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Neuroscience and the Near-Death Experience: Roles for the NMSA-PCP Receptor, the Sigma Receptor and the Endopsychosins

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Abstract — The Near-Death Experience (NDE) is a dissociative mental state with characteristic features. These can be reproduced by ketamine which acts at sigma sites and blocks N-methyl-D-aspartate (NMDA) linked phencyclidine (PCP) receptors to reduce ischaemic damage. Endogenous ligands, alpha and beta-endopsychosin, have been detected for these receptors which suggests an explanation for some NDE's: the endopsychosins may be released in abnormal quantity to protect neurons from ischaemic and other excitotoxic damage, and the NDE is a side effect on consciousness with important psychological functions.

Introduction

The NDE, once the subject of popular books and films, has now assumed a lower profile due to lack of new data and repeatable experiments. Although well verified and of medical significance (1–4, 13, 16, 45), researchers have also been deterred by claims that it is evidence for life after death, which impart the air of a pseudoscience to its study (5). That the NDE can be reproduced by ketamine has, with some exceptions (6, 7), been seen as no more than a curiosity as the dying are not given such drugs. Discovery of endogenous peptides which act at the same receptors as ketamine (8, 9, 10), and the neuroprotective effects of this drug (11, 12, 40), suggest a specific mechanism for some NDE's which may be tested by experiment.

The near-death experience

NDE's during a medical crisis typically include ineffability, timelessness, a sense that what is experienced (such as 'seeing spirits') is 'real' and one is actually dead, and predominant feelings of calm, peace and tranquillity. There may be analgesia, apparent clarity of thought, a perception of separation from the body, and hallucinations of vivid landscapes, angels, people, and religious and mythical figures (1–5, 16, 17). A five stage continuum has been defined: feelings of peace and contentment; a sense of detachment from the body; entering a transitional world of darkness (some describe rapid movement through a tunnel); emerging into bright light; 'entering the light', (13). Ring found 60% experienced stage 1, with a decline to only 10% at stage 5 (13).

Transcendent mystical states are common while panoramic life reviews are rare (16, 45). More mundane accounts also occur, e.g. children who may 'see' their teachers and schoolfellows rather than angels (14).

Explanations for the NDE

Some declare that the NDE must have a single explanation and then present anecdotes to counter each scientific theory (13). It is more likely to be a final common pathway for several causes, with a multi-levelled interpretation being the most useful (15, 16). The PCP hypothesis does not apply to all NDE's nor is it incompatible with the theories below.

Psychological

1. Depersonalisation: an adaptive mechanism which alerts one to the threat of death while potentially overwhelming emotion is held at bay, allowing the reality to be integrated without panic (15, 17, 18). This is most applicable where death is psychologically near as when falling from a cliff (17, 18). While protection from ischaemia is then irrelevant, PCP and sigma receptors may still be involved in generating the altered state.
2. Regression in the service of the ego: confronting death cuts off the external world, resulting in regression to a pre-verbal level experienced as mystical ineffability (15).
3. A state dependent reactivation of birth memories (19, 20).
4. Sensory deprivation: memories may normally be suppressed by a mechanism which acts as a gate to data from the outside. If this external input is decreased while awareness remains, stored perceptions are released and may be dynamically organised (6, 7).

Drug-induced hallucinations

Administered drugs may explain a few cases, but in most no hallucinogens have been given (4, 5, 13).

Endorphin release

Positive effects on survival time when opiate antagonists are given in fatal circumstances (21, 22, 23) may support the view that a flood of opiates is released near death (23, 26). Release of centrally active peptides may be a general feature of dying, regardless of means, just as other sets of hormonal/neurochemical responses are seen in such situations as women giving birth, leading to 'peak experiences' (23). All are familiar with the abrupt mental and physical changes resulting from a severe fright, an effect partly due to an adrenaline deluge. However, while endorphins may play a role in the NDE, they are not potent hallucinogens. Furthermore, injection of beta-endorphin into CSF has effects lasting well over 22 hours (24). Ketamine can produce profound analgesia for a short period (25).

Temporal lobe epilepsy

This is another complementary theory as NMDA-PCP receptors may play a role in epilepsy (27), and ketamine has some anti-convulsant properties (28). Thus a natural PCP channel blocker may also be an anti-convulsant.

Blood gas derangements

1. Hypoxia: while dismissed by some because studies involving a slow fall in inspired O_2 show mental clouding rather than NDE (4, 29), these are not an accurate model of events in, for example, cardiac arrest. Nevertheless, hypoxia per se is not of itself sufficient explanation as has been claimed (30).
2. Hypercarbia: a CO_2-enriched breathing mixture can produce classic NDE elements, including bodily detachment, a bright light, ineffability etc. (31). Very different personalities produce similar results, suggesting that hallucinations of this type arise from a common physiological function of a brain structure (31). This is an interesting conclusion in view of the finding that NDE's are not substantially different in diverse personalities (2–5, 13), and strengthens the argument for a neural substrate.

Ketamine

This short acting anaesthetic is a congener of PCP (32). Advantages include no cardio-respiratory depression and no requirement for airway support (25). It can reproduce every feature of the NDE, from rapid trips through dark tunnels into light and the conviction that one is dead, to 'seeing spirits', 'telepathic communion with God', out-of-body experiences, mystical states, peace and tranquillity (5, 7, 32–34, 44). If given i.v., it can have a short duration of action with an abrupt end. Describing Ketamine effects Grinspoon 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."

NDE anecdotes have been closely matched with those of Ketamine and PCP (6, 7). Explanations of NDE as hallucinations are sometimes rejected because so many insist that it was 'real' (5, 13). 30% of normal subjects given ketamine insisted they had not been dreaming or hallucinating but that the events had really happened (34). The American Psychiatric Association definition is also worth noting: 'a hallucination has the immediate sense of reality of a true perception . . . transient hallucinatory experiences are common in individuals without mental disorder' (35). Examples of this occur in the recently bereaved (36). The clear sensorium of some dying patients has also been used to argue against hallucinations (5, 13) yet those of schizophrenia typically occur in clear consciousness (35), a key diagnostic feature, and some LSD takers claim their minds to be clearer than usual (32). Cardiac arrest survivors sometimes describe the resuscitation in detail (4). Ketamine permits sufficient sensory input to allow occasional accounts of surgical procedures (6).

A common origin for NDE and Ketamine effects was proposed in 1981 (5, 6), the theory involving sensory deprivation and CNS stimulation, e.g. the 'white light' may result from CNS stimulation mimicing light on the retina, and a lowering of the phosphene perceptual threshold. No attempt at a neurochemical interpretation was made (6).

PCP and sigma receptors

It is clear that PCP and sigma receptors are two different entities (8, 37, 38), and that the expression 'PCP-sigma opiate receptor', which implies that they are one, is obsolete. The definitions used here are those unanimously adopted by the International Seminar on Phencyclidine and Sigma-Like Compounds, 1987 (38). PCP and Ketamine are active at both sites (38). The sigma receptor is still an unknown quantity with few ascribed functions. MK-801, an anticonvulsant with high specificity for the PCP site and virtually none for sigma, does not produce PCP-like psychotomimetic effects in studies with human volunteers (39). They may thus result from either sigma receptors or sites not yet discovered. NMDA and PCP receptors are two linked parts of one complex (8–10, 37). The NMDA neurotransmitter is probably L-glutamate, an excitatory amino acid which may kill the neuron if present in excess ('excitotoxicity'). Blockade of PCP sites by Ketamine reduces this damage, which occurs in ischaemia and other conditions (8, 11, 12, 40, 41). Thus an endogenous blocking agent would be neuroprotective.

Sufficient activation of NMDA-PCP receptors produce long term potentiation (LTP), a change in neuronal status thought to be involved in memory formation and/or retrieval (41). Ketamine prevents LTP (41), suggesting a neural substrate for the 'gate' of the sensory deprivation theory — i.e. it closes the 'gate' to external input so that old memories come to the fore instead.

The discovery of endogenous ligands for PCP and sigma receptors, alpha and beta-endopsychosin respectively, suggests that these may mimic ketamine. Both ligands act at both receptors with varying affinities (8, 9, 10) although whether they are agonist or antagonists has not been established. Thus alpha endopsychosin, if released to reduce excitotoxicity, may still effect the sigma site with resulting changes in consciousness.

The implications of our new knowledge of these receptors and the substances which effect them extend well beyond the NDE, ranging from stroke and epilepsy through Alzheimer's disease and Huntington's chorea to schizophrenia and drug abuse (8, 10–12, 39–41, 53). Understanding how Ketamine and its congeners alter higher brain function may lead to new anti-psychotics and other medicines (8).

Ketamine as a model for the NDE

The physiological significance of the endopsychosins has yet to be proven. However, even if they prove irrelevant to the NDE, Ketamine remains a good model which suggests controlled experiments, thus moving the NDE beyond the data gathering stage. Many studies attest to its safety (25), although prolonged abuse in large daily doses may be toxic (32). The NDE dose, .7 $mgkg^{-1}$, is less than the anaesthetic dose which may be up to 4 $mgkg^{-1}$ (33, 51). Some who receive the drug as an anaesthetic find the experience unpleasant. This is partly a result of set (expectations and attitudes), and setting (physical and psychological environment). Negative responses can be considerably reduced with good rapport and communication (43) and many

non-medical users express favorable opinions (33, 44).

The subjective effects could be assessed with valid NDE measures such as the NDE Scale (45). This might provide numerical data of greater strength than a collection of anecdotes.

Medical relevance

The NDE is important because it is relatively common and affects values, goals, death anxiety and affective states (4, 13, 46, 47). It occurs in at least 35% of adult Americans who have a near death crisis (4, 13, 48). Altered values include less concern with material success, reduced death anxiety and increased altruism (4, 13, 46, 47). The event can be a turning point, encouraging positive life changes. Among those who attempt suicide, the subsequent risk for completed suicide is increased 50 to 100 times (46). However, attempts involving a transcendental NDE reduce the risk (46). Of those who survived a Golden Gate bridge jump and had such an NDE, none went on to commit suicide and all were united in their support for a barrier (50). This occurred despite an increased belief in an afterlife. Psychodynamic explanations centre on the benefits of 'ego death' followed by 're-birth' (49). Thus safe reproduction of the NDE's therapeutic features might be useful in psychiatry. Given in a psychotherapeutic context, Ketamine may involve fewer ethical dilemmas than electroshock treatment and lower side-effects than chronic anti-depressants. In the Third World, it has been given to psychotic patients for very different reasons but with remarkably positive results (42, 51).

Psychedelic drugs have been used to reduce death anxiety in the dying with good results (19, 32, 52). These drugs can no longer be given to humans. Ketamine, however, is accepted in medicine, of brief duration, less capricious, has rarely attracted intense controversy and creates a state of more relevance to death and dying (25, 32, 42, 51).

NDE research should also be encouraged so that NDE's are more widely accepted. Many still feel that these personally significant events cannot be discussed with physicians for fear of ridicule (4, 13).

Conclusion

The NDE is an important phenomena strikingly similar to Ketamine experiences. The proposed hypothesis has used recent advances in neuroscience to suggest a common origin in events occurring at PCP and sigma receptors. The endopsychosins may be released in large quantity to protect the brain by blocking the PCP receptor, affecting consciousness via the sigma or other receptors as a psychologically important side-effect. The hypothesis is not claimed to be the only valid explanation for the NDE, which is probably a final common pathway for several causes. Ketamine is proposed as a model for the NDE itself, and for re-creating therapeutic aspects to treat suicidal and dying patients. The importance of studying these receptor systems, and their relationship with higher brain functions, extends far beyond the NDE to improving our understanding of a range of psychiatric and neurological diseases.

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