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The Ketamine Model of the Near-Death Experience: A Central Role for the N-Methyl-D-Aspartate Receptor

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ABSTRACT: Near-death experiences (NDEs) can be reproduced by ketamine via blockade of receptors in the brain for the neurotransmitter glutamate, the N-methyl-D-aspartate (NMDA) receptors. Conditions that precipitate NDEs, such as hypoxia, ischemia, hypoglycemia, and temporal lobe epilepsy, have been shown to release a flood of glutamate, overactivating NMDA receptors and resulting in neurotoxicity. Ketamine prevents this neurotoxicity. There are substances in the brain that bind to the same receptor site as ketamine. Conditions that trigger a glutamate flood may also trigger a flood of neuroprotective agents that bind to NMDA receptors to protect cells, leading to an altered state of consciousness like that produced by ketamine.

The near-death experience (NDE) is a phenomenon of considerable importance to medicine, neuroscience, neurology, and psychiatry (Greyson and Stevenson, 1980; Jansen, 1989a, 1989b, 1990b; Ring, 1980; Sabom, 1982; Stevenson and Greyson, 1979). Recent advances in neuroscience are bringing us closer to a scientific understanding of this intriguing altered state of consciousness. Irrespective of personal religious and philosophical beliefs, NDEs are not evidence for life after death on simple logical grounds: death is defined as the final, irreversible end. The *Oxford English Dictionary* (Sykes, 1982) refers to death as the "*final* cessation of vital functions" (*italics added*). Those who have "returned" did not, by definition, die, al-

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though their minds, brains, and bodies may have been in a very unusual state. The theory developed in this paper makes no attempt to address religious beliefs about events after death, but does argue that persons who report NDEs have not died.

There is overwhelming evidence from thousands of studies relating brain events to alterations in mental state that "mind" results from neuronal activity. The dramatic effects on the mind of adding hallucinogenic drugs to the brain, and the religious experiences that sometimes result, provide further evidence for this (Grinspoon and Bakalar, 1979). Within a scientific paradigm, it is not possible that the "spirit rises out of the body, leaving the brain behind, but somehow still incorporating neuronal functions such as sight, hearing, and proprioception" (Morse, 1989, p. 225).

Features that have been associated with NDEs can be reproduced by the intravenous administration of 50 to 100 milligrams of ketamine (Collier, 1972; Domino, Chodoff, and Corssen, 1965; Ghoneim, Hinrichs, Mewaldt, and Peterson, 1985; Grinspoon and Bakalar, 1979; Jansen, 1989a, 1989b, 1990b, 1993; Lilly, 1978; Rogo, 1984; Rumpf, Pedick, Teuteberg, Munchhoff, and Nolte, 1969; Siegel, 1978, 1980, 1981; Sputz, 1989; Stafford, 1977; White, Way, and Trevor, 1982). There is increasing evidence suggesting that the reproduction of NDEs by ketamine is unlikely to be a coincidence. This evidence includes the discovery of the major neuronal binding site for ketamine, known as the phencyclidine (PCP) binding site of the N-methyl-D-aspartate (NMDA) receptor (Thomson, West, and Lodge, 1985); the importance of NMDA receptors in the cerebral cortex, particularly in the temporal and frontal lobes; the key role of these sites in cognitive processing, memory, and perception; their role in epilepsy, psychoses (Jansen and Faull, 1991), hypoxia/ischemia, and epileptic cell damage (excitotoxicity); the prevention of this damage by ketamine; the discovery of substances in the brain called "endopsychosins," which bind to the same site as ketamine; and the role of ions such as magnesium and zinc in regulating the site (Anis, Berry, Burton, and Lodge, 1983; Barnes, 1988; Ben-Ari, 1985; Benveniste, Drejer, Schousboe, and Diemer, 1984; Choi, 1988; Coan and Collingridge, 1987; Collingridge, 1987; Contreras, DiMaggio, and O'Donohue, 1987; Cotman and Monaghan, 1987; Jansen, 1989a, 1989b, 1990a, 1990b, 1991, 1993; Jansen and Faull, 1991; Jansen, Faull, and Dragunow, 1989; Jansen, Faull, Dragunow, and Leslie, 1991; Jansen, Faull, Dragunow, and Synek, 1990; Mody and Heinemann, 1987; Monaghan, Bridges, and Cotman, 1989; Nowak, Ber-

gestovski, Ascher, Herbet, and Prochiantz, 1987; Quirion, Chicheportiche, Contreras, Johnston, Lodge, Tam, Woods, and Zukin, 1987; Quirion, DiMaggio, French, Contreras, Shiloach, Pert, Everist, Pert, and O'Donohue, 1984; Rothman and Olney, 1987; Simon, Swan, Griffiths, and Meldrum, 1984; Sonders, Keana, and Weber, 1988; Thomson, 1986; Westbrook and Mayer, 1987).

Characteristic Features of the Near-Death Experience

There is no internationally determined and agreed upon set of criteria that define the NDE, no list of "research diagnostic criteria" similar to those provided by the American Psychiatric Association (APA) for psychiatric disorders. This lack has allowed some critics of neurobiological models to dismiss those models because some particular criterion they consider important was not fully accounted for by the model being proposed, although it may well be that a consensus, statistical definition of the key features of the NDE would not include those features—just as, for example, the APA definition of schizophrenia (American Psychiatric Association, 1994) represents an international consensus and avoids the sectarian views of a few, or inclusion of obscure cases that do not meet the general rule.

For example, Glen Gabbard and Stuart Twemlow (1989) argued that Juan Saavedra-Aguilar and Juan Gómez-Jeria's neurobiological hypothesis (1989), which was based on temporal lobe electrical abnormalities, did not have general validity because Gabbard and Twemlow had identified five cases in which hypoxia and stress did not appear to be a triggering factor. These cases are certainly not adequate grounds for the dismissal of neurobiological models.

Ketamine administered by intravenous injection in appropriate dosage can reproduce all the features of the NDE that have been commonly described in the most cited works in this field (Collier, 1972; Domino, Chodoff, and Corssen, 1965; Ghoneim, Hinrichs, Mewaldt, and Peterson, 1985; Grinspoon and Bakalar, 1979; Jansen, 1989a, 1989b, 1990b, 1991, 1993; Lilly, 1978; Rogo, 1984; Rumpf, Pedick, Teuteberg, Munchhoff, and Nolte, 1969; Siegel, 1978, 1980, 1981; Spitz, 1989; Stafford, 1977; White, Way, and Trevor, 1982), and the account outlined below is based upon these works and also upon NDEs described to me. Unfortunately, the study in which persons who have had NDEs are given ketamine and asked to compare the

two experiences has yet to be carried out. Information in this area remains anecdotal.

I have experienced several NDEs and have also been administered ketamine as an anesthetic and within experimental paradigms. The NDEs and the ketamine experiences were very similar. Ketamine produced effects that were like the NDEs described by Bruce Greyson and Ian Stevenson (1980), by Melvin Morse, Doug Conner, and Donald Tyler (1985), by Raymond Moody (1975), by Russell Noyes and Roy Kletti (1976a), by Kenneth Ring (1980), and by Michael Sabom (1982). Ketamine produced travel through a tunnel, emergence into the light, and a "telepathic" exchange with an entity that could be described as "God," although I have no religious beliefs and had no particular expectations on first experiencing the drug. Neither the NDEs nor the ketamine experiences bore any resemblance to the effects of psychedelic drugs such as dimethyltryptamine (DMT) and lysergic acid diethylamide (LSD), in contradistinction to a previous assertion by Scott Rogo that ketamine "induces a short psychedelic 'trip' resembling that induced by lysergic acid diethylamide (LSD)" (1984, p. 88).

Important features of NDEs include a sense that what is experienced is "real" and that one is actually dead, a sense of ineffability, timelessness, and feelings of calm and peace, although some cases have been frightening. There may be analgesia, apparent clarity of thought, a perception of separation from the body, and hallucinations of landscapes and beings such as "angels" or people, including partners, parents, teachers and friends (who may be alive at the time), and religious and mythical figures. Transcendent mystical states are commonly described. Memories may emerge into consciousness, and are sometimes organized into a "life review" (Greyson, 1983). Hearing noises during the initial part of the NDE has also been described (Greyson and Stevenson, 1980; Morse, Conner, and Tyler, 1985; Noyes and Kletti, 1976a; Osis and Haraldsson, 1977; Ring, 1980; Sabom, 1982).

Kenneth Ring (1980) classified NDEs on a five-stage continuum: (1) feelings of peace and contentment; (2) a sense of detachment from the body; (3) entering a transitional world of darkness (the "tunnel experience"); (4) seeing a bright light; and (5) "entering the light." Sixty percent of NDErs interviewed by Ring experienced stage 1, but only 10 percent attained stage 5 (Ring, 1980). As might be expected in a mental state with a neurobiological origin, more mundane accounts also occur, such as children who may "see" their schoolfellows rather than God and angels (Morse, Conner, and Tyler, 1985).

Ketamine and Phencyclidine

Ketamine, first synthesized in 1962 by Calvin Stevens (McCarthy, 1981), is a short-acting, hallucinogenic, dissociative anesthetic related to phencyclidine (PCP). Both ketamine and PCP are arylcyclohexylamines; they are not opioids and are not related to LSD. In contrast to PCP, ketamine is relatively safe, an uncontrolled drug in most countries, and is used as an anesthetic for children (White, Way, and Trevor, 1982). Anesthetists attempt to prevent patients from having NDEs or "emergence phenomena" by the co-administration of benzodiazepines and other sedative substances that produce "true" unconsciousness rather than dissociation (Reich and Silvay, 1989).

Ketamine produces an altered state of consciousness that is very different from that of "psychedelic" drugs such as LSD (Grinspoon and Bakalar, 1979). As noted in the references cited above, it can reproduce all features of the NDE, including travel through a dark tunnel into light, the conviction that one is dead, apparent "telepathic communion with God," hallucinations, out of-body experiences, and mystical states. If given intravenously, it has a brief action with an abrupt end. Lester Grinspoon and James Bakalar wrote of

becoming a disembodied mind or soul, dying and going to another world. Childhood events may also be re-lived. The loss of contact with ordinary reality and the sense of participation in another reality are more pronounced and less easily resisted than is usually the case with LSD. The dissociative experiences often seem so genuine that users are not sure that they have not actually left their bodies. (1979, p. 34)

A psychologist who had had experiences with LSD described ketamine as "experiments in voluntary death" (Leary, 1983, p. 375). Ramses Sputz noted:

One infrequent K [ketamine] user reports a classic near-death experience during his first trip. "I was convinced I was dead. I was floating above my body. I reviewed all of the events of my life and saw a lot of areas where I could have done better." (1989, p. 65)

Psychiatrist Stanislav Grof stated: "If you have a full-blown experience of ketamine, you can never believe there is death or that death can possibly influence who you are" (Stevens, 1989, p. 481-482). Anesthesiologist Barbara Collier reported that "ketamine allows some patients to reason that . . . the strange, unexpected intensity and

unfamiliar dimension of their experience means they must have died" (Collier, 1981, p. 552).

Attempts to explain NDEs as hallucinations are sometimes rejected by spiritualists because many persons insist upon the reality of their experiences (Osis and Haraldsson, 1977; Ring, 1980). However, 30 percent of normal subjects given ketamine were certain that they had not been dreaming or hallucinating, but that the events had really happened (Rumpf, Pedick, Teuteberg, Munchhoff, and Nolte, 1969; Siegel, 1978). The American Psychiatric Association defined a hallucination as "a sensory perception that has the compelling sense of reality of a true perception but that occurs without external stimulation Transient hallucinatory experiences may occur in people without mental disorder" (American Psychiatric Association, 1994, p. 767).

The apparently clear sensorium of some persons who have had NDEs has also been used to argue that the NDE is "real" and not a hallucination (Osis and Haraldsson, 1977; Ring, 1980). It is thus important to note that hallucinations in schizophrenia typically occur in clear consciousness and are perceived to be real (American Psychiatric Association, 1994). A personal conviction of the "reality" of an NDE does not invalidate scientific explanations. Some users of LSD have claimed that their minds were clearer than usual, and that the LSD world is real while the "normal" world is a veil of illusion (Grinspoon and Bakalar, 1979). Cardiac arrest survivors sometimes describe their resuscitation in detail (Sabom, 1982). Ketamine can permit sufficient sensory input to allow accounts of procedures during which the patient appeared wholly unconscious (Siegel, 1981).

One of the objections that has been raised against ketamine models of the NDE is that NDEs have been reported to be characterized by a sense of peace and well-being (Ring, 1980), while ketamine experiences are sometimes unpleasant, involving considerable anxiety. This objection arises largely from the manner in which data have been collected. For example, to investigate the NDE as Ring did requires that one have a pre-existing definition of what one is investigating. Such a definition will exclude many other mental phenomena that may be produced by the same neurochemical events as the NDE, just as ketamine produces a considerably wider range of phenomena than the NDE. It is reasonable to suppose that if all persons who had a cardiac arrest and were "unconscious" for a period were to be interviewed, many would not be able to report an altered state of any kind, just as many persons given ketamine can recall

nothing of the experience. There would then be varying percentages in both the cardiac arrest and ketamine groups who would report a range of phenomena, of which the NDE would be only one. Certainly a percentage of persons who have had cardiac arrests, for example, would report nightmares, anxiety, and panic.

Thus the argument that the neurochemical events induced by ketamine cannot explain "real" NDEs because ketamine also has other effects is weakened by the probability that factors precipitating "real" NDEs also have other psychological effects. As Rogo (1984) has pointed out, set and setting may go some way toward explaining the occasional incidence of anxiety reported in the ketamine literature. Anesthetists have reported that manipulations of set and setting can eliminate negative ketamine reactions (Cunningham and McKinney, 1983; Sklar, Zukin, and Reilly, 1981). It is also the case that ketamine's popular reputation for inducing nightmares is not well supported by the published scientific data; the "negative affect" is partly a myth. For example, the plastic surgeons Bruce Cunningham and Peter McKinney found "that many patients felt the hallucinatory phenomena to be pleasant and experienced no real concern or fear" (1983, p. 24). Garry Sklar, Stephen Zukin, and Thomas Reilly (1981) demonstrated that an informed patient who had good rapport with the anesthesiologist could experience the vivid imagery of full-dose ketamine without becoming frightened or alarmed. The marked increase in recreational use of ketamine (Stafford, 1992) is unlikely to have occurred were it to induce a large number of experiences characterized by negative affect.

Peter Stafford (1992) has described six broad categories of ketamine experience, and five of these can be related to near-death phenomena. This does not suggest that there is an endless heterogeneity of experience. A survey of both NDE and ketamine literatures does not support the argument that NDEs are more homogeneous and invariant than ketamine experiences.

Glutamate, NMDA and Sigma Receptors, and the Hippocampus

Most large neurons in the cerebral cortex use glutamate as their neurotransmitter. Glutamate, an excitatory amino acid, is central to the function of the hippocampus, a structure in the medial temporal lobe involved in memory and emotion and in integrating inputs from

many parts of the brain (Cotman, Monaghan, Ottersen, and Storm-Mathisen, 1987; Fagg and Foster, 1983; Greenamyre, Young, and Penney, 1984; Jansen, Faull, and Dragunow, 1989; Jansen, Faull, Dragunow, and Synek, 1990; Monaghan, Bridges, and Cotman, 1989; White, Nadler, Hamburger, Cotman, and Cummins, 1977) and plays a vital role in all cognitive processes involving the cerebral cortex, including thinking, memory, and perception (Monaghan, Bridges, and Cotman, 1989; Oye, Paulsen, and Maurset, 1992; Squire and Zola-Morgan, 1988).

There is a binding site for ketamine and PCP, called the PCP receptor, attached to the NMDA receptor (Monaghan, Bridges, and Cotman, 1989). As they are part of the same entity, the two terms "PCP receptor" and "NMDA receptor" are sometimes used interchangeably. It was formerly believed that the sigma and PCP sites were the same entity, but it is now clear that sigma receptors have a unique distribution in the central nervous system and are not a form of opioid receptor (Jansen, Faull, Dragunow, and Leslie, 1991; Walker, Bowen, Walker, Matsumoto, De Costa, and Rice, 1990).

When the glutamate theory of the NDE was first proposed (Jansen, 1990b), it was not clear whether the hallucinogenic properties of ketamine were due to NMDA or sigma receptors. It is now known that these effects are due to NMDA receptor blockade (Krystal, Karper, Seibyl, Freeman, Delaney, Bremner, Heninger, Bowers, and Charney, 1994), and that sigma receptors do not play an important role. Substances that bind to sigma receptors frequently have some affinity for NMDA and kappa opioid receptors at higher doses; but substances that bind to sigma receptors with a high degree of specificity, such as (+)pentazocine, do not produce NDEs at doses at which most of the binding is to sigma rather than NMDA and kappa opioid receptors (Musacchio, Klein, and Canoll, 1990; Walker, Bowen, Walker, Matsumoto, DeCosta, and Rice, 1990).

Glutamate is excitatory. When present in excess, neurons die via a process called excitotoxicity. This is the mechanism of neuronal cell death in hypoxia/ischemia and epilepsy, conditions that have been proven to lead to excessive release of glutamate (Rothman, 1984; Rothman and Olney, 1986, 1987). Blockade of PCP receptors prevents cell death from excitotoxicity (Meldrum, 1987; Rothman, Thurston, Hauhart, Clark, and Solomon, 1987). This suggests that the brain may have a protective mechanism against the detected glutamate flood: a counter-flood of a substance that binds to the PCP receptor, preventing cell death. The brain is a well-protected organ with many

known defenses; it is reasonable to propose that it has protective mechanisms against excitotoxicity. This hypothetical defensive flood of substances to block the PCP receptors is the only speculation in the process outlined above; the other statements are strongly supported by experimental evidence (Ben-Ari, 1985; Benveniste, Drejer, Schousboe, and Diemer, 1984; Hoyer and Nitsch, 1989; King and Dingledine, 1986; Lobner and Lipton, 1990; Rothman, Thurston, Hauhart, Clark, and Solomon, 1987; Simon, Swan, Griffiths, and Meldrum, 1984; Westerberg, Monaghan, Cotman, and Wieloch, 1987). Endogenous substances have been found in the brain that bind to the PCP receptor, one of which is a peptide called alpha-endopsychosin (Quirion, DiMaggio, French, Contreras, Shiloach, Pert, Everist, Pert, and O'Donohue, 1984).

Explanations for the NDE

Some investigators have argued that the NDE must have a single explanation and then presented anecdotes to counter each of the scientific theories that have been proposed (for example, Ring, 1980) or have required that any scientific theory put forward must explain all of the experiences that have been labeled as NDEs (for example, Gabbard and Twemlow, 1989). It is more likely that the NDE is a final common expression of several different causes. Even then, the final "common" expression contains sufficient variability to suggest different types of NDE with different explanations. A multi-leveled interpretation is thus the most useful. The glutamate hypothesis of the NDE is not intended to apply to all NDEs, nor is it incompatible with many of the theories described below.

Psychological hypotheses

Depersonalization. The NDE may be an adaptive mechanism that alerts one to the threat of death while potentially overwhelming emotion is held at bay allowing the reality to be integrated without panic (Greyson, 1983; Noyes and Kletti, 1976a, 1976b). This model is applicable when death is psychologically near, as in falling from a cliff. While protecting nerve cells from ischemic damage is then largely irrelevant, glutamate and NMDA receptors would certainly be in-

volved in producing the experience, as they play a key role in cognition and perception.

Regression in the Service of the Ego. Confronting death cuts off the external world, resulting in regression to a preverbal level of development experienced as mystical ineffability (Greyson, 1983). Loss of contact with the external world is one of the most characteristic effects of ketamine, and is probably due to blockade of NMDA receptors involved in sensory transmission. NMDA receptors play a central role in the transmission of incoming signals from all sensory modalities (Cline, Debski, and Constantine-Paton, 1987; Cotman, Monaghan, Ottersen, and Storm-Mathisen, 1987; Davies and Watkins, 1983; Greenamyre, Young, and Penney, 1984; Headley, West, and Roe, 1985; Kisvardy, Cowey, Smith, and Somogyi, 1989; Monaghan, Bridges, and Cotman, 1989; Oye, Paulsen, and Maurset, 1992).

State-Dependent Reactivation of Birth Memories. Movement through tunnels towards light may be a memory of being born, a "near-birth experience" (Grof and Halifax, 1977). NMDA receptor blockade could be the underlying mechanism for such a reactivation of primitive memories.

Sensory Deprivation. John Lilly (1978) explored ketamine as a means of inducing sensory deprivation, as a development of his work with sensory deprivation induced by flotation tanks. The observation that ketamine induces sensory deprivation was also explored by Barbara Collier (1972), who provided detailed accounts of NDEs induced by ketamine, including patients who claimed that they had died, separated from their bodies, and ascended to heaven.

How can sensory deprivation produce an altered state of consciousness? Memories may normally be suppressed by a mechanism that acts as a gate, admitting primarily external signals when we are fully conscious and concentrating on an external task (Siegel, 1980, 1981). If this input is dramatically reduced, for example, by ketamine or a heart attack, in combination with central stimulation, for example, by excessive glutamate release during hypoxia or epilepsy, stored perceptions are released and become "organized" into a meaningful experience by the mind (Greyson, 1983).

The hippocampus is the anatomical location of such a gate, and NMDA receptors form the molecular substrate of the gate. NMDA receptors have their highest concentration in the hippocampus, a part of the medial temporal lobe where data from the external world are integrated with internal programs. The NMDA receptor plays an important role in learning, and in the formation and retrieval of memo-

ries. The PCP receptor is referred to as a "gated channel" (Foster and Flagg, 1987). Whether the gate is open or closed depends on the degree of excitation, specifically, the position of a magnesium ion in the channel (Mayer, Westbrook, and Guthrie, 1984). Ketamine blocks this channel and closes the gate to incoming data (Collingridge, 1987; Cotman, Monaghan, and Ganong, 1988; McNaughton and Morris, 1987; Monaghan, Bridges, and Cotman, 1989; Morris, Anderson, Lynch, and Baudry, 1986).

The "white light" may result from central nervous system stimulation mimicking light on the retina, and a lowering of the phosphene perceptual threshold (Siegel, 1980, 1981). Sensory deprivation itself can produce profound alterations in consciousness (Lilly, 1961, 1978).

Drug-Induced Hallucinations

Administered drugs may explain some cases of NDEs, but in many no drugs were given with effects resembling the NDE (Sabom, 1982).

Temporal Lobe Epilepsy

Michael Persinger and Kate Makarec (1987) and Juan Saavedra-Aguilar and Juan Gómez-Jeria (1989) have reviewed evidence for the similarity between the phenomena experienced in temporal lobe epilepsy and NDEs. Glutamate is the key neurotransmitter in the temporal lobe, particularly in the hippocampus, and plays an important role in epilepsy. The neuropathology of epilepsy is believed to result from excitotoxic cell death (Ben-Ari, 1985; Cotman, Monaghan, and Ganong, 1988; King and Dingledine, 1986; Mody and Heinemann, 1987; Olney, Collins, and Sloviter, 1986; Sloviter, 1983).

It is possible that the postulated endogenous neuroprotective system becomes active in any excitotoxic situation, including temporal lobe epilepsy. The degree of excitotoxic cell damage, and the mental state, resulting from an incident in which there is a glutamate flood, whatever the cause, may depend on the final balance in each neuronal pathway between excitotoxic forces and neuroprotective mechanisms. This theory is supported by reports of persons who were oxygen deprived for prolonged periods, had a profound NDE, and survived the episode unimpaired (Sabom, 1982). The lack of apparent brain damage in these cases is hard to explain unless we postulate

that these may be persons with a particularly effective mechanism for glutamatergic blockade.

It is also possible that there is no protective mechanism, and that ketamine exerts its effects by mimicking some of the processes seen in temporal lobe epilepsy. Even though ketamine blocks glutamatergic transmission and prevents excitotoxic cell death, the effect of ketamine upon the human electroencephalograph (EEG) suggests that the final result of ketamine acting in the brain is the result of a complex interplay of forces. There is a reduction in alpha wave activity, while beta, delta, and theta wave activity are increased (Pichlmayr, Lips, and Kunkel, 1984; Schwartz, Virden, and Scott, 1974).

Ketamine has been reported to act both as an anticonvulsant (Ceslesia and Chen, 1974; Leccese, Marquis, Mattia, and Moreton, 1986; Mares, Lansitiakova, Vankova, Kubova, and Velisek, 1992; McCarthy, Chen, Kaump, and Ensor, 1965; Taberner, 1976) and as a convulsant (Bennet, Madsen, Jordan, and Wiser, 1973; Gourie, Cherian, and Shankar, 1983; Myslobodsky, Golovchinsky, and Mintz, 1981). M. S. Myslobodsky, V. Golovchinsky, and M. Mintz (1981) reported that ketamine could produce epileptiform EEG patterns in human limbic and thalamic regions, but that there was no evidence that this affected other cortical regions or that clinical seizures were likely to occur. This is quite consistent with the NDE model presented by Saavedra-Aguilar and Gómez-Jeria (1989) involving limited electrical abnormalities in the limbic system.

Thus the production of NDEs by ketamine is not necessarily at odds with the proposal that NDEs may result from abnormal electrical activity. David Reich and George Silvay concluded: "It is hard to draw objective conclusions regarding the anti-convulsant properties of ketamine Animal data are particularly difficult to interpret, because of inter-species variations" (1989, p. 188). Nevertheless, the weight of the evidence favors the conclusion that ketamine is probably anticonvulsant at the doses required to produce the NDE (Myslobodsky, Golovchinsky, and Mintz, 1981), favoring the hypothesis that an NMDA receptor blocker is released to produce the NDE.

Franz Vollenweider (1996) recently investigated the effects of ketamine using fluorodeoxyglucose-positron emission tomography (FDG-PET), a method that permits the imaging of metabolic activity in the brain. Subjects were given the drug and then had their altered states assessed using the Altered States of Consciousness Question-

naire, the Ego Pathology Inventory, and the inventory of the Association for Methodology and Documentation in Psychiatry. Imaging of brain activity indicated that "oceanic boundlessness" was strongly correlated with metabolic hyperactivity in the frontal cortex, "visionary restructuralization" was linked mainly to changes in the occipital cortex, and "dread of ego dissolution" was linked with changes in the thalamus and subcortical areas.

Endorphin Release

Daniel Carr (1981, 1989) proposed that NDEs resulted from a flood of endogenous opioids, or endorphins, as survival time was increased by giving opiate antagonists, such as naloxone, in fatal circumstances (Holaday and Faden, 1978). More recently, a sudden increment of beta-endorphin has been reported in the brain and body fluids of dogs who are "conscious" at the moment of death (Sotelo, Perez, Guevara, and Fernandez, 1995). The concept of a flood release of endogenous compounds is valuable, and it has now been established, as noted above, that a glutamate flood results in excitotoxic cell death in hypoxia/ischemia and epilepsy.

However, endorphins are not responsible for the NDE, as they are not potent hallucinogens (Oyama, Jin, Yamaga, Ling, and Guillemin, 1980). Injection of beta-endorphin into the cerebrospinal fluid has analgesic effects lasting well over 22 hours (Oyama, Jin, Yamaga, Ling, and Guillemin, 1980). This does not match the time course of a typical NDE, which is relatively brief.

Ketamine produces brief, deep analgesia (White, Way, and Trevor, 1982) due to NMDA or PCP receptor blockade (Parsons, Gibbens, Magnago, and Headley, 1988; Schoenberg and Sjolund, 1986). The limited psychotomimetic properties of some opioids, such as (-)pentazocine, result from binding to kappa opioid receptors, and to PCP receptors at higher doses (Musacchio, Klein, and Canoll, 1990; Pfieffer, Brantl, Jerz, and Emrich, 1986). However, the effects of (-)pentazocine binding to kappa receptors are described as feelings of cheerfulness and strength (Bellville and Forrest, 1968). The effects of selective and specific drug binding to kappa receptors do not match the profound alterations in consciousness produced by ketamine. With higher doses, more marked effects may appear as a result of binding to PCP receptors.

Claims that sigma-selective (+)isomers of benzomorphan opiates have psychotomimetic effects are not supported by the extensive literature based on research in humans, carried out in the 1960s, which demonstrated that it is the (-)isomers that have psychotomimetic properties, and those may prefer PCP receptors rather than sigma sites (Musacchio, Klein, and Canoll, 1990). The naloxone-reversible component is due to kappa opioid receptor binding, while the naloxone-insensitive component is due to PCP or NMDA receptor binding, not sigma binding (Walker, Bowen, Walker, Matsumoto, De Costa, and Rice, 1990). The role of opioid receptors in ketamine effects is controversial (Reich and Silvay, 1989). Naloxone could not reverse the effects of ketamine in humans (Amiot, Bouju, and Palacci, 1985), nor in dogs (Vaupel, 1983).

It is important to note that ketamine is supplied as a mixture of (+)ketamine and (-)ketamine isomers. Some of the controversy may be resolved by an improved understanding of the separate effects of the isomers and the doses at which they appear. As doses rise, the probability that drugs will bind to a wider range of receptors also rises. In this context, it is important to note that ketamine can induce NDEs at doses about four times less than those required for anesthesia (Grinspoon and Bakalar, 1979; Lilly, 1978; Sputz, 1989; Stafford, 1977).

Paul White, Jay Ham, Walter Way, and Anthony Trevor (1980) reported that it was (+)ketamine that has some opioid binding properties and that produced the most anesthesia, while (-)ketamine produced more "psychic emergence reactions," or NDEs. White, Jurgen Schuttler, Audrey Schafer, Donald Stanski, Yukio Horai, and Trevor (1985) went on to show that (+)ketamine is about four times more potent as a hypnotic and analgesic, and has different effects upon the EEG than (-)ketamine, which may explain some of the confusion concerning whether ketamine is an anticonvulsant or a convulsant (Myslobodsky, Golovchinsky, and Mintz, 1981).

Saavedra-Aguilar and Gómez-Jeria (1989) have presented evidence from animal experiments that beta-endorphin may be epileptogenic (Henriksen, Bloom, McCoy, Ling, and Guillemin, 1978; McGinty, Kanamatsu, Obie, and Hong, 1986) to support their argument that beta-endorphin produces NDEs. While beta-endorphin may have these effects within the rat experimental paradigms used, it is common clinical experience that opioids do not induce epilepsy in humans (Meltzer, 1987). It seems more probable that released peptides would have protective functions rather than contributing further to excito-

toxicity. Saavedra-Aguilar and Gómez-Jeria (1989) also cited the finding of Tsung-Ping Su, Edythe London, and Jerome Jaffe (1988) that some steroids bind to sigma receptors, suggesting that steroids could play a role in NDEs. In fact, the steroid in question was progesterone, which is certainly not a hallucinogen, and S. Schwarz, P. Pohl, and G.-Z. Zhou (1989) have suggested that the affinity of progesterone for the sigma site is insufficient to result in significant receptor occupancy. It is possible that the endogenous ligand for the PCP channel is not a peptide but an ion or some other class of compound. Magnesium and zinc are involved in inhibiting the action of the NMDA receptor (Cotman, Monaghan, and Ganong, 1988; Thomson, 1986; Westbrook and Mayer, 1987).

Abnormalities in Blood Gases

Hypoxia. Richard Blacher (1980) suggested that hypoxia might give rise to the NDE. This proposal has been criticized by some authors (Sabom, 1982), because studies involving a slow fall in inspired oxygen produce mental clouding rather than NDEs (Henderson and Haggard, 1927). However, these studies are not an accurate model of events in, for example, cardiac arrest. Sudden hypoxia causes an excessive release of glutamate with resulting excitotoxicity, which can be prevented, as noted above, by ketamine.

Hypercapnia. A carbon-dioxide-enriched breathing mixture can result in typical near-death phenomena such as bodily detachment and the perception of being drawn towards a bright light. Diverse personality types produced similar reports, suggesting a shared neurological substrate (Meduna, 1950).

Serotonin

Like endorphins, serotonin effects may be contributory but do not play a central role in the NDE. Psychedelic drugs such as LSD are serotonergic in action, yet the psychedelic mental state is very different from the NDE. LSD frequently involves an overwhelming increase in sensory input from the external environment (Grinspoon and Bakalar, 1979), in sharp contrast to the cataleptic dissociation produced by ketamine. Psychedelic visual phenomena bear little relationship to the dreamlike images of ketamine and the NDE. The

"ego dissolution" experienced on LSD has a different quality from the conviction of having died that may arise with ketamine, and loss of contact with the external environment leading rapidly to the "tunnel experience" is not a typical psychedelic drug effect, although it may occur. Alexander Shulgin, a pioneer in the psychedelic movement, has argued that the dissociative anesthetics have little in common with psychedelic drugs (Shulgin and Shulgin, 1991).

Conclusion

The NDE is an important phenomenon that can safely be reproduced by ketamine, and the glutamate theory of the NDE can thus be investigated by experiment. Recent advances in neuroscience strongly suggest a common origin for ketamine experiences and the NDE in events occurring at glutamatergic synapses, mediated by the NMDA (PCP) receptor.

This theory represents an extension of previous hypotheses, and incorporates most of the neurobiological and psychological theories that have been put forward. It links many of these ideas, such as hypoxia, peptide release, temporal lobe epilepsy, regression in the service of the ego, reactivation of birth memories, and sensory deprivation, rather than being an alternative to them. Most of the planks on which this hypothesis is built are strongly supported by experimental evidence implicating glutamate and the NMDA receptor as unifying entities in the processes leading to an NDE. The main exception to this is the postulate that anti-excitotoxic agents can flood the brain, which remains to be clearly established.

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