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Mini Review

Why There is an Increased Number of Deaths from Heroin Mixed with Fentanyl in the USA: Potential Roles of Unrecognized Hypomagnesemia and Elevated Levels of Ceramides and Platelet-Activating Factor Particularly in Brain Stem Area and Potential Relationship to Euphoria and Hallucinations

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Abstract

Currently, there is a widespread number of deaths, particularly in the USA, from ingestion/imbibing a combination of heroin and fentanyl. Young and old adults are becoming rapidly addicted to this drug combination. Many of these victims believe they are being sold heroin unaware that the latter is often "laced" with fentanyl. Until now, the mechanism(s) for inducing coma followed by death has been thought to be respiratory and cardiac failure. However, new evidence from human and experimental animal studies, reviewed herein, indicates a major underlying cause of euphoria, hallucinations, coma and death is a consequence of cerebrovascular actions in the cerebrum, medulla, and hippocampus which appears to be brought about by rapid, intracellular reduction in free magnesium ions coupled to elevation in cellular and blood levels of ceramides and platelet-activating factor.

Keywords: Hypomagnesemia; Brain; Euphoria; Hallucinations

Today, both fentanyl and heroin are major problems accounting for more than 65,000 deaths per year in the USA alone. This combination has resulted in what is now termed "the opioid epidemic in the USA". Young and old adults are becoming addicted rapidly to these drugs and are dying as a result of overdosing. Although fentanyl is prescribed by physicians legally for pain, and heroin is not, both drugs create senses of euphoria, hallucinations and strong well-being. The mechanisms for these mood alterations, however, remain up to considerable speculation. The mechanisms for inducing death in the addicted victims are attributed to respiratory and cardiac failure. However, the underlying molecular mechanisms remain unclear [1-4]. Both heroin and fentanyl unlike many other drugs of abuse are extremely fast-acting. The high lipid solubility of both opioids allow access to pass the blood-brain barrier and cell membranes very rapidly, hence why they are so dangerous.

Both fentanyl and heroin are becoming seen on "the streets" in increasing numbers and doses, often because repeated prescriptions for fentanyl are becoming more difficult to acquire and that the prices are becoming lower and lower. The porous Southern border of the USA is making it very easy for mounting illegal shipments of these extremely dangerous drugs to be sold at cheaper and cheaper prices from drug traffickers in North America, Mexico and China. Most of the raw heroin arrives from Afghanistan where it is cultivated by eight major drug cartels in Mexico; although most of the fentanyl is manufactured in China, it is mainly transited to the USA through Mexico [The Council on Foreign Relations].

Fentanyl is about 100 times stronger than heroin, but people are buying what they think is heroin only much later finding that it has been "laced" with fentanyl, thus producing a sense of extreme eu-

phoria often leading to aphasias, then coma. However, the addicted subjects find they require higher and higher doses of the combination, in order to get the extreme euphoric feelings, thus leading to a very high risk of coma followed by death. What exactly do these drugs do to brain hemodynamics and microvascular structures in key tissue sites within the brain?

Mood -altering drugs of abuse, cerebral vasospasms, stroke-like events and magnesium

Ever since two of us reported that LSD, psilocybin, mescaline, alcohol, cocaine, marijuana, amphetamines and related mood-altering drugs resulted in vasospasm and rupture of cerebral blood vessels, and stroke-like events in diverse mammals, including subhuman primates [5- 26], our laboratories have been interested in the cardiovascular and cerebrovascular actions of mood-altering drugs, and their molecular mechanisms of action, and why they result in strong feelings of euphoria, hallucinations, rapid addiction and, often, death.

Approximately 40 years ago, two of us found that lowering magnesium ion concentration in an artificial salt- solution, containing rabbit aortic smooth muscle, resulted in a continuing, increased vasospasm of the blood vessel muscle cells [27]. Using additional blood vessels, large and small in size and a variety of mammals, including monkeys, baboons and humans, we found that most all types of blood vessels, including cerebral and coronary arteries would go into intense vasospasms in solutions bathed in low ionized Mg levels (Mg^{2+}); the lower the Mg^{2+}, the greater the vasospasm [10,28-50,52,54,57]. Using in-situ, high magnification video microscopy, at magnifications up to 6,500x-normal, we noted similar results on intact microcirculatory blood vessels in intestinal, skeletal muscle, cutaneous, coronary, and cerebral microvasculatures in animals/tissues exposed to low Mg diets/perfusates [28,32,34,35,39,43,49,57]. Having these in-vitro and in-vivo studies, as a background, we began to wonder whether drugs of abuse (i.e., cocaine, alcohol, LSD, PCP, marijuana-cannabinoids, mescaline, amphetamines, designer mood-altering drugs) would result in vasospasm of cerebral blood vessels as a possible result of rapidly lowering cellular levels of Mg^{2+} and cause rupture of microvessels, thus resembling stroke-like events.

Using intact rats and 31Phosphorus- nuclear magnetic resonance spectroscopy (31P-NMR), digital image analysis, and near-infrared spectroscopy (NIRS), we have found that most drugs of abuse, so far investigated (cocaine, alcohol, LSD, mescaline, heroin, amphetamines, PCP, among others), cause rapid lowering of Mg^{2+} levels in most brain structures examined (i.e., cerebral hemispheres, cerebellum, hippocampus, and medulla oblongata) [17,19,20,22,24-26,61]. These changes in brain intracellular free Mg2+ are followed by loss of ATP and ADP with elevation of inorganic phosphorus and intracellular hydrogen ion concentration coupled to increased levels of deoxygenated hemoglobin and decreased levels of mitochondrial cytochrome oxidase., all leading to intense cerebral ischemia and brain death as the doses of the drugs were elevated [20,22,24-26,61,62]. A combination of heroin "laced" with fentanyl resulted in rapid biochemical, physiological and vascular changes in the rat brains probed with 31P-NMR and NIRS [62,65]. But, can these biochemical, physiological and vascular alterations help to explain the rapid euphoric and hallucinogenic responses seen in human subjects after ingestion of heroin in combination with fentanyl?

Euphoria and hallucinations with a combination of heroin plus fentanyl may be due to reversible constriction of cerebral blood vessels and formation of reactive oxygen and nitrogen species

Approximately three years ago, four of us suggested that alcohol-induced euphoria may be due to a reversible constriction of cerebral blood vessels, brought about by an unrecognized hypomagnesemia coupled to a release of ceramides and platelet-activating factor (PAF) [63]. Four decades before the latter, two of us, using high magnification TV microscopy on the in-situ brain microcirculation, at magnifications up to 6,500x normal, found that alcohol induced dose-dependent arterial and arteriolar vasospasms [64]. We suggested, like that seen in pilots in World War II, in non-pressurized cockpits, who experienced a euphoric sense of well-being when approaching 15,000 ft., drinking of alcohol and the taking of diverse drugs of abuse and psychoactive/designer- drugs can reversibly induce vasoconstriction of the cerebral, medullary and hippocampal blood vessels, thus resulting in oxygen- lack, temporary light-headedness and euphoria [63,64]. Our *in-vivo* ^{31}P-NMR and NIRS data, discussed above, indicating a lowered intracellular $Mg^{2+}$and pH, in concert with reduced.

ATP and ADP, and reduced oxyhemoglobin levels coupled to reduced mitochondrial cytochrome oxidase levels all would lend support to our hypothesis.

Breathing is controlled by the medulla oblongata which clearly, in our experiments, demonstrate severe vasoconstriction under direct injection of heroin plus fentanyl [65]. Cutting off the blood supply to the neurons, glial cells, dendritic cells, etc., that regulate breathing may produce euphoria at very low concentrations of a heroin-fentanyl combined assault, inducing even hallucinations

as has been seen in people at high levels of these drugs of abuse. What, however, is the exact molecular mechanism (s) that induces euphoria and hallucinations?

Approximately 25 years ago, our research group reported that low extracellular Mg^{2+} resulted in formation of reactive oxygen species (ROS) (i.e., hydrogen peroxide, hydroxyl ions) and reactive nitrogen species (RNS) (i.e., 4-hydroxy-2-nonenal) in vascular smooth muscle cells, glial cells, and hippocampal cells [for recent review, see 57]. Recently, we reported that low levels of $[Mg^{2+}]0$ resulted in formation of malondialdehyde in isolated cerebral vascular muscle and glial cells [58,59] as well as in cardiovascular tissues excised from rats exposed to low dietary intake of Mg for 21 days [60]. Interestingly, all of these ROS and RNS have been reported to produce powerful contractions of arterial and arteriolar blood vessels both *in-vivo* and *in-vitro* [57,66]. Our laboratories have extended these observations to where we have found many of the signaling mechanisms [67-75]. Moreover, in preliminary experiments, we have found that heroin-fentanyl, when given to rats, over a period of days, produce similar arrays of these oxidative ROS and RNS in brain tissues [unpublished findings]. Clearly, these studies collectively indicate that either low levels of Mg or a heroin-fentanyl combination result in oxidative stress, vasospasm and signs of impending doom.

Low $[Mg^{2+}]_0$ or heroin plus fentanyl result in similar forms of programmed cell death, autophagic cell death and downregulation of telomerase

In this context, we recently found that the low levels of Mg produced three forms of programmed cell death, namely apoptosis, ferroptosis and necroptosis [60,74-79]. Not surprisingly, we have found that prolonged administration of heroin plus fentanyl (i.e., 21 days) also resulted in similar types of programmed cell death in cardiovascular and cerebral tissues [80].

Cell death is now known to be dependent on activation of autophagy [81], and telomere dysfunction specifically triggers autophagy [82]. We have recently found that Mg deficiency in rats downregulates telomerase in cardiovascular tissues and cells [82] which would tend to reduce the length of the telomeres and trigger senescence. When we injected rats every other day with a combination of heroin- fentanyl for 21 days, the same length of time we produced Mg deficiency in rats [60], cardiovascular and cerebral arterial smooth muscle cell autophagic proteins, ATG3 and ATG5, were found to be upregulated as they were found to be in the Mg deficient animals [83]. Pretreatment of rats with Mg markedly reduced the latter as well as apoptotic and necroptotic cell death markers and the ROS and RNS moieties [unpublished findings]. We believe our findings on programmed cell death and autophagic proteins, if found in humans imbibing heroin-fentanyl mixtures, may go a "long-way" towards indicating why cognitive and memory processes become severely impaired in the abusers of these very dangerous opiates.

Roles of Membrane Ca^{2+}, Mg^{2+} and Generation and Release of Ceramides and Platelet-Activating Factor in Reversible/Irreversible Vasospasm and Ischemia in Brain Structures: Importance of NF-kB and Proto-oncogenes

Using isolated canine and sub-human primate cerebral basilar and medullary arteries, as well as primary cultured canine and baboon cerebral vascular smooth muscle cells, our laboratories have reported that lowering extracellular Mg^{2+}, results in increases in membrane entry of Ca^{2+} as well as intracellular release of free Ca from the sarcoplasmic reticular elements, thus producing profound rises in total free intracellular Ca and cerebral vasospasm [27-54]. Loss of membrane-

bound Mg and intracellular free Mg, when the various drugs of abuse were placed in contact with the cerebral vascular smooth muscle cells, also resulted in cerebral vasospasms; the greater the concentrations of the drugs of abuse, the greater the losses in Mg^{2+} and the more developed force of the cerebral vasospasms [17,24-26,63].

Using proton-nuclear magnetic resonance spectroscopy (1H-NMRS), and isolated cerebral vascular smooth muscle cells, we found that low extracellular Mg^{2+} rapidly-induced increased cellular levels of both sphingolipids (i.e., ceramides, sphingosine, sphingosine-1-phosphate) and platelet-activating factor (PAF) [73,76,77,80]. Interestingly, we have demonstrated that both ceramides and PAF can induce vasospasms of both isolated and intact cerebral arterioles and arteries as well as muscular venules in the cerebral and brain medullary microvasculatures [81]. Moreover, microscopic examination of the in-situ postcapillary venules, at high magnification (e.g., 1,000 -3,500x normal with a TV microscope recording system), indicated that the venules showed rolling and adhesion of leukocytes, macrophages and monocytes to the endothelial walls, rupture of some postcapillaries with transudation of these blood- formed elements to the perivascular tissue spaces [81]. This, thus. represents a "true" inflammatory response followed by a hemorrhagic stroke. Preliminary in-vivo studies, using similar microscopic technology, indicates that a combination of fen-

tanyl-heroin appear to also produce almost identical reactions in the intact rat brain postcapillary venules in the cerebral and medullary microvasculatures [62,65]. If we utilized specific antagonists of ceramides or PAF, the ability of low extracellular Mg^{2+} to produce cerebral vasospasms and the latter postcapillary events was greatly attenuated [57,81]. However, neither naloxone (an opioid antagonist) nor gabapentin was able to reverse these inflammatory and stroke-like actions [unpublished findings].

It is our contention that the combination of heroin and fentanyl by reducing membrane-bound and intracellular free Mg, and increasing intracellular free Ca^{2+}, ROS and RNS thus cause cerebral vasospasms and rupture of postcapillary venules with synthesis and release of both ceramides and PAF. Using NIRS, on

Intact pial- and medullary-cerebral microvasculatures, showed that the resultant ischemic events produced increased levels of reduced mitochondrial cytochrome oxidase and increased levels of deoxygenated hemoglobin [62]. If our hypothesis is correct, then intravenous administration of $MgSO_4$ followed by orally-administered Mg compounds, along with antagonists of both ceramides and PAF, should be helpful in the prevention and amelioration of the brain -damage and strokes induced by a combination of heroin and fentanyl. It is our belief that a combination of use of 31P-NMRS and NIRS on the brains of victims who have succumbed to overdoses of fentanyl-heroin will be quite important in the diagnosis, management and treatment of subjects who have imbibed these very toxic drugs of abuse.

Conclusion

We believe the experimental and human studies performed by our research group are the first to provide compelling evidence for the causation and brain –damaging effects of fentanyl-heroin on the human brain. Our data also strongly provide new evidence that the combination of fentanyl-heroin can result in inflammatory responses, followed by severe stroke-like events resulting in transudation of macrophages, red blood cells, leukocytes, and monocytes into brain parenchymal tissues in the cerebral hemispheres, cerebellum and medulla oblongata. Furthermore, our studies demonstrate that a marked, rapid reduction in membrane Mg and intracellular free Mg^{2+} are triggers in setting into motion the brain -damaging and stroke-like events induced by a combination of fentanyl-heroin, leading to synthesis and release of ceramides and PAF, and formation of ROS as well as RNS which are, most likely, needed to sustain the brain -damaging and pathophysiological of this drug combination. It would, appear from our new results, that therapeutic use of a combination of intravenous $MgSO_4$, orally-administered Mg along with receptor blockers for PAF and antagonists of ceramides, should prove useful in ameliorating the brain-damaging, euphoric, and hallucinatory actions of fentanyl-heroin. Whether such a combination of medications could be useful in the treatment of addiction to fentanyl remains to be tested.

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