Schizophrenia, dissociative anaesthesia and near-death experience; three events meeting at the NMDA receptor

Iván L. Bonta

Department of Pharmacology, Erasmus University Rotterdam, The Netherlands

Received 8 April 2003; accepted 15 October 2003

Summary The three events, viz. schizophrenia, dissociative anaesthesia and Near-Death Experience, despite their seemingly unrelated manifestation to each other, have nevertheless similar functional basis. All three events are linked to the glutamate sensitive N-methyl-D-aspartate (NMDA) receptor complex, which serves as their common functional denominator. Arguments and speculations are presented in favor of the view that, the three events might be considered as functional models of each other. Antagonism to the recognition NMDA-site of the receptor induces dissociative anaesthesia and precipitates Near-Death Experience. Agonist reinforcement at the modulatory glycine-site of the receptor counteracts negative symptoms of schizophrenia. Both types of challenges towards the receptor are compatible with a glutamate deficiency concept which underlies the meeting of the three events at the NMDA receptor.

Three seemingly unrelated events

Schizophrenic behavior, dissociative anaesthesia and Near-Death Experience are events which have seemingly little in common with each other. Nevertheless, there is a common denominator which serves as a link between these events. In this article arguments will be presented to back up the view that intervention with the N-methyl-D-aspartate (NMDA) receptor complex, either at the modulatory glycine site or at some other challenging location, will be modifying these events. The hypothesis will be forwarded that, despite an apparent lack of commonality between them, all of the three events are in such way linked to the NMDA receptor that this receptor serves as their common functional denominator.

Glycine site of the NMDA receptor

In the central nervous system one subtype of the excitatory amino acid (EAA) receptors is the NMDA receptor complex, which is a ligand gated ion channel. Besides the principal excitatory transmitter l-glutamate, the NMDA receptor has a modulatory binding site for glycine. Blocking of the glycine site is an alternative way to produce antagonism to glutamate [1]. Alternately, agonistic reinforcement of the glycine site would compensate for a shortage of glutamate. The glycine site is also a suitable target of pharmacological interventions which are aimed at to influence the NMDA receptor. Several substances have been shown either as competitive [2] or non-competitive [3] NMDA antagonists. Amongst several non-competitive antagonists, extensive investigations directed the interest towards the compound 1-hydroxy-3-amino-pyrrolidone-2 (HA-966). Partial reason for this interest was the
circumstance that, in contrast to the majority of the other substances, which had poor CNS bioavailability and were only weakly active when given systematically, HA-966 proved to have several marked CNS effects when administered in vivo. When HA-966 was first described, in 1971, the main emphasis was on its unusual effects on behavior of laboratory animals [4]. Thereafter the compound was somewhat neglected for a number of years, until it was shown to have glutamate antagonist properties, reducing the actions of NMDA, but not acting at the NMDA recognition site [5,6]. Thus HA-966 was claimed as NMDA antagonist without a known site of action. Subsequently, however, it has been recognized that HA-966 was an antagonist of the specific glutamate agonist-potentiating action of glycine [7]. This antagonism towards the facilitation of channel opening by NMDA was reversed not only by glycine itself but also by ß-serine, a glycine-like agonist [8]. In this context it is noteworthy that the chemical structure of HA-966 is closely resembling that of cycloserine, which is the ring-closed analogue of serine. Ultimately HA-966 was shown to be a partial agonist of glycine [9].

Glutamate deficiency in schizophrenia

The situation, as described above, was valid until the findings which evidenced a link between EAA receptors and schizophrenia. In fact there was an increasing interest in the glutamate system as a new target in schizophrenia. This interest originated from several observations, which ultimately led to the concept that schizophrenia might be related to a dysfunction of glutamate transmission. Further it appeared that there is a close interrelationship between glutamate and dopamine systems, providing a conceivable explanation for the efficacy of dopamine antagonists in ameliorating a disorder in which there is a defect in glutamate transmission [11]. Subsequently it was shown that a glutamate receptor gene is expressed in lower quantity in schizophrenics than in normals and that NMDA receptor-mediated glutamate release is deficient in synaptosomes from schizophrenics [12].

Schizophrenic positive and negative symptoms; their response to therapy

Schizophrenic disorders are characterized by fundamental distortions of thinking and perception and by blunted affective sensations. Hallucinations are common and may comment on the individual’s behavior or thoughts. Perception is occasionally disturbed in other ways: colors or sounds may seem unduly vivid or altered in quality. Mood is characteristically shallow and may appear as inertia or stupor. Schizophrenic patients may display either a predominance of positive symptoms, e.g., hallucinations and paranoid ideation or a predominance of negative symptoms, e.g., anhedonia, social withdrawal, paucity of speech and loss of volition.

Perturbations in the neurotransmitter systems are considered as important events for therapeutic interventions in schizophrenia. Thus excessive levels of dopamine or hypersensitivity of dopamine \( D^2 \)-receptors have long been implicated in this mental disorder. This concept resulted in the therapeutic application of \( D^2 \)-antagonists, also called typical antipsychotic drugs, a prototype of which is haloperidol. Positive symptoms of schizophrenia indeed respond beneficially to dopaminergic antipsychotic drugs, which though fail to influence the negative symptoms. In contrast, the later on developed atypical antipsychotic compounds, such as, e.g., olanzepine, improve, — at least to some extent — the negative symptoms as well [10]. Olanzepine has a preferential affinity to 5-hydroxytryptamine 5-HT\(^2\) receptors rather than to \( D^2 \)-receptors.

Glycinergic approach to negative symptoms

Postmortem data which suggested a link between shortage of glutamate discharge and schizophrenia prompted the question whether underactivity of NMDA-receptor mediated glutamate release might have resulted from a deficient stimulus from the glycine agonist site. In turn this led to clinical trials with high dose of glycine. Indeed high dose glycine proved an effective means for the treatment of negative symptoms of schizophrenia [13]. These results supported the concept that underactivity of NMDA-receptor mediated transmission may play a crucial role in the pathophysiology of schizophrenia [14]. It was subsequently shown that therapeutic benefit towards the negative symptoms was achieved by treatment with the glycine-site agonist \( \beta \)-cycloserine [15]. Also it appeared that schizophrenic patients having low serum glycine levels may represent the population of choice for treat-
ment with glycine-site agonists. Further the possi-
bility has been considered for clinical use of gly-
cine-agonists other than 3-cycloserine.

In view that the compound HA-966 is a close
chemical analogue of 3-cycloserine and because of
its easy penetration through the blood-brain bar-
rrier, this compound could have been a rather
suitable candidate for such clinical trials. However
HA-966 itself is a racemic substance, the glycine-
site activity having been conferred by the (R)(+)
enantiomer of it, whilst the (S)(–) enantiomer ap-
peared responsible for its y-butyrolactone-like
sedative effects [16]. In addition, a substitution
with methyl at the 4-position resulted in an in-
crease in activity of (R)(+)HA-966 [17]. So far nei-
ther (+)HA-966, nor its 4-methyl substituted
derivative got the chance of being clinically tested
towards negative symptoms of schizophrenia. This
is all the more regretful, because on the basis of
high affinity of these compounds to the glycine-site
of the NMDA receptor, a rather ameliorating effect
in schizophrenic patients would not have been
surprising.

All included, the glycinergetic approach towards
negative symptoms appears a rewarding one and
further advantageous developments of this field
are expectable in the future. An alternative,
hypothetical, possibility would be to pharmacologi-
cally inhibit the reuptake of glycine at neuronal
synapses. Still another, recent approach focuses on
glycine transporters [18]. Thus glycine transport
inhibitors seem to have preclinical behavioral ef-
serts similar to those of glycine or 3-serine. This
type of compounds may represent a future suc-
cessful approach for the treatment of negative
symptoms of schizophrenia.

Recognition NMDA-site; its relevance to
dissociative anaesthesia

Amongst the non-competitive antagonists of NMDA
there is a range of substances which, dissimilar to
3-serine and related compounds, act at a site dif-
fering from the modulatory glycine receptor. These
substances reduce the excitatory effect of NMDA
by blocking the ion channels which are opened
through the agonist-receptor interaction [19].
Some of these substances have influence on con-
sciousness and indeed there is evidence in favor of
ligand-gated ion channels as site of action of ana-
esthetics [20]. In context of the present article
particularly important is the group of substances
which chemically belong to the sigma opioid type
of agents. Two essential members of this group are
phenycyclidine and ketamine. In humans phenycy-
clidine causes periods of disorientation and hallu-
cinations and is presently mainly applied as a drug of
abuse. Ketamine is chemically related to phen-
cyclidine, but produces less euphoria. When given
intravenously ketamine causes an effect known as
dissociative anaesthesia. This is a peculiar anaes-
thetic state in which marked sensory loss and an-
glesia as well as amnesia is not accompanied by
actual loss of consciousness. There is evidence that
the effects of ketamine to cause alteration in
sensory perception and dissociative anaesthesia
are largely attributed to non-competitive antago-
nism of the NMDA receptor [21,22]. Ketamine has
affinity to the NMDA receptor, the activity of which
can be visualized through binding of labeled keta-
mine to the receptor site [23].

Support for the involvement of the NMDA re-
ceptor in dissociative anaesthesia is also gained
from effects of the NMDA challenging compound
HA-966 under laboratory conditions [4]. In experi-
ments on monkeys HA-966 caused electroenceph-
alography (EEG) changes which are characteristic
patterns of EEG during sleep, whilst the animal was
completely alert. This disconnection between
sleep-EEG and behavior is likely to be an experi-
mental equivalent of clinical dissociative anaes-
thesia. From the racemic HA-966, used in these
experiments, the part responsible for dissociative
anaesthesia-like effect was almost certainly not
the (R)(+)-enantiomer which is a glycine-site agonist
[16], but the (S)(–)-enantiomer. This is in agree-
ment with the view that, the event of dissociative
anaesthesia is linked to the non-glycine site of the
NMDA receptor.

Near-death experience’s relevance to
the NMDA receptor

The Near-Death Experience is a dissociative mental
state with characteristic phenomenological fea-
tures. This mental condition is of considerable in-
test to medicine, neuroscience, neurology,
psychiatry and, — because of its supposed preter-
natural features — theology. It is estimated that
10–20% of people who are imminent to die have a
Near-Death Experience. Sensationalist claims that,
Near-Death Experiences are evidence for life after
death, have unfortunately had a deterring influ-
ce on conducting research to clarify a sound
explanation of this state of mind. There is no in-
ternationally determined and agreed set of criteria
which define the Near-Death Experience, no list of
"research diagnostic criteria" similar to those
provided for psychiatric disorders. Nevertheless, despite the above counterproductive circumstances, there are reasonably acceptable descriptions available of features characteristic for Near-Death Experience [24]. These features include ineffability, timelessness, feelings of calm, analgesia, a perception of separation from the body and hallucinations of, e.g., people (who, though distant, may be alive at the time) and mythological or religious figures. Occasionally transcendent mystical states have been experienced.

Several pathophysiological explanations have been offered for the Near-Death Experience. The claim that hypoxia of the brain might play a role in this state [25] is unlikely on basis that hypoxia causes mental clouding rather than hallucinations. Increased release of endorphins has also been proposed [26]. This claim would support the analgesia during Near-Death Experience, but endorphins are not potent hallucinogens. Most noteworthy, however, is the speculation that deficient release of the EAA glutamate is an essential event in the pathogenesis of Near-Death Experience. In view that glutamate is a powerful agonist of the NMDA receptor, a shortage of it to precipitate Near-Death Experience is much in agreement with the circumstance that administration of the NMDA antagonist ketamine is capable of reproducing all of the features of Near-Death Experience [27]. Hence the phenomenology of Near-Death Experience is largely attributable to an inadequate challenge of the NMDA receptor. This is of importance in view that it provides a rational biological explanation of an event which often has been considered as a preternatural phenomenon.

About disease-models; their promise and danger

The term model is frequently used in context of explaining or interpreting the fundamental background of a disease. Occasionally, however, the use of a model concept is somewhat loose or imprecise. What does, generally speaking, cover the term model? It is a simplified representation of a system or phenomenon, with any hypotheses required to describe the system or explain the phenomenon [28]. Included in this definition is the dichotomy of models either for the phenotype of a disease or functional aspects of it. Phenomenologic models refer to readily recognizable symptoms of a disorder, whereas functional models have relevance to some of the basic physiological, biochemical, cellular or immunological processes which underlie the respective disease. Models of diseases have the advantage that, because they are simplified representation of the reality, they may serve as blue prints for a hypothesis on novel diagnosis or therapy. This is the predictive value of disease models. On the other hand disease models carry the inherent danger of oversimplifying the complicated network of reality. This is a pitfall, which ultimately may lead to diagnostic errors or therapeutic failures. These notions should be considered as precautions to the final section of the present paper.

NMDA receptor dysfunction and/or glutamate deficiency

Dissociative anaesthesia induced through NMDA antagonism by ketamine displays several phenomena which closely resemble or even are identical with features of Near-Death Experience. Indeed, the consequence of NMDA blockade is considered as a phenomenological model of Near-Death Experience [27]. Furthermore NMDA antagonism, which is in fact what ketamine exerts, is proposed as a functional model for schizophrenia [29]. Thus it appears that, following NMDA blockade there is a sequence of events which indicates that the two conditions, Near-Death Experience and schizophrenia, might be related to each other. Further continuing this train of thoughts the speculation seems to be justified that, the three conditions, schizophrenia (at least some aspects of it), dissociative anaesthesia and Near-Death Experience, respectively, could be considered as models of each other. The connecting link which renders them as each other’s model is hypofunctional derangement of the NMDA receptor. Such dysfunction may result either from shortage of glutamate supply or deficient access of glutamate to the receptor (resulting from application of receptor antagonist) or some derangement of the receptor proper. Provided the hypothesis being correct to indicate that, the three conditions are indeed models of each other, it would be not unreasonable to expect that successful intervention into one of them could also be applicable to another one. Although this implies a somewhat risky extrapolation, there is some support in favor of it as follows. Antagonism to the NMDA receptor, — known to result in dissociative anaesthesia — was reversible by glycine and the glycine uptake inhibitor glycyldodecylamide [30]. Glycine-site directed intervention towards negative aspects of schizophrenia proved indeed successful [13,15]. Thus results from dissociative anaesthesia
="\text{"model A"}\) appear applicable to schizophrenia ("\text{"model B"}"). Accordingly one model may hold beneficial promise towards the other. But caution should be exercised to prevent undue expectations.

The involvement of the NMDA receptor is obvious in both, dissociative anaesthesia and schizophrenia. Nevertheless, the role played by this receptor is dissimilar between the two conditions. The receptor-site, which is sensitive for glutamate, is apparently permissive for dissociative states, such as hallucinations and related conditions. Blockade of this site precipitates the event of dissociative anaesthesia and possibly Near-Death Experience. On the other hand, the glycine-ergic modulatory-site is permissive for negative symptoms of schizophrenia. Agonist reinforcement of the glycine-site results in amelioration of these negative symptoms. Despite this paradoxical circumstance both mechanisms, viz. receptor-site blockade and modulatory-site reinforcement, are compatible with the hypo-glutamatergic concept which underlies all three conditions discussed in this paper.

Acknowledgements

I am indebted to Professor David Lodge (Department of Physiology, Royal Veterinary College, University of London, UK) who, via a correspondence in 1988, led me to recognize that the EGG observation on a monkey treated with 1-hydroxy-3-amino-pyrrolidone-2 (compound HA-966) was the experimental equivalent of dissociative anesthesia. Further my thanks are due to my former study mate Dr. Robert Balázs (Gillespie Neuroscience Facility, University of California Irvine, USA) who perused this paper and commented on it. He also provided me with some recent literature on the glycine site.

References


