoptosome (Green et al., 2014). Therefore, mitochondrial physiology during intoxication with certain toxicants is very likely to cause cell death by, at least in part, two generally distinct routes. However, there are other forms of cell death that differ from apoptosis and necrosis by the cellular and molecular apparatus involved in its orchestration, as necroptosis (Galluzzi and Kroemer, 2008; de Almagro and Vucic, 2015) and oncosis (Weerasinghe and Buja, 2012).

The aim of the present work is to discuss data obtained from cultured mammalian cells and experimental animals, as well as human brain samples obtained from cocaine-abusing subjects regarding the effects on mitochondria and signaling pathways associated to the organelle (Fig. 1).

2. The *in vitro* effects of cocaine upon neuronal and glial mitochondria

Cocaine concentrations tested by different researchers *in vitro* are very similar to cocaine plasma concentrations observed in human drug abusers (ranging from 0.3 μM–1 mM, Yuan and Acosta, 2000). Moreover, some cocaine metabolites (as for instance, ecgonine, methylecgonine, and benzoylecgonine) did not affect viability of neuronal cells, as previously reported (Nassogne et al., 1998). Therefore, the effects discussed here are very dependent on cocaine *per se*, and not a result from the exposure to its metabolites. Data discussed here are organized according to the *in vitro* experimental model tested involving either isolated mitochondria or cultured cells.

2.1. Isolated mitochondria

Cunha-Oliveira et al. (2013) described that cocaine (1 mM for 1 min) impaired respiration in mitochondria isolated from rat brain. Cocaine caused direct inhibition of complex I without affecting complex II activity. The exact interaction site between cocaine and complex I was not studied by the authors in that work. Moreover, cocaine concentration utilized is considered high, but may be found in the plasma of cocaine abusers, as mentioned above. Nonetheless, to perform a dose–response curve using mitochondria isolated from experimental animal brain would help understanding the mitochondrial behavior during exposure to cocaine. Additionally, it is necessary to identify the exact subunit (s) to which cocaine binds causing inhibition of complex I activity. Also, it is necessary to examine whether and how cocaine metabolites (such as norcocaine, norcocaine nitroxide, and N-hydroxynorcocaine, among others) interact with brain mitochondria, since it was demonstrated that these metabolites impaired function of mitochondria isolated from mouse liver (Boess et al., 2000).

2.2. PC12 cells

Oliveira et al. (2002) studied the effects of certain stimulant drugs of abuse on undifferentiated PC12 cells (which have been frequently utilized as a model for dopaminergic neurons, since produces dopamine and is also a target of such neurotransmitter due to the expression of dopamine receptors (Pothos et al., 1996; Presse et al., 1997)) and found that cocaine (500 μM–3 mM for 4 days) decreased cell viability without altering membrane integrity (as assessed through the quantification of LDH release). Cocaine did not change the ATP/ADP ratio (an index of general metabolic/bioenergetics, mainly mitochondrial function) in PC12 cells. Cocaine did not elicit DNA fragmentation in that experimental model. Dopamine levels decreased in PC12 cells exposed to cocaine. Authors did not find any change regarding ROS production in those cells. In this context, Cunha-Oliveira et al. (2006a) found that