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Review Article

Why Functional Non-Invasive Near-Infrared Spectroscopy Coupled with ^{31}P-Nuclear Magnetic Resonance Spectroscopy should be used to Predict, Diagnose and Manage Substance Abuse-Induced Strokes and Deaths: A Personal Perspective

Burton M Altura[1-7]*, Asefa Gebrewold[1], Anthony Carella[1] and Bella T Altura[1,3-7]

[1]*Department of Physiology & Pharmacology, SUNY Downstate Medical Center, New York, USA*

[2]*Department of Medicine, SUNY Downstate Medical Center, New York, USA*

[3]*The Center for Cardiovascular and Muscle Research,SUNY Downstate Medical Center, New York, USA*

[4]*The School for Graduate Studies in Molecular and Cellular Science, The State University of New York Downstate Medical Center, Brooklyn, New York, USA*

[5]*Bio-Defense Systems, Inc, Rockville Centre, New York, USA*

[6]*Orient Biomedica, Estero, Florida, USA*

[7]*Magnesium for Health Foundation, Patterson, California, USA*

Abstract

For more than 40 years, it has been known that substances of abuse (i.e., alcohol, psychedelics, cocaine, amphetamines heroin, etc.) can induce brain-vascular damage, inflammatory responses in the brain, and strokes in several different areas of the human brain. However, it has been difficult to precisely investigate the mechanisms of action or the precise developmental changes occurring with chronic abuse. We have found that a combination of Near-Infrared Spectroscopy (NIRS) and ^{31}P-Nuclear Magnetic Resonance Spectroscopy (^{31}P-NMRS) has allowed us to gain considerable , precise knowledge about the biochemical, physiological and metabolic actions of numerous substances of abuse, enabling us to demonstrate , at discrete brain micro-areas of the brain, quantitative changes in reducedvs. oxygenated hemoglobin, mitochondrial alterations in reduced vs. oxygenated cytochrome oxidase aa3 , intracellular pH, ATP, ADP, PCr, free inorganic phosphorous , blood flows, and intracellular free Mg. This technology, as reviewed herein, has allowed us, at least in experimental animals, to gain considerable insights into what biochemical, biophysical, physiological and metabolic alterations probably are responsible for substance abuse-induced brain damage, blackouts, functional neuronal deficits, and strokes. We believe these emerging technologies can be utilized, clinically, to predict impending doom, cell death and strokes and should be used in major hospitals-trauma centers to better diagnose, manage and prevent strokes.

***Corresponding authors:** Burton M Altura, SUNY Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, New York, USA,Tel: +1 7182702194; E-mail: burton.altura@downstate.edu

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Introduction

For close to 50 years, our laboratories have been interested in how various substances of abuse induce brain damage, strokes and death [1-74]. The biggest problem we have faced in this area is, how to detect substance abuse-induced vascular and functional changes in the brain, at discrete, localized areas of the brain, without opening the cranium? Clinical and experimental studies have now, unequivocally, established that ingestion, intravenously-administered, or sometimes snorting cocaine, amphetamines, heroin, morphine-derivatives, fentanyl, or psychedelic drugs (i.e., LSD, phencyclidine and derivatives, mescaline, psilocybin, etc.) can produce a variety of dangerous effects in different areas of the brain, including profound vascular damage, inflammatory responses, hallucinations, euphoria, reductions in blood flows, diverse forms of programmed cell death, and strokes [4,10,14-16,18,20,22,27,30,33-35,39,40,48,59,61,64,65,75-89]. These actions include atrophy of cortical, subcortical, and prefrontal cortical, hippocampal, medullary and cerebral areas of the brain associated with headaches, blackouts, functional neuronal deficits and psychoses which could lead to dementias. Clinically, it is known that all substances of abuse can lead to strokes and/or sudden-death.

Direct In-situ Microvascular Observations and *In-vitro* Studies on Isolated Blood Vessels Using Diverse Substances of Abuse

Previous studies from our laboratories, using image-splitting in-vivo television microscopy, at very high magnifications (up to 6,500 x normal) , on opened craniums in anesthetized mammals (e.g., rats, mice, guinea-pigs, rabbits and monkeys), have shown that alcohol, cocaine, cocaine derivatives, amphetamines, heroin, heroin derivatives, fentanyl combinations, and a variety of psychedelic drugs produced graded concentration-dependent spasms of cerebral and

medullary arterioles, small arteries, and venules in the intact brains causing rupture of venular postcapillaries (microvessels<60um in diameter) [2,8,10,14,16,18,20,22,26,28,30,40,53,61,64,70,71,unpublished findings]. Our laboratories were the first to demonstrate that most substances of abuse can induce intense contractions of isolated cerebral and basilar arteries from rats, mice, rabbits, guinea-pigs, monkeys, sheep, and baboons viadirect actions on the vascular smooth muscle cells as well as on isolated human umbilical-placental blood arteries and veins [4,11,15,19,34,35,66,72, unpublished findings]. Further investigations by our group revealed the probable mechanisms whereby most substances of abuse cause the intense vasospasms and rupture of postcapillary microvessels [4,12,15,32,33,35,36,38,39,40,44,48,51,52,61,66,68,71-74, unpublished findings].

Limitations of Current Structural and Functional Imaging Methods for Studying Brain-Vascular Actions of Drugs of Abuse in Unopened Craniums

Since the mid-1970's, it has been known that substances of abuse can cause serious brain -vascular damage and strokes, both hemorrhagic and ischemic [see 75-89, for reviews]. However, up until recently, it has been difficult to gain specific information on exact target sites and mechanisms of action in the living, unopened human brain.

Obviously, we cannot follow either the brain-vascular or metabolic actions after ingestion, intravenous injections, or snorting substances of abuse by opening craniums. In view of this dilemma, non-invasive methods for studying unopened brains, in-situ, had to be devised. As of this writing, the available techniques used for diagnostic brain imaging can be classified into structural and functional methods. Structural imaging of the brain is utilized to acquire anatomical information (e.g., X-ray Computed Tomography [CT], Magnetic Resonance Imaging [MRI], and ultrasound imaging) while the goal of functional imaging of the brain is to acquire information on the physiological state of cerebral and other brain areas (e.g., blood flows, oxygen consumption, metabolic activities, neuronal activities, etc.). These latter methods include functional MRIs (fMFRIs), Electroencephalography (EEG), Magneto Encephalography (MEG), Positron Emission Tomography (PET), and Single Photon Emission Computed Tomography (SPECT).

Use of Near-Infrared Spectroscopy

Near-Infrared Spectroscopy (NIRS) was designed to measure concentration changes in hemoglobin (oxygenated vs. deoxygenated) and mitochondrial cytochromes in the brain (e.g., cytochrome oxidase aa_3), noninvasively [90]. NIRS, although primarily utilized to assess brain tissue oxygenation, has also demonstrated considerable potential for neuroimaging (e.g., functional NIRS) [91,92]. Approximately 20 years ago, Villinger and Chance used noninvasive approaches employing near-infrared light to interrogate the human cortex through the intact scalp and skull [93]. It is now thus, possible, as we have found in lab animals to utilize visible light to illuminate discrete areas of the intact brain to measure, mitochondrial levels of cytochrome oxidase aa_3 (reduced vs. oxidized), tissue oxygenation, and reduced vs. oxygenated hemoglobin concentrations before and after administration of drugs of abuse [17,40,48,69,94, unpublished data]. By combining these NIRS measurements with high-resolution ^{31}P-nuclear magnetic resonance spectroscopy (^{31}P-NMRS), we have been able to probe discrete areas of the unopened brain for intracellular levels of pH, ATP, ADP, phosphocreatine (PCr),inorganic phosphate, and metabolic controlling cations such as magnesium (Mg^{2+}), thus allowing us to get a pretty- good, quantitative picture of discrete localized cerebral, cortical, medullary, and frontal brain blood flows, tissue oxygenation and cellular energy metabolism [30,32,33,40,42,46,48,54,59,60,94]. In addition, our quantitative brain measurements allow us to predict whether discrete cellular areas are on the verge of dysfunction and cellular death by the intracellular level of inorganic phosphate; the higher the intracellular level of free inorganic phosphate, the greater the chance of irreversible cell death [33].

Tissue sections of brains of rats, and primary cultured cerebral vascular muscle cells, administered stroke-doses of either alcohol, cocaine, amphetamines, or heroin-fentanyl combinations indicated at least four different forms of programmed cell death on cerebral vascular smooth muscle cells, viz., apoptosis, necroptosis, pyroptosis, and ferroptosis, similar to what we have seen on coronary arteries and cardiac muscle cells excised from animals fed Mg-deficient diets [73,74,95-97]. Whether any of these forms of programmed forms of cell death are found on cerebral vascular smooth muscle cells in human brains impacted with substances of abuse remains to be investigated.

Proof of Principle with NIRS and ^{31}P-NMR Spectroscopy with Substances of Abuse in Live Experimental Animals

For almost the past 30 years, our laboratories have utilized NIRS and ^{31}P-NMRS to evaluate whether a combination of these technologies could yield quantitative information on the vascular and metabolic states of the effects of diverse substances of abuse in discrete, localized areas in brains of lightly -anesthetized rodents. So far, our experiments have shown that administration of cocaine, cocaine derivatives, amphetamines (including methamphetamines), alcohols (including methanol), heroin, heroin-derivatives, fentanyl-mixtures, marijuana-cannabis products, and psychedelic drugs (including LSD, PCP, mescaline, peyote, and psilocybin) suppress the firing of pyramidal cells in freely -moving animals, and increase levels of deoxyhemoglobin and reduced cytochrome oxidase aa_3 in discrete areas of the brain (i.e., frontal cortex, cerebral hemispheres, and medulla) in aconcentration-dependent manner; the greater the doses of the substances of abuse, the greater the degrees of localized ischemia [10, 14,16,17,18,19,20,26,28,30,32,33,37,40,42,45,54,59,60,62,69,94,unpublished observations]. Application of ^{31}P-NMRS technology, utilizing specialized holders for the anesthetized animals concomitant with a magnet of 9.4 tesla strength, one of the strongest magnets available, allowed us to show that administration of the diverse substances of abuse caused profound reductions in intracellular pH, ATP, ADP, phosphocreatine (PCr), and Mg^{2+} with concomitant rises in intracellular inorganic phosphate (P_i)levels; the higher the doses of the substances of abuse, the greater the lowering of intracellular ATP, ADP, PCr, Mg^{2+}, and pH while the P_i kept rising towards severe vascular damage followed by hemorrhagic strokes (observed on autopsies) and death [32,33,42,54,55,59,60,94]. Collectively, our intracellular P_i measurements on more than 350 animals leads us to believe that a fast- rising intracellular level of P_i may be a clear diagnostic and prognostic biomarker of impending strokes followed by death unless steps for intervention are rapidly taken.

Conclusion and Future Thoughts

It is now known that substances of abuse (viz.; alcohol, psychedelics, cocaine and derivatives, amphetamines and derivatives, morphine-derivatives, heroin and derivatives, fentanyl, and designer substances of abuse) can all induce brain-vascular damage, inflammatory responses, and strokes in different areas of the human brain. However, until now, it has been difficult to investigate the mechanism (s) of action in the living intact brain without opening the cranium.

Although various biophysical and brain-imaging techniques have been devised to get some semi-quantitative biochemical and metabolic information, the reliable data, for the most part, centers on mostly structural alterations. Over the past 30 years, in collaboration with several scientists, we have found that a combination of Near-Infrared Spectroscopy (NIRS) with ^{31}P-nuclear magnetic resonance spectroscopy (^{31}P-NMRS) has allowed us to gain a considerable amount of knowledge about the biochemical, physiological and metabolic actions of numerous substances of abuse, thus enabling us to:

1. Demonstrate, at discrete brain micro-areas, quantitative changes in reduced vs. oxygenated hemoglobin, mitochondrial alterations in reduced vs. oxygenated cytochrome aa_3, intracellular pH, ATP, ADP, PCr, free inorganic phosphorus (P_i), blood flows,and intracellular levels of free Mg^{2+}. This technology has allowed us, at least in experimental animals, to gain insights into what biochemical, biophysical, physiological, and metabolic alterations probably are responsible for substance abuse-induced brain damage, blackouts, functional neuronal deficits, and strokes
2. Predict impending doom, cell death, and strokes. In view of our experiments, so far, we believe a combination of NIRS and ^{31}P-NMRS should be used in hospitals to better determine the state of the human brain after ingestion, intravenous administration, or snorting a substance of abuse in order to be able to better diagnose, manage and treat patients

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