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The Role of Cerebral Hypercarbia in the Induction of the Near-Death Experience

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Cerebral Hypercarbia and the Near-Death Experience

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Abstract

The near-death experience (NDE) is an altered state of consciousness which arises when a person is critically ill or injured and possibly clinically dead. It should not be conflated with other mental events such as the deathbed vision or the fear or anticipation of death. Many believe that the NDE represents a genuine paranormal phenomenon providing a glimpse of an otherworldly existence and proof of an afterlife. Those who are skeptical of such a survivalist or supernatural interpretation have long pointed out that the core components of the NDE can be readily simulated with a variety of states, conditions and agents. In this conception, the NDE is reduced to no more or less than an extraordinarily complex hallucination. Since its rediscovery in the 1970s, multiple, often ingenious, attempts have been made to account for the NDE in such naturalistic or neuroscientific terms. None has so far proven completely satisfactory. One of the oldest, least considered but still promising is the CO_2 theory which argues that a hypercarbic brain is a necessary precursor for the induction of a NDE. Supportive evidence that CO_2 does play a pivotal role in the generation of the NDE can be gathered from diverse sources. These include: 1. measurement of blood gases; 2. Meduna's now abandoned CO_2 therapy; 3. analysis of the very limited number of pathophysiological conditions underlying the NDE; 4. recent discoveries of the role of 5-HT neurons in the central respiratory system. A model is proposed in which CO_2 molecules are considered to be functionally equivalent to those of the classical hallucinogens (LSD, mescaline, psilocybin, dimethyltryptamine). These agents can mimic the phenomenology of the NDE with remarkable fidelity. What is still missing from any such explanation is the long-sought transduction mechanism which converts physical events into mental ones. This is a generic problem which confronts all attempts to explain the neurogenesis of mystical, psychedelic or visionary activity.

Introduction

It has been known for eons that persons who survive a life-threatening medical crisis sometimes report that they underwent a vivid but weird mental journey or adventure during the period when they were unconscious [1, 2, 3, 4, 5, 6, 7, 8]. This unearthly phantasmagoria has been somewhat loosely described as being a near-death experience (NDE) and characteristically consists of well-defined cognitive, perceptual, affective and transcendental components or qualities which

may unfold in a generally orderly and predictable manner [9] although this feature may have been over emphasized [10].When knowledge of the NDE first became widely publicized following its rediscovery by psychiatrist Raymond Moody [8], there was a certain and understandable skepticism regarding its authenticity. Nonetheless, there is now virtual unanimity that it at least possesses a genuine subjective reality similar to that of a dream, vision or hallucination [11].

The actuality of the NDE reinforces the Cartesian notion that mind and body are quite separate entities. In other words, concepts such as consciousness, spirit, self, psyche or soul are not simply epiphenomena arising from the brain's neuronal activity but have a distinct existence as some kind of non-material essence [12, 13]. This is an idea which is still taken seriously even by Nobel laureates in neuroscience. For example, the late Sir John Eccles wrote that "We have to recognize that we are spiritual beings with souls existing in a spiritual world as well as material beings with bodies and brains existing in a material world" [14].

What intrigues investigators of the paranormal and tantalizes the popular imagination is that if the NDE also embodies a kind of objective reality, it may therefore provide a unique type of empirical evidence in favor of the belief that some form or part of our being or personality is able to survive bodily death and the loss of brain function [15, 16, 17, 18, 19, 20, 21, 22]. Further, the graphic imagery and nature of the core components of the NDE are thought to provide a glimpse of the initial stages of such a post-mortem existence. Thus, the eerie odyssey of the NDE is literally an otherworldly trip into the realm of death itself [29].

Those who remain wary about such a metaphysical, supernatural, survivalist or spiritual interpretation have long pointed out that it is not necessary for a person to be near fatally ill in order to experience some or all of the elements of the NDE [1, 5, 22, 23, 24, 25, 26, 27, 28]. Most of the basic phenomenology of the NDE can occur naturally or spontaneously during different states of consciousness, be induced artificially with a variety of psychoactive drugs and other chemical agents or arise as a consequence of a neuropsychiatric disorder.

If a NDE-type of experience is not ineluctably or specifically associated with being physically on the brink of death, then this would undermine the appeal of a paranormal explanation and, conversely, lend support to a simpler materialistic or reductionist account. Nonetheless, the difficulty with a naturalistic model has always remained how being on the brink of biological death and sometimes clinically dead (absent heartbeat, respiration and other vital signs) can give rise to such an ecstatic vision. Under such circumstances, the cerebral circuits needed to activate such a complex internally-generated experience might not be expected to be preserved or at least remain operational.

Despite many, often ingenious, attempts over the past half century, so far no completely satisfactory, cohesive and unified materialistic explanation of the NDE has yet emerged. Those who are unsympathetic towards a naturalistic paradigm sometimes argue that this failure represents *de facto* evidence in support of a transcendental status for the NDE beyond the scope of orthodox scientific understanding. It therefore nurtures the belief that the experience has authentic eschatological and spiritual significance [18, 30, 31, 32]. As Shermer [216] has pointed out, specifically in the context of the NDE, this is a fallacious argument but it is nonetheless persuasive and many commentators and investigators of the NDE seem to at least tacitly adhere to it [33]. In fact, Fischer and Mitchell-Yellin devote much of their book to demonstrating the superiority of a natural explanation of the NDE over a deceptively and superficially simpler supernatural one.

During the last half century, at least 20 so-called physicalistic theories have been proposed to account

for the NDE in scientific terms. Examples include hypoxia or anoxia theories such as Blackmore [35] and Woerlee [195], endorphin theories such as Thomas [196] and Carr and Prendergast [197], serotonin theories such as Morse et al. [198], multi-faceted neurobiological theories such as Saavedra-Aguilar and Gomez-Jeria [199], endogenous psychedelic theories such as Jansen [37], Strassman [139] and Jourdan [200], memories of birth experience such as Grof and Halifax [192] and Sagan [201], REM sleep- intrusion theories such as Nelson et al [204], gamma oscillation and electrical surge theories such as Borjigin et al. [202] and Chawla et al. [203], and a Reissner's fiber theory [205]. There are also more generic explanations involving, for example, autoscopy, temporal lobe dysfunction and pharmacology [30, 34, 35, 36, 37]. Notwithstanding all of these, it is ironic that one of the oldest and most enduring hypotheses is also among the least considered. This is the hypercarbia or hypercapnia theory which argues that it is an abnormal accumulation and retention of CO_2 in the fluids and tissues of the CNS which is the primary trigger for eliciting the NDE. The hypercarbia theory is an orphan hypothesis with no proponents or apologists. No prominent NDE investigator has ever attached their name to it and become its champion or sponsor in a similar manner to those categorized above. When or if attention is paid to the hypercarbia theory, it is usually in the context of the putative role of altered blood gases in the generation of the NDE. Even here, it is often just a minor adjunct or appendage to a much longer discussion of the merits of the more highly favored anoxic explanation [9, 34, 36, 38, 39, 40, 41]. More detailed, substantial and serious analyses of the potential role of CO_2 are available but these are seldom supportive and mostly either agnostic or critical [35, 42, 43, 44, 45, 46].

Despite the lack of appreciation, the hypercarbia explanation has persisted while many of its concomitant older theories have long been discarded. A resilient scientific model is often a sign it is worth pursuing even if it is not popular. In fact, evidence has continued to accumulate that CO_2 may play a key role in the induction of the NDE. At least three strands of evidence implicate CO_2 narcosis. One is rarely acknowledged; one is longstanding and one is quite recent.

It is the purpose of this review to critically evaluate the present status of the hypercarbia theory. It should also be taken into account that NDE is an ambiguous term. There are other mental events which may occur near death such as the deathbed vision and the anticipated or fear of death experience. These are not the purview of the present article and should not be conflated with the NDE as currently defined.

The Phenomenology of the NDE

The features of the NDE have been exhaustively and extensively investigated and reported [8, 9, 29, 35, 36, 42, 45, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58].

Below, the main components or qualities of the NDE are briefly set out. A person could be surmised to have had a NDE if they reported at least some of these [9, 59].

Ironically the most common description of the NDE is probably the inadequacy of words to describe it. "Ineffability" is the term most often invoked to define the experience. Despite this limitation, the NDE is overwhelmingly one of positive affect and well-being. This is despite the occasional report of hellish or distressing rather than heavenly visions [58, 60, 61, 62, 63].

During the early part of the NDE, the subject may have the feeling of separation and floating away from their dead or dying body. This dissociative component of the NDE is often compared to the well-documented altered state of consciousness dubbed the out-body-experience (OBE) [64, 65, 66, 67, 68, 69, 70, 71] or its more supernatural moniker astral projection [72]. It is also thought to be related to the rare neuropsychiatric syndrome known as autoscopy [73, 74]. During an OBE, the disembodied

spirit, mind or parasomatic body may subsequently be reported to have observed the world from a position external to the physical body.

Next, many subjects may feel themselves flying in a long usually dark cylindrical void variously identified as a well, cave, valley, trough, stairway, channel or pipe. This is the so-called tunnel experience Moody [75]. At the end of the tunnel, a pinprick of light is glimpsed which rapidly expands and becomes brighter as the subject draws near and merges with it. The light is depicted as brilliantly luminous and radiant. Subjects feel themselves embraced, enveloped and caressed by it. Moody [8] defined it as a "being of light", implying that it seemed to possess a kind of empathic personality.

The rendezvous with the "being of light" may be associated with a condensed life review, a phenomenon sometimes described as a panoramic memory. This may consist of a rapid continuous replay of seemingly the entire life or just some highlights.

In addition to the apparition of light, the subject may also encounter and attempt to communicate with other spiritual beings and guides. These characteristically take the form of deceased friends and relatives or other heavenly creatures.

Eventually, the subject may discover themselves dwelling in a sublime celestial realm which perhaps could be identified as heaven or paradise. Time and space appear to have been dissolved and the atmosphere may be diffused with ethereal music.

At some point during the NDE, the person may find themselves returned to their body. This may occur abruptly often with a pronounced jolt.

In his original book, Moody [8] distilled the quintessential nature of the experience into a now famous composite NDE. This is widely reproduced in the NDE literature. However, in the Introduction to his book *Religion, Spirituality and the Near-Death Experience,* Fox provided an actual NDE which in a single example manages to encapsulate much of the phenomenology of the NDE (apart from the OBE). This account is from the archives of the Religious Experience Research Centre maintained at the University of Wales. The patient had suffered a postpartum hemorrhage, a common trigger for the NDE.

"Hovering on the brink of death during emergency surgery, she suddenly lost consciousness and found herself sucked into a great whirling void in which sound was not sound but a tremendous vibrating hum. At the point at which she felt she could stand no more of this deafening sound, her speed through the void slowed, and she found herself surrounded by a brilliant light. Alone, save for the felt presence of a seemingly invisible guide, she was led onwards, feeling overwhelming sensations of love and warmth. Caught up in her experience, she wanted nothing more than to move closer to an even greater light (which) seemed to be radiating from somewhere just ahead, all thoughts of her stricken medical condition now forgotten. Finally, she felt an overwhelming sense of desolation as she heard the firm instruction to return to your family, there will be another time for you here" [45].

Professional skeptic Keith Augustine reviewed all the core components of the NDE [76]. He concluded that each fulfilled the criteria to be considered a genuine visionary event. It is therefore difficult to disagree with Oliver Sack's assessment of the NDE as being no more or less than an extraordinarily complex kind of hallucination [77].

Life-threatening conditions which give rise to the NDE

Most persons suffering a near-fatal medical crisis or emergency, will not undergo a NDE while unconscious and the proportion who do is difficult to determine. Schroter-Kunhardt [86] concluded that

it lies between 10-50%. In the case of cardiac arrest survivors, it probably lies between 10-20% [78, 79, 80, 81, 82, 83]. What is more certain is that not all life-threatening crises, disorders or episodes are equally potent at inducing a NDE [9]. Beginning with Moody's original study in 1975, there have been numerous books and articles detailing the conditions under which a NDE may arise [8, 9, 34, 42, 45, 46, 53, 54, 55, 56, 78, 80, 81, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97].

Despite the vast number of examples of the NDE now available in the various literatures, the range of acute medical disorders or illnesses which seem capable of inducing such an experience is actually quite limited despite what is sometimes claimed [214]. In fact, the great majority of NDEs seem triggered by little more than a dozen pathophysiological events. In adults, this is most commonly cardiac arrest or cardiopulmonary arrest (CPA) as a consequence of myocardial infarction [41]. In children, it is most likely to be near - drowning. Other life-threatening conditions, afflictions and accidents which may give rise to a NDE include electrocution, pneumonia, poisoning, drug overdose, apnea, asthma attack, tracheal obstruction, breathing toxic gases or smoke, diabetic coma, anaphylactic shock, postpartum or perioperative hemorrhage, suffocation and hypothermia. Viral or bacterial infection and inflammation of the CNS are not commonly associated with reports of the NDE but neither are they especially rare [53, 55, 98, 99, 100]. It is quite unusual to find a genuine NDE which has not been induced by one of the above causes.

Conversely, this analysis must also raise the question as to whether there is any kind of near-death catastrophe or emergency where a patient or victim will never experience a NDE. This possibility is difficult to assess with any assurance because most NDE researchers, unless they are also physicians, do not usually provide adequate clinical details concerning their subjects [101]. Despite this, there is circumstantial and inferential evidence that patients knocked unconscious following traumatic brain injury (TBI) seldom, if ever, report undergoing a classic Moody type. For instance, not one of the 50 subjects studied by Sutherland [34] was described as having suffered a head injury. Likewise, Morse et al. [84] surveyed a group of comatose children who might have suffered a near-death episode. Only one had sustained a head injury and this patient did not report a NDE. Just one of Parnia's [46] approximately 20 NDE subjects reportedly had a head injury. This person had a road traffic accident (RTA) and suffered multiple injuries including skull fracture. Whether he also suffered brain damage is uncertain as details are vague and the episode had occurred almost two decades previously. However, there was no evidence of retrograde amnesia and therefore of any concussive injury.

In his book *Evidence of the Afterlife,* physician Jeffrey Long provides abundant testimonies from NDE subjects [53]. In more than 50, he also furnishes very brief details of the medical mishap suffered by his subjects. Almost half had undergone some form of CPA. Other triggers were hemorrhage, electrocution, near-drowning, asphyxia, pneumonia, asthma, drug overdose, and allergic reaction. Quite a few had also survived RTAs, but for most of these, no clear evidence was presented that they had specifically suffered concomitant TBI. Only one patient seems to have been knocked unconscious and therefore have sustained a genuine concussive type of injury. This was a young boy and his subsequent description is barely recognizable as a conventional NDE.

Baptist minister Don Piper believes his NDE represented an actual sojourn in heaven [102]. He also seems to believe that the NDE, whatever its status, must have been triggered by TBI following a catastrophic RTA. Soon after, he had been declared clinically dead by an emergency medical technician who could detect no pulse. Later, he was reassured by his physicians that there was no evidence that he had suffered any brain damage or head injury. It seems more likely therefore that his

loss of awareness and subsequent NDE were caused by a state of hypovolemic shock and hypotension due to exsanguination following massive leg and arm trauma. It would also explain a feeble and apparently absent pulse.

Journalist Judy Bachrach did an informal survey of 20 or so NDE subjects in her book *Glimpsing Heaven* [103]. Among the medical crises and emergencies which triggered the NDE in her cohort were cardiac arrest, hemorrhage, electrocution, near-drowning and asphyxiation. So far as can be determined, only a single case was clearly associated with a TBI. The victim was a 10 yr old girl who was stunned while clambering over rocks and fell into a creek where she remained submerged for several min. The girl, now a physician, attributed her NDE to near-drowning and not to any concussive injury. Another of Bachrach's subjects was a war correspondent who had a hole blown in the side of his neck following an explosion. The circumstances are too ill-defined to decide if head injury could have contributed to his vaguely-remembered NDE.

Intensive care physician Laurin Bellg recorded near-classical NDEs from a dozen of her patients. She subsequently devoted most of them a chapter each in her book *Death in the ICU* [104]. For the majority of her subjects, the medical catalyst for the NDE was heart attack followed by cardiac arrest. Other precipitating factors were respiratory arrest due to emphysema, hemorrhage, near-drowning, meningitis and pneumonia. None of the patients had had a TBI. Nonetheless, one of her subjects did claim she had undergone a similar experience when she had suffered a "severe head injury" during a RTA a decade previously. However, this patient had also ceased breathing when discovered by the emergency medical technician and needed artificial respiration at the scene of the accident.

All the examples discussed above are essentially anecdotal. However, there has been at least one large formal study which strongly supports the idea that NDEs seldom arise following TBI [105]. Subjects were 86 patients who had suffered severe head trauma (GCS < 8) and remained comatose for at least 72 hours. Once they regained consciousness, they were interrogated as to the occurrence of a NDE. Just three subjects (3.5%) subsequently reported what would be considered a genuine and clearly recognizable experience. This most commonly consisted of light visions of creatures and figures obviously equivalent to Moody's encounters with " beings of light". Other elements of the NDE were occasionally described although no one disclosed having had an OBE.

The authors did not seem overly impressed with the quality of the three post-head injury NDEs. They rated them as second tier experiences when compared with the archetypal variety. Unfortunately, they do not provide any specific clinical details regarding these three, not even ages. Therefore, it is uncertain whether they might have suffered an additional pathophysiological event which could otherwise account for their NDEs. No definitive explanation is offered for why 96% of TBI survivors did not recount a NDE, although a number of hypotheses are explored. Notwithstanding this, their findings represent the most persuasive evidence so far available that there is little or no link between TBI and the NDE.

This dearth of NDEs in patients with TBI is little, if ever, commented upon. Nonetheless, if this apparent lack of a relationship between TBI and the NDE is ultimately borne out by further research, it may also provide some useful insight into the psychophysiology of the latter.

The evidence that CO_2 plays a pivotal role in the NDE

The first piece of evidence which ties CO_2 intoxication to the NDE is circumstantial. It will be recalled from the previous discussion that only a very limited number of life-threatening medical emergencies seem capable of evoking the prototypic Moody NDE. What is distinctive about this list is that they are

all associated with an acute state of hypercarbia [106]. Medical conditions or catastrophes not usually affiliated with hypercapnia seldom, if ever, generate a NDE. The best example of this failure is TBI. This suggests that a state of cerebral hypercarbia is not just a common factor among these pathophysiological conditions, but may also be an indispensable and principal catalyst for any subsequent induction of a NDE.

The second line of evidence is possibly more compelling. It concerns the use of a psychotherapeutic treatment usually labelled CO_2 therapy (CDT). CDT had first been established in the late 1920s by psychiatrist A.S. Loevenhart in an attempt to relieve the symptoms of catatonia although it produced only very temporary remissions [107]. Loevenhart died soon after but these findings were confirmed by others who also reported only transient improvements (10-15 min) in lucidity and responsiveness [108].

CDT was reintroduced by the Hungarian-American psychiatrist L.J. von Meduna in the mid-1940s at the University of Illinois. In this case, it was recommended as a cheap, accessible and effective treatment for a range of psychoneurotic complaints [109]. These included obsessive-compulsive behavior, hysterical, conversion and dissociative disorders, anxiety and phobias. Use of CDT was prevalent during the 1950s with both ardent supporters and skeptics but began dying out in the early 1960s although not entirely abandoned despite Meduna's death in 1964. During the mid-1970s, it was still being used by the controversial New York psychiatrist Albert LaVerne, this time as a treatment for drug addiction.

In a typical CDT procedure, the patient would breathe a combination of O_2 and CO_2, the so-called Meduna mixture or carbogen. Normally, this gaseous concoction consisted of 30% CO_2 and 70% O_2. Approximately 25 inhalations were necessary for loss of awareness or insentience to ensue, although sometimes this could be achieved with much less. Each session consisted of a maximum of 50 breaths and, typically, several treatments were scheduled each week. During intoxication with the carbogen mixture, both patients and normal subjects experienced a range of sensations, perceptions, illusions and feelings which could be variously described as captivating, dream-like, ineffable, spiritual, noetic, ecstatic, otherworldly and ultra-realistic. There were reports of both simple and complex imagery, geometric shapes, figures and patterns, bright lights and vivid colors. Rotating circles could expand into tunnels or tubes with a shining light sighted at the far end, sucking the subject towards it. OBEs with associated feelings of floating and bodily detachment were described. Universal truths and cosmic insights could be gained and memories of the subject's early life may resurface. Not all the experiences during CDT were bewitching, affirmative or beneficial. Some were reported to be alarming, dismaying or shocking.

In his influential essay on the origins of mystical experience, Aldous Huxley described intoxication with the Meduna mixture as follows:

"A mixture of...carbon dioxide produces …. certain physical and psychological changes.... Among these changes the most important....is a marked enhancement of the ability to see things when the eyes are closed. In some cases, only swirls of patterned color are seen. In others there may be vivid recalls of past experiences...In yet other cases carbon dioxide transports the subject to the Other World at the antipodes of his everyday consciousness, and he enjoys very briefly visionary experiences entirely unconnected with his own personal history or with the problems of the human race in general" [110].

In one of the later formal reports on the use of CDT, Uhler depicted the subjective experience in a hypothetical patient.

"Then he goes on to mention without prompting some visual sensations, a flaky scene, rapidly moving

flashes, symmetrical cubes and dots in motion or a long hole in a cave with a bright opening at a great distance, many vehicles moving very fast, millions of them. Some patients, after inquiry, relate views of childhood activities or portraits of long deceased relatives, much to their amazement" [111].

Many of its core elements can be recognized in this passage in this passage, yet it was composed more than a decade before the phenomenology of the NDE was popularized.

The similarity between the two types of experiences is also well illustrated in the following three quotes from Meduna's subjects [109]. The first of these with its obvious allusion to the OBE has been extensively reproduced in the NDE literature.

"After the second breath came an onrush of color, first a predominant sheet of beautiful rosy-red, following which came successive sheets of brilliant color and designs, some geometric, some fanciful and graceful – purple and rose coloring predominate. As these sheets came towards me, they seemed to engulf me and leave me breathless in the mad rushing sensation. Then the colors left and I felt myself being separated; my soul drawing apart from the physical being, was drawn upward seemingly to leave the earth and to go upward where it reached a greater Spirit with whom there was a communion, producing a remarkable, new relaxation and deep security. Through this communion I seemed to receive assurance that the petit problems or whatever was bothering the human being that was me huddled down on the earth, would work out all right".

"I felt as though I was looking down at myself, as though I was way out here in space.... I felt sort of separated".

"It was a wonderful feeling. It was marvelous. I felt very light and I didn't know where I was...And then I thought that something was happening to me. This wasn't night. I wasn't dreaming.... And then I felt a wonderful feeling as if I was out in space".

With the rediscovery of the NDE in the mid-1970s, researchers soon latched onto the resemblance between the phenomenology of the NDE and that of CDT with the realization that carbogen intoxication could be a key to unlocking the NDE portal. Among the useful insights with particular reference to the NDE was Meduna's finding that all four of Kluver's form constants could be recognized during CDT [112, 113]. These are simple recurring images or geometric patterns usually understood to be the building blocks of more complex components of visionary phenomena including that of the NDE [35, 114, 115]. Equally important was the observation that those undergoing CDT, like the NDE subjects, all had essentially the same otherworldly or ecstatic experience [44, 109]. There was relatively little inter-individual variability. In addition, it must be considered just how quickly complex visual phenomena could evolve following the commencement of CDT. The NDE also seems to possess a quite rapid onset of action.

The first argument canvassed above in favor of a role for CO_2 in the generation of the NDE is inferential. It implies that a state of hypercarbia should almost always accompany a classical Moody NDE. In contrast, the second argument is empirical. It seeks to prove that inhaling a high concentration of CO_2 can rapidly induce a psychedelic state which closely resembles the NDE. Neither of these two assertions, however, directly links the NDE with a state of hypercarbia. In contrast, quite recent study provides a more clear-cut demonstration of the association between the NDE and CO_2 [116].

Fifty-two cardiac arrest survivors were recruited consecutively as subjects by researchers from the University of Maribor, Slovenia. Physiological measurements analyzed were those made immediately upon admission to an intensive care unit. Patients who had had a NDE were subsequently identified

using the Greyson scale [59]. Eleven patients (21%) were judged as having had a NDE at some stage during their cardiac arrest. Findings revealed that the occurrence of NDEs was significantly associated with higher levels of CO_2 both in expired breath and in the blood stream. This was indicated by an increase in the partial pressure of end-tidal CO_2 and in $PaCO_2$. Conversely, the authors could find no relationship between the NDE and the age, sex, education, religious beliefs and fear of death of the patient. Nor could any be discovered between the NDE and medications used during resuscitation or to the return of spontaneous circulation. There was also no significant correlation between the advent of a NDE and PaO_2. With the possible exception of serum potassium levels, hypercarbia was therefore the only useful predictor of a NDE. Taken in conjunction with the other evidence mustered above, then the authors' conclusion "that CO_2 might be one of the major factors for provoking NDEs" seems justified.

Critique of the hypercarbia theory

Various criticisms have been leveled at the CO_2 theory of NDE generation [44]. The gold standard among these is a quasi-scientific study cited by Sabom [42]. As recently as 2010, it was still being used in an attempt to demolish the findings of Klemenc-Ketis [117]. The patient was a 62 yr old male who was admitted to hospital complaining of chest pains and soon after suffered myocardial infarction and cardiac arrest. While unconscious, he had an OBE where he alleged, he witnessed physicians attempting to resuscitate him. This included "viewing" a blood sample being drawn from his femoral artery. This procedure had actually been carried out. When analyzed, there was no indication of raised CO_2 levels in the blood. In fact, contrary to the expectations of the hypercarbia theory, the $PaCO_2$ was below normal (28 mm Hg). The observation that an OBE could occur in the absence of hypercarbia seemed to definitively rule out CO_2 as making a critical contribution to the generation of the NDE.

There are fundamental problems with this conclusion [35]. Gliksman and Kellehear [211] have questioned the value, accuracy and utility of blood gas measurements especially with regards to NDE research. Judging by the information they discuss, peripheral (i.e., arterial) assessments may underestimate or minimize rather than reliably reflect concurrent abnormalities in CO_2 levels in more central locations. This may be particularly true of CO_2 concentrations in the tissues and fluids of the dying brain. Specifically, the authors analyze a report by Benzel et al. [210] where $PaCO_2$ was systematically measured in a group of 20 dying patients. If peripheral blood gas measurements are not a sensitive indicator of a potentially hypercapnic brain, then Sabom's much vaunted case study does not provide much of a threat to a CO_2 theory of NDE generation. Blackmore [35] concluded that it was more likely that Sabom's subject genuinely did have an excess of CO_2 in his CNS contrary to the blood gas analysis.

There is another deficiency in Sabom's example. It involves the question of whether the patient's visionary experience of having blood withdrawn actually occurred at the same time as the real procedure. There is no way of independently verifying this and so it is impossible to pinpoint exactly when the OBE arose during an extended period of unconsciousness. The doubts surrounding this matter would probably be sufficient reason by themselves to disregard Sabom's subject irrespective of Gliksman and Kellehear's concerns over the dependability of blood gas samples.

A further difficulty with Klemenc-Ketis' results is that they are contrary to the earlier ones of Parnia et al. [78]. The latter could detect no difference between NDE subjects and controls in the CO_2 content of arterial blood. It was concluded that hypercarbia was not a causative agent in the induction of NDEs. The reason for this discrepancy is probably due to the same combination of confounding factors discussed above in relation to Sabom's example. In addition, Klemenc-Ketis' data is probably more

reliable simply because they had three times as many patients. This is a weakness which the earlier authors had acknowledged.

The Neurobiology of the classical hallucinogens

The classification and phenomenology of the classical hallucinogens

The biggest uncertainty facing a CO_2 theory is not whether it might be involved in the NDE but rather how a state of cerebral hypercarbia and respiratory acidosis can ultimately translate into an intense and vivid visionary experience. This is, in fact, just a variation of the abiding and fundamental problem of how intoxication with a classical hallucinogen can evoke very similar subjective and mental events to the NDE. More specifically, this concerns the question of exactly what the nature and location of the sequence of physiological, chemical and molecular events between intoxication with the hallucinogen and the subsequent induction of psychedelic phenomena is [118, 119, 120, 121].

The classical hallucinogens are a group of mostly naturally-occurring alkaloids derived from plants and many have entheogenic functions. They can be divided into two categories on the basis of their chemical structure. One class comprises the tryptamine or indoleamine psychedelics. Prominent members include lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), and psilocybin. Many tryptamine hallucinogens are chemical congeners of serotonin. The second category contains the phenethylamine psychedelics whose best-known example is mescaline. Despite their differences in chemical structure, what the tryptamines and phenethylamines share in common is that they induce essentially identical perceptual, cognitive, affective, psychic and somatic phenomena. In addition, their psychoactive effects are mediated via the serotonergic system. It is for this reason that they possess the alternative title of serotonergic psychedelics. They also display cross tolerance among themselves thus also implying a common mode of action at the molecular level [118, 122, 123].

The classical hallucinogens are capable of evoking ecstatic, visionary, spiritual and otherworldly mental experience at moderate and sometimes minute doses [122, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134].

False, distorted or enhanced perceptions and sensations from all sensory systems are their main expression. Depersonalization, derealization, fragmentation of the self and body and obscuring of borders between the person and environment are also characteristic. There is a disturbed sense of time. The emotional ambience can range from the positive, benign, captivating, enchanting and enthralling to the negative, terrifying, disturbing, despairing and panic stricken. It is hardly surprising that these drugs are among the agents which can most faithfully simulate the NDE.

The archetype example of these so-called mind-expanding or mind-altering drugs is LSD [122, 135]. LSD is a semi-synthetic alkaloid derivative of lysergic acid. Lysergic acid is a constituent of the ergot fungus (*Claviceps purpurea*) supplying the nucleus for ergot alkaloids but in isolation is inactive. LSD was first synthesized by the Swiss chemists Albert Hofmann & Arthur Stoll in 1938. Its potent psychedelic qualities were adventitiously discovered by Hofmann in 1943. LSD may induce fantastically vivid colorful visions, mystical dream-like states and revelations, heightened perceptions and sensations and feelings of elation and ecstasy. Notably, past experiences may also be relived as if watching a film. Bates and Stanley [209] have tabulated the impressive similarity between experiences under LSD and the phenomenology of the NDE.

The similarity between LSD intoxication and the NDE is also well illustrated by the following account which was sent by a correspondent to Oliver Sacks.

"Then I left my body and hovered in the room above the whole scene, then found myself traveling through a tunnel of beautiful light into space and was filled with a feeling of total love and acceptance. The light was the most beautiful, warm and inviting light I ever felt. I heard a voice ask me If I wanted to go back to Earth and finish my life or.... to go into the beautiful love and light in the sky. In the love and the light was every person that ever lived. Then my whole life flashed in my mind from birth to the present, with every detail that ever happened, every feeling and thought, visual and emotional was there in an instant. The voice told me that humans are Love and Light" [77].

Mescaline is the psychoactive compound in the small spineless cactus peyote and is prevalent in northern Mexico and southwest U.S.A. [136]. It was the agent that psychobiologist Heinrich Kluver self-administered during his research into psychedelic experience and from which he identified the four hallucinatory form constants mentioned previously. Psilocybin and psilocin are the active hallucinogenic ingredients of so-called "magic mushrooms" [137]. There is a large number of such fungi growing predominantly in tropical and subtropical areas. The best-known genus is *Psilocybe mexicana.* The Aztecs were sufficiently beguiled by psilocybin that they ordained it as teonanacatl or "flesh of the gods".

DMT is the active ingredient of the tea *ayahuasca* still widely imbibed by members of Amazonian tribes and whose use continues to spread elsewhere [138]. Unlike LSD, mescaline and psilocybin, DMT is sometimes referred to as an endogenous hallucinogen. This is because small amounts of the compound are synthesized within the human body and possibly the brain. DMT has recently acquired fame as the so-called "spirit molecule" and as such forms the basis of a major neuroscientific theory of NDE generation [139]. In a more recent formal study, Timmermann et al. [218] described a "striking similarity" between the phenomenology of DMT intoxication and that of the NDE.

The molecular biology of the classical hallucinogens

Exactly how these compounds interact with serotonin (5-HT) neurons has proven to be an arduous and confusing exercise. Much of the research conducted on this matter involved LSD although it is usually accepted that the findings can be extrapolated to other classical hallucinogens with little qualification [127, 140, 141, 142, 143]. Initially, it was thought that the site of action of the hallucinatory compounds lay on the membranes of the 5-HT neurons originating in the raphe nuclei [118, 119, 132, 144]. LSD and other indoleamine hallucinogens bind tightly to 5-HT1A autoreceptors prolifically present on the raphe nuclei cell bodies causing a severe depression of neuronal firing. Inhibition of 5-HT activity was therefore conceived as an early step in the cascade of reactions leading to the perception of visionary experience. This so-called presynaptic hypothesis eventually proved unsatisfactory and attention subsequently shifted to 5-HT receptors located on the membrane of the target cells to which the raphe nuclei neurons projected [118, 119, 143, 145, 146, 147, 148, 149]. Of the 20 or more subtypes of 5-HT receptors, LSD demonstrated an infinity with several but phenethylamine hallucinogens bound with just one of these subtypes: 5-HT2A, a receptor subtype which reputedly does not exist on the raphe nuclei cell bodies. This implied that it is the exclusive stimulation of 5-HT2, and more specifically 5-HT2A, subreceptors which is uniquely responsible for eliciting hallucinatory experience [120, 123]. The post-synaptic hypothesis has now acquired the status of a near-doctrine with the operation of the subreceptor being agonistic or partially agonistic in nature. There remains speculation, nevertheless, that other types of hallucinogen-serotonin receptor modes of interaction may be a mixture of the agonistic and antagonistic and some of these may contribute to the overall experience including non-subjective somatic phenomena [131].

There is one further potentially useful insight concerning the molecular biology of the serotonergic psychedelics. 5-HT2A subreceptors are widely expressed throughout the brain [118] but are notably prevalent in the cerebral cortex and, in particular, on the apical dendrites of pyramidal neurons [119, 123, 150, 151]. They appear to be most densely concentrated in laminae II and III and laminae V and VI. This provides *prima facie* evidence that the principal site of action of the classical hallucinogens resides at the neocortex [120].

Following receptor activation, the functional status of the neuron seems most likely to be excitatory. Beyond this, however, little if anything, is known with certainty about the electrogenesis of hallucinatory experience. This is despite many attempts to explain how the sequence of chemical and electrical events ultimately translates into the perceptions and sensations which compose a hallucination. The pyramidal cells have prolific cortico-cortical connections and projections and are also a hub for intracortical and thalamo-cortical processing. Such conditions therefore allow for fairly unrestrained speculation and guess-work about these matters.

Also potentially relevant to the question of the psychobiology of hallucinatory experience is a study from the Scripps Research Institute [152]. This suggests that the psychedelic effects of the hallucinogens and the manifold regulatory functions (although non-hallucinatory properties) of serotonin may be mediated via quite distinct signaling routes and cascades from the 5-HT2A receptor. This is despite both classes of molecules having a common affinity for this subreceptor.

Subjects were either wild-type (WT) or mutant mice in whom the regulatory β-arrestin2 gene had been knocked out. The β-arrestins are intracellular scaffolding proteins which can modulate the functions of receptors such as 5-HT2A. Head twitch responses were monitored as a behavioral index that the 5-HT2A receptor had been stimulated and activated in the rodent.

Treatment with serotonin failed to elicit the head twitch in the knockout (KO) mice although it was vigorously present in the WT mice. In comparison, when N-methyltryptamines were injected into the β -arrestin2 KO mice, the head twitch response persisted and was more pronounced than in the WT animals. The psychoactive agents employed were N-methylserotonin and 5-MeO-DMT. 5-MeO-DMT is a close chemical relative of DMT with similar psychedelic and entheogenic properties. One anomalous feature of these *in vivo* findings was that at high levels of serotonin, a head twitch response did appear in the β-arrestin2 KO animals. The authors accounted for this discrepancy as being due to the activity of the N-methyltryptamines at the receptor site rather than directly to serotonin. Overall, it was concluded that a β-arrestin2 cascade governs the serotonergic effects while a G-protein-mediated, β-arrestin2- independent messenger system controls the hallucinatory events following 5-HT2A receptor activation. The authors described such an arrangement as agonist-directed signaling.

Schmid and Bohn's research is useful because it does furnish a comparatively simple explanation for a seeming paradox and, as such, it may provide a central insight into the nature of hallucinogenesis at the molecular level. This is the question of why some 5-HT2A receptor agonists are capable of eliciting hallucinatory phenomena whereas others are not. For example, both the antimigraine and antiparkinsonism agent lisuride and LSD are powerful 5-HT2A agonists. However, unlike LSD, lisuride is devoid of hallucinogenic properties [123, 153]. A corollary is that the induction of a visionary state may not necessarily depend upon interference with normal serotonergic function contrary to what is commonly suspected.

The role of CO_2 in the regulation of breathing

A state of cerebral hypercarbia may arise from circulatory or respiratory collapse. Alternatively, it may

be artificially or experimentally produced such as with CDT and the inhalation of carbogen. As $PaCO_2$ levels in the cerebral blood vessels begin to rise, CO_2 molecules both easily and quickly diffuse across the semi-permeable blood-brain barrier into the extracellular fluid (ECF) and the cerebrospinal fluid (CSF) [154, 155, 156, 157, 158, 159, 160, 161]. CO_2 rapidly dissolves in water and this hydration process forms carbonic acid by the following conversion reaction catalyzed by the enzyme carbonic anhydrase in the CSF:

$$CO_2 + H_2O \longrightarrow H_2CO_3$$

Carbonic acid immediately dissociates into free H^+ ions and bicarbonate:

$$H_2CO_3 \longrightarrow H^+ + HCO_3^-$$

The liberation of large amounts of H^+ ions by this reaction quickly reduces the pH of the CSF. It is this increasing acidification of the CSF (and the ECF) due to the build-up of H^+ ion or proton concentration which directly activates the central chemoreceptors. Chemoreceptors are sensory nerve cells with afferent connections to respiratory motor nuclei. They are characteristically divided into peripheral (or external) and central (or internal) chemoreceptors. Peripheral chemoreceptors are located in the carotid and aortic bodies and are concerned with monitoring both $PaCO_2$ and PaO_2 levels. In contrast, central chemoreceptors were originally believed to be concentrated largely on the surface of the ventrolateral medulla. However, they are now thought to be more widely distributed throughout the lower parts of the brain including the cerebellum, hypothalamus and midbrain as well as in other locations in the pontomedullary brainstem [157, 162, 163, 164].

Once the chemoreceptors are stimulated, excitatory afferent impulses are transmitted to the central respiratory networks and circuits of the brainstem reticular formation located in both the medulla and pons. This most notably comprises the dorsal respiratory group and ventral respiratory group of the medulla and the pontine respiratory group (aka the pneumotaxic center). Their increased firing triggers an immediate adjustment in rate and depth of breathing. Under usual conditions, this comparatively simple negative chemical feedback system very efficiently (within sec) restores $PaCO_2$ to normal levels and decreases the H^+ ion (proton) concentration in the CSF and interstitial fluid. This mechanism of restoring normal systemic CO_2/pH levels is also known as the hypercapnic ventilatory response (HCVR). The chemoreceptors, deprived of their acidic stimulation, cease their activating input signals to the breathing centers thereby diminishing the respiratory drive. However, in conditions such as CPA or inhalation of carbogen, this corrective mechanism will not operate appropriately, blood chemistry abnormalities and acid-base imbalance cannot easily be rectified. Such a state will produce an increasing accumulation and persistence of H^+ ions in the CSF and the ECF with progressive acidification and eventually CO_2 narcosis and neurotoxicosis.

The role of 5-HT neurons as central respiratory chemoreceptors

As discussed previously, exactly how a state of hypercarbia induces graphic ecstatic experience which resembles the NDE is unknown. Still, James and Erowid [213] offer an intriguing suggestion which has become increasingly persuasive. They argue that the psychedelic properties of CO_2 intoxication may be mediated by the same serotonergic pathways as those involved with classical hallucinogens. In support of this idea, there do seem to exist in the brainstem and midbrain raphe nuclei a class of 5-HT neurons which act as central respiratory chemoreceptors. That is, they are differentially sensitive to a state of respiratory acidosis, are connected to ventilatory nuclei and therefore help monitor and maintain blood gas homeostasis and acid-base balance.

The role of the serotonergic system in governing central breathing behavior has been controversial and is still not adequately understood [163, 164, 165, 166, 167, 168]. Nevertheless, it is now well established that 5-HT neurons do provide tonic pace-making excitation which drives normal spontaneous rhythmic or eupneic respiration. This is achieved by medullary raphe serotonergic stimulation of various brainstem nuclei.

Within the past two decades, it has also become increasingly apparent that 5-HT neurons may play an equally important role in chemoreflexion. It is not claimed that all brainstem 5-HT cells are chemosensitive nor that all chemoreceptors are serotonergic in origin [164]. In this respect, it has been suspected that glutamatergic and noradrenergic neurons may also function as central respiratory chemosensors. In addition, the putative role of 5-HT neurons in blood gas homeostasis is not yet definitive. Much of the research on 5-HT neurons as tentative CO_2/pH chemoreceptors has been conducted by George Richerson and co-workers at Yale. During the present century, this group has also published a series of reviews and the present discussion is largely adapted from these [164, 167, 169, 170, 171, 172] A heterogeneous collection of neurobiological data using both *in vitro* and *in vivo* preparations have been assembled to support the alleged link between 5-HT neurons and chemoreflexion. Just some of this information is summarized below.

The first kind of evidence implicating 5-HT neurons as central respiratory chemoreceptors is natomical. The 5-HT neurons of the medullary raphe and also the dorsal raphe of the midbrain are concentrated closely by the basilar artery or its subdivisions and so are in an ideal position to detect abnormally high levels of arterial CO_2 [173, 174]. In addition, as noted above, pathways exist directly and specifically between medullary and 5-HT neurons and the brainstem ventilatory circuits and excitation of these cells activates the premotor and motoneurons [165, 170].

The second is functional. Some 5-HT medullary and midbrain neurons have an acute endogenous chemosensitivity which persists in isolated *in vitro* brainstem slices and primary tissue culture [169, 175, 174]. The third is electrophysiological. *In vitro* and *in vivo* recordings from unanesthetized animals show increased firing rate from 5-HT neurons following hypercapnic stimulation. For example, Veasey et al. [219, 220] demonstrated that the HCVR is associated with increased discharge from a subset of both medullary raphe and dorsal raphe (midbrain) neurons in awake cats after inhaling a CO_2 mixture. The fourth involves chemical lesioning studies. In this case, populations of brainstem serotonergic neurons are selectively destroyed with focal injections of a neurotoxin. Typically, the HCVR is severely weakened.

The fifth involves transgenic preparations. The introduction of gene KO techniques employing animals with genetic modifications may provide a more elegant and efficacious method than alternative lesioning studies and pharmacological treatments. For instance, Hodges et al. [212] utilized conditional KO mice as subjects in which the transcription factor *Lmx1b* in Pet1-expressing 5-HT cells had been removed thereby totally preventing the expression of 5-HT neurons in the CNS. Bereft of any 5-HT cells, mutant animals displayed a serious impairment of the HCVR in comparison with the WT mice. The sixth is neurodevelopmental. There is a strong relationship between the acquisition of chemosensitivity in 5-HT cells during the post-natal period and the maturation of the HCVR in the rat [164, 176, 177, 178]. Such findings provide near unequivocal support for the crucial part that 5-HT neurons must play in central chemosensitivity.

The concept of 5-HT neurons as sensors for CO_2 /pH is not universally accepted [179]. Richerson and co-workers review some contrary arguments but these are fairly persuasively dismissed [164, 172]. In

particular, they identify anesthesia as a compromising and confounding factor and hence the precaution of conducting such *in vivo* experiments using awake subjects. It has also been contended that while the chemosensitive medullary raphe 5-HT neurons control the HCVR, their midbrain equivalents are responsible for the arousal component of the response to hypercapnia [180].

The preceding summary demonstrates that there is a high probability that a subset of 5-HT neurons located mostly in the brainstem and midbrain raphe do act as central CO_2/pH chemoreceptors and so help maintain CO_2/pH homeostasis. This raises the possibility that a state of respiratory acidosis activating 5-HT chemoreceptors could have dual properties. It might trigger not just motor events (the HCVR) but also internally generated mental events i.e., graphic visionary, ecstatic and psychomimetic experience. If there really is such an association between hypercarbia, the classical hallucinogens and 5 -HT neurons, then this relationship would obviously be strengthened if it could be shown that the alleged 5-HT chemoreceptors include the 5-HT2A subtype. As discussed previously, it is by a common binding to this particular 5-HT subreceptor that the psychedelic phenomena of the classical hallucinogens are also elicited.

It is well established that pontomedullary 5-HT2A receptor activity plays a significant role in many aspects of the neurobiology of breathing in mammals [181, 182, 183, 184, 185]. This includes the supervision, control and modulation of not just the central pattern generator circuits but also of respiratory motor output. For example, 5-HT2A subreceptors are commonly expressed in the hypoglossal (XII) cranial nerve which acts as a conduit for respiratory motoneuronal output [182]. This also occurs in the pre-Botzinger complex (PBC) serving as the pre-eminent rhythmic or pattern generator [181] as well as in the nucleus ambiguus involved (in conjunction with the hypoglossal nucleus) with ensuring an open upper airway [184].

Since there exist a subset of 5-HT receptors which clearly do act as CO_2/pH chemosensors, it is a reasonable inference therefore that such interactions would also likely include the 5-HT2A receptor. Unfortunately, at this juncture, there still does not seem any direct evidence which specifically links the 5-HT2A receptor with CO_2/pH chemosensitivity. There is, as alluded to above, a good deal of information on how 5-HT2A receptor activation helps to exercise a normally excitatory control over respiratory motoneurons, circuits, networks and nuclei. Below is a sample of research findings which demonstrate the involvement of the 5-HT2A subreceptor in brainstem respiratory function.

For example, Pena and Ramirez [181] examined the crucial (but not exclusive) role of 5-HT2A subreceptors on the rhythmogenetic circuits of the PBC. Medullary brainstem slices containing the PBC were obtained from neonatal mice. Such *in vitro* preparations can still maintain the intrinsic respiratory bursts generated within the PBC. Application of a 5-HT2A receptor agonist increased neuronal inspiratory activity whereas application of three specific 5-HT2A pharmacological blockers progressively decreased their amplitude, firing frequency and regularity. Although, eupneic activity was almost invariably seriously disordered, it was never entirely lost. In contrast, application of a specific 5-HT2C receptor antagonist had no influence on respiratory bursting. It was concluded the pace-making qualities properties of the PBC were largely fueled by the release of endogenous 5-HT which acts quite specifically via the 5-HT2A subreceptor.

In a further study, these investigators also explored the role of the serotonergic system in the modulation of gasping behavior [183]. This is thought to be involved in the pathophysiology of sudden infant death syndrome and sleep apnea. The preparation employed was a mouse brainstem slice also containing the rhythmogenetic PBC. It is proposed that normal intrinsic rhythmicity underlying eupneic

breathing is generated by a pair of pacemaker neurons in the PBC. One labelled cadmium (Cd)-sensitive and the other Cd-insensitive. These pace-makers are themselves activated following stimulation by endogenous 5-HT. A state of hypoxia was induced in the *in vitro* preparation using non-oxygenated artificial CSF. This engendered fictive gasping activity in the medullary slice associated with a loss of bursting in the Cd-sensitive neurons. Two types of 5-HT2A antagonists were applied to the slice. Both abolished gasping activity. In a subsequent experiment, it was confirmed that both 5-HT2A receptor blockers have differential effects on the two PBC pacemaker neurons [181]. Bursting activity was extinguished in the Cd-insensitive pacemaker but preserved in the Cd-sensitive neuronal subtype. The authors interpreted their findings as indicating that the fictive gasping rhythmic was specifically governed by endogenous serotonergic excitation of the 5-HT2A subreceptors acting via the Cd-insensitive PBC pacemaker neurons.

Also relevant are a series of experiments reported by Hodges et al. [186] using rat and mouse pups. In one study, respiratory activity was studied using an arterially perfused brainstem-spinal preparation obtained from neonatal rats. Inspiratory bursts were measured from the hypoglossal motoneuron. When a 5-HT2A receptor antagonist was perfused into the preparation, respiratory motor output systematically declined in amplitude and frequency and was eventually terminated.

Complementary findings were obtained using transgenic neonatal *Lmx1b* mice. Immature mice with a complete absence of central 5-HT neurons exhibited acute breathing difficulties manifested by stringent apnea and a significant mortality rate. This was in contrast to WT mice whose breathing behavior was robust, periodic and uninterrupted. However, *Lmx1b* animals which did survive eventually acquired a normal breathing pattern.

In a further experiment, neurophysiological activity was recorded from the hypoglossal nerve in isolated brainstem-spinal cord preparations. Subjects were either neonatal *Lmx1b* mice or WT mice. WT mice displayed normal spontaneous bursting motor activity. In contrast, that of the *Lmx1b* animals was weak, erratic and unstable. Infusion of a 5-HT2A receptor agonist rectified the abnormal breathing pattern in the *Lmx1b* animals although it had little effect on the hypoglossal burst frequencies and amplitudes recorded from WT mice. In a subsequent experiment, it was also demonstrated that the severe apnea suffered by the *Lmx1b* mice during the neonatal period could be almost totally counteracted by subcutaneous injection of the same 5-HT2A receptor agonist.

A concurrent study by some of the same co-workers as in the previous one reported a number of experiments exploring how medullary raphe neurons regulate neuronal networks underlying respiration [165]. One of these investigated the comparative utility of different 5-HT subreceptors in this process. Two preparations were employed. One was an *in vitro* neonatal rat medullary raphe slice. It incorporated spontaneously discharging 5-HT neurons with afferent connections to both the PBC and hypoglossal motoneurons. Activity in these two nuclei was used as a measure of respiratory motor output. The second preparation was an arterially perfused *in situ* brainstem-spinal cord preparation using juvenile rats. Facilitatory 5-HT agonists were used to energize the respiratory neural circuits and networks. A variety of 5-HT subreceptor antagonists were employed including several 5-HT blockers with varying degrees of selectivity. Almost all of these had at least some negative influence on the amplitude or frequency of the inspiratory motor output from the PBC or the hypoglossal motoneurons. Overall, however, the greatest impact was caused by blockade of the 5-HT2A receptors. For example, 5 -HT2A antagonists almost obliterated *in vitro* hypoglossal motoneuron firing when applied at higher doses. This suppressive effect was also observed with other 5-HT subreceptor antagonists (5-HT2C,

5-HT4) but was not nearly as pronounced. More or less similar findings were obtained from the *in situ* preparation which included recordings of PBC activity. The authors concluded that while a number of 5 -HT subreceptors seem to be operating in the serotonergic control of breathing, the participation of the 5-HT2A subtype appeared to be most vital.

The findings summarized in the present section must be treated with a degree of caution and conclusions may need to be tempered. This is because they were derived in some instances from neonatal subjects and from *in vitro* or *in situ* preparations. Care must be taken when extrapolating results to mature intact subjects. Otherwise, the four sets of experiments discussed in this section reinforce the impression that an indispensable role for serotonergic neurons is to deliver tonic excitatory input to the neural circuits responsible for respiratory motor output. More relevant, however, is the conclusion that this regulation appears to be exercised predominantly via innervation of the 5-HT2A subreceptor system. This excitatory capacity is also a necessary condition for a cell to be considered to have chemosensitive properties [186] and so is consistent with the proposed model that a subset of 5-HT neurons function as central CO_2/pH chemoreceptors. A further corollary from this research is that if 5-HT neurons do act as central respiratory chemoreceptors, then these properties are likely to be mediated at least in part via 5-HT2A subreceptors and their signaling pathways.

It follows therefore that the process whereby a state of respiratory acidosis is converted into hallucinatory experience may share a final common pathway with the classical hallucinogens. This would be via interaction with, binding to and activation of the 5-HT2A receptors. This means that under these circumstances, the proton could be considered functionally equivalent to and therefore a kind of congener of LSD, DMT, mescaline psilocybin and other classical hallucinogens. Such an insight would not completely solve the riddle of the psychobiology of visionary experience including that of the NDE. However, it would certainly simplify and probably clarify it.

This proposal does not, of course, imply that the same ventilatory pontomedullary neurons which express 5-HT2A receptors might also be involved in the generation of psychedelic imagery and sensations. As discussed earlier, 5-HT2A receptors have a widespread, if uneven, distribution throughout the brain [187, 188, 189, 190]. They are virtually omnipresent in every cortical region and reputedly most prominently expressed on the apical dendrites of pyramidal cells. High concentrations are also found in selected pontomedullary nuclei (such as the brainstem respiratory network)) as well as the olfactory bulb. By contrast, subcortical, limbic system and cerebellar structures may be less endowed with such receptors. It therefore seems that the circuits and networks involved in the generation of visionary experience would be suprapontine, quite distal from the raphe nuclei and closely connected to populations of cortical 5-HT2A receptors.

If both the protons and the classical hallucinogens do have an affinity for the 5-HT2A subreceptor, it follows that they likely share a common binding site with regards to the elicitation of visionary experience. According to the current model, therefore, the site of action of the protons in inducing a NDE or similar ecstatic or psychedelic experience would be the pyramidal cells of the cortical layers where the 5-HT2A receptors are prevalent. It would also be predicted that once bound to the subreceptor, the protons would activate the psychedelic sub-pathway and not the alternative serotonergic route.

Conclusions summary and future perspectives

The supportive evidence that a state of hypercarbia is the catalyst which triggers the cascade of mental

events which rapidly culminates in the NDE is gathered from quite diverse sources. The first is Meduna's pioneering use of CDT to treat minor psychiatric and personality disorders. There was a very swift onset of psychedelic visions closely resembling the NDE following inhalation of the carbogen mixture. Second is the recent formal clinical studies in which blood gas tension was monitored in cardiac arrest patients. A strong link was discovered between abnormal increases in $PaCO_2$ and subsequent reports of elements of the NDE. Third is the previously over-looked insight that the NDE arises in conjunction with a quite restricted range of acute medical emergencies, conditions or illnesses. All of these are, or at least can be, associated with a state of cerebral hypercapnia. Finally, recent advances in the molecular biology of the brainstem respiratory system have demonstrated that 5-HT neurons and therefore potentially 5-HT2A neurons can serve as central chemoreceptors. 5-HT2A subreceptors are also the common target of the molecules of the classical hallucinogens which can induce psychotomimetic and ecstatic experience almost identical to the NDE.

According to the present incarnation of the hypercarbia model, A NDE may arise when a medical catastrophe or emergency produces an acute and sustained increase in $PaCO_2$. Large quantities of CO_2 molecules begin to migrate across the blood-brain barrier where under the enzymatic action of carbonic anhydrase, they are dissolved into unstable carbonic acid. Carbonic acid breaks up immediately liberating bicarbonate ions and positively-charged hydrogen ions (protons). In an attempt to activate the HCVR, the protons bind to and stimulate the central respiratory chemoreceptors, at least some of which are assumed to be of the 5-HT2A subclass. However, under the circumstances where a NDE may arise (commonly CPA), the HCVR falters or breaks down and the usually corrective negative feedback system fails to operate and restore eupneic breathing. Persisting absent or inefficient respiration means concentrations of CO_2 continue to build up in the bloodstream and are therefore pumped and released into the CSF and ECF.

The resulting surfeit of protons will soon shift their attention from just ineffectually stimulating the brainstem chemoreceptors to interacting with additional binding sites with which they have an affinity. This would include the dense populations of 5-HT2A receptors residing on pyramidal cells in cortical laminae. This is the same target as attracts the molecules of the classical hallucinogens. Once bound to them, it is assumed that the protons would differentially activate the non-serotonergic (hallucinogenic) signaling sub-pathway in the same way as the classical hallucinogens also do. From this stage on, therefore, the question of how the visionary experiences of the NDE could be generated has essentially been reduced to the same problem of how the classical hallucinogens induce similar psychedelic phenomena. It has long been acknowledged that there is a close resemblance between the NDE and that of LSD, DMT, mescaline, psilocybin and the like. This is exemplified by the example Sacks provides of intoxication with LSD although he does not make any specific comparison with the NDE.

This is a cursory summary of how the proposed hypercarbia model of NDE generation might work. The key principle is that the proton has dual properties. It acts not only to stimulate the respiratory chemoreceptors but also functions as a *de facto* classical hallucinogen and so activate the cortical networks and circuits underlying visionary experience. Two difficulties remain to be settled. First, it is necessary to confirm that 5-HT2A receptors can actually serve as central chemoreceptors. This does not seem an unreasonable expectation as it is well-established that 5-HT receptors do serve such tasks and that the 5-HT2A subtype does play a focal role in the operation of the brainstem ventilatory network as a whole.

The second problem is the perennial one of identifying the step in the hallucinogenic algorithm whose

activity converts physical events into mental ones. Aldous Huxley possibly expressed the nature of this long-sought after but elusive instrument best in his essay on psychedelic experience.

"This mystery (how hallucinatory patterns are elicited with the stroboscopic lamp) is merely a particular case of a larger, more comprehensive mystery- the nature of the relations between visionary experience and events on cellular, chemical and electrical levels." [110].

This is a generic difficulty which besets the study of all hallucinogenic substances and conditions. For example, when dealing with his own research into DMT, Strassman [139] writes:

"It is important to remember that while we understand a great deal about the pharmacology of psychedelics, we know nearly nothing about how changes in brain chemistry directly relate to subjective or inner experience.....That is, we are far from comprehending how activating particular serotonin receptors translates into a new thought or emotion".

Irrespective of its origin, one of the distinctive and curious properties of hallucinatory experience is the restricted range of its phenomenology. No matter what the source of the hallucinogenic event, essentially the same range of traits, motifs, perceptions and attributes tend to be evoked. This is also a point which Oliver Sacks stressed both explicitly and implicitly in his final neuroscientific work *Hallucinations* [77]. He described the recurring content of visionary experience as "fixed", "uniform" and "stereotyped". It stands to reason therefore that there must exist some type of shared or common transduction mechanism which can transform the raw heterogeneous hallucinogenic material into relatively homogeneous hallucinatory fare. This can be inferred because otherwise it would be difficult to account for the mostly limited, almost formulaic, content of visionary experience which is also one of the most distinctive and compelling features of the NDE. It is also a reasonable assumption that this hypothetical transduction operation also serves as the physical to mental transformer unit. It would be predicted therefore that the discovery of one should simultaneously uncover the other.

Of the two residual questions, discovering the transduction mechanism is probably a much more challenging problem than that of the role of the 5-HT2A receptor in controlling respiration. However once, or if, these two matters have been resolved, a near complete hypercarbia model of NDE generation should become available. It may also represent the most satisfactory neuroscientific explanation of the NDE so far.

Addendum: The Osirian temple initiation rites

There is some indication that the ancient Egyptians may have devised a technique for deliberately manufacturing synthetic NDEs [9]. This secret practice appears to have taken place in temples during consecration ceremonies for trainee priests. The purpose was to provide the young adepts with first hand evidence for the immortality of the soul as well as gaining a personal familiarity with the afterlife.

This potentially dangerous initiation rite involved a symbolic re-enactment of the death and subsequent resurrection of Osiris as king of the underworld. According to legend, Osiris was murdered by his jealous brother Seth by being trapped in a casket which was then sealed with molten lead and set adrift on the Nile. Eventually, Seth discovered Osiris' body and dismembered it. Later on, the pieces of the mutilated corpse were collected and reassembled by Osiris' sister-wife Isis with the help of his other sister Nephthys and son Horus. The myth of Osiris and his relatives (of which the above is only the barest description) is a powerful metaphor for ancient Egyptian beliefs concerning death, renewal and immortality [191, 193].

In a book originally published towards the end of the 19th century, The French historian and playwright

Edward Schure recreated what the otherworldly experience induced in the adepts entailed.

"His life passes before him in successive scenes....and his earthly consciousness becomes more and more vague and diffuse. But as he feels his body disintegrate, the ethereal part, the fluid of his being, is disengaged. He enters into ecstasy.... What is that shining, far distant point that appears imperceptible against the black background of the shadow? It is coming closer, it is growing larger, it is becoming a five-pointed star, whose rays include all the colors of the rainbow, and which shoots into the darkness discharges of magnetic light. Now there is a sun that attracts it into the brightness of its incandescent center...it is disappearing and in its place a flower blooms in the night, a flower not of matter, but sensitive and endowed with soul! It opens before him like a white rose;….then the ecstatic one feels flooded with a warm, caressing breeze. Having assumed strange forms, the cloud condenses and becomes a human figure...smiling and radiant...But everything bursts; the vision fades. With a horrible rending, the adept finds himself hurled into his body as into a corpse. He returns to a state of conscious lethargy.... a terrible weight presses upon his brain; he awakens." [194]

Ring [9] has remarked on the close association between the phenomenology of the NDE and the rapturous, shining and mystical vision induced during the initiation ritual. Exactly how such a NDE-like event was actually generated in the initiates remains uncertain. It could have conceivably involved hypothermia, psychedelic drugs or hypnotic trance. Be that as it may, there is circumstantial evidence that the crucial element involved the calculated and methodical suffocation of the subject while entombed in a sealed chest for several min before being revived [206, 207, 85, 19]. With the young priest temporarily entombed, the CO_2 concentration in the box would gradually rise as the O_2 supply diminished and more and more CO_2 is expired. These are ideal conditions for cultivating a state of asphyxia which may be defined as interference or disruption of normal respiration resulting in a progressive deprivation of O_2 accompanied by an accumulation of CO_2. Left uncontrolled, these circumstances will lead inexorably to death.

The asphyxiation technique employed in the Osirian initiation rites was basically just a more unpleasant variation of the rebreathing method which has been routinely employed to study ventilatory responses to CO_2 [208]. It would also be functionally similar to the CDT administered by Meduna and others. However, it would not be physiologically equivalent. This is because the carbogen mixture in CDT never had less than 70% O_2 content. Still, providing the dimensions of the chest plus the dwelling time inside were carefully controlled, this should have been a reasonably safe, albeit rather agonizing procedure. Morse has facetiously commented that probably quite a large number of slaves were sacrificed while the applied physiologists of ancient Egypt calibrated their apparatus [85].

It is also of historic scientific interest that the Scottish physiologist John Scott Haldane actually utilized a device quite reminiscent of the Osirian Temple's sealed casket. More than a century ago, Haldane and co-workers conducted a classic series of studies on the role of the HCVR in the regulation of breathing [217]. In one set of experiments, the subject's head was enclosed in an air tight box. This arrangement allowed the CO_2 in the expired breath to slowly accrue. Haldane himself served as one of the subjects but, for safety reasons, he terminated the procedure when the concentration of CO_2 in the box reached about 5%. Under these conditions no psychotomimetic symptoms would have been expected and none were reported in the paper.

When assessing the Osirian temple ritual, it is quite difficult to determine what is fact and what is merely imaginative speculation. One thing can be said with confidence is that if such a revelatory ceremony really did take place in the manner described, then the ecstatic experience can only have been

triggered by a state of suffocation. This is a realistic possibility because many of the pathophysiological events, conditions or circumstances which give rise to a NDE also involve a state of asphyxia. It can be inferred therefore that it must have been the well-documented visionary qualities of hypercarbia which were responsible for the otherworldly experience of the adept.

The present discussion demonstrates that the system employed by the Osirian disciples should have been quite capable of fabricating an artificial NDE. In addition, it is compatible with the hypercarbia model of how the NDE is generated. Further, the utility of the suffocating box in eliciting such visionary phenomena adds credibility to the idea that the particular Osirian temple practices outlined above were a genuine event and not just a fanciful and ingenious historic reconstruction.

The Osirian rites described here also a share a number of characteristics with the Eleusinian Mysteries [221]. The Mysteries were initiation ceremonies which were practiced in ancient Greece for the best part of a millennium. One point of difference was that of exclusivity in the case of the Egyptian rituals whereas in the Eleusinian Mysteries, there was relatively little restriction over those wishing to participate. At the climax of the Eleusinian ceremonies all the initiates underwent a transformative and transcendental event. Judging by contemporary accounts, this was an ethereal and spiritual experience near identical to that of the Osirian adepts.

The similarity between the peak experience of the Eleusinian Mysteries and the NDE has also been highlighted. For example, Zaleski [1] cites Plutarch when discussing his own initiation.

“The soul (at the point of death) has the same experience as those who are being initiated into the great mysteries.”

The NDEs described in both Plato’s *Republic* (The Vision of Er) and Cicero’s *Republic* (The Dream of Scipio) also probably owe much to the Eleusinian Mysteries as both men were celebrity initiates. Exactly what induced the ecstatic and otherworldly state in the Eleusinian graduates is itself an enduring mystery. It most definitely was not systematic suffocation. Instead, it was likely to have been a plant-derived psychedelic agent mixed into the cyceon beverage. In more recent times, Albert Hofmann popularized the idea that the active substance might have been a primitive congener of LSD derived from the fungus *Claviceps paspali* [222]. Irrespective of the exact nature of this hallucinogenic substance, it does seem plausible that it shared a final site and mode of action in the evocation of visionary phenomena with the asphyxia operating in the Osirian temple rituals. In both instances, it would be predicted that this involved the activation of the cortical circuits and networks underlying a psychedelic state by the agonistic stimulation of 5-HT2A subreceptors.

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