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SPECIAL ISSUE-EDITORIAL

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Neuroprotection – what does it mean? – what means do we have?

Neuroprotection – what does it mean?

Neuroprotection – only a fashionable phrase that has raised hopes and public confidence, particularly among patients affected from neuropsychiatric disease and their relatives? An expression that emphasizes the power of neuroscience research and satisfies the concepts of pharmaceutical companies? Is it simply a relic of the 1990s, the "decade of the brain" with its initial over-optimism (Aldhous, 1992; Jones and Mendell, 1999)?

Neuroprotection – does it mean protection of neurons? Why would neurons have to be protected? Or does neuroprotection rather mean protection of neural tissue, including all cell types that contribute to the integrity of the nervous system, e. g., neurons, oligodendrocytes providing myelination of axons, astrocytes ensuring undisturbed metabolic satisfaction of neurons (see Kirchhoff et al. in this issue), microglia as the immune police of the brain, or the brain endothelial cells as pivotal components of the blood-brain barrier. Do all these cells have to be protected? Do they perhaps have to be protected from each other once they get out of control? For instance, microglia (over)activation may in many cases enhance cell death and tissue destruction (Kreutzberg, 1996).

Neuroprotection may be defined as the effort to maintain the highest possible intactness of cellular interactions/intercellular communication in the brain resulting in an overall undisturbed function. Thus, neuroprotection actually means protection of neural function. Loss of brain function will eventually be detrimental, whereas loss of cells may not even be measurable. Also, saving cells, i. e., prevention of cell death, may not always be desirable. Elimination of dysfunctional or altered/transformed cells also contributes to the maintenance of the highest possible function, perhaps at the price of increased cell death.

Neuroprotection may be *prophylactic* or therapeutic. In the first case, it means prevention of functional loss before it occurs. For that, functional loss has to be anticipated. Anticipation in turn means identification of predictors/risk factors (genetic or environmental) based on our knowledge on etiology/pathogenesis of brain disease (Fig. 1).

Therapeutic neuroprotection means to maintain/safeguard as much function as possible of what is left. Here, basically all diseases of the nervous system are addressed to some extent. Therapeutic "maintenance of function", however, can also be temporary, substitutional or symptomatic, while the underlying process of destruction/degeneration proceeds, e. g., in Parkinson's disease (substitution of dopamine) or schizophrenia (symptomatic neuroleptic treatment). How could neuroprotection – in addition to substitution/symptomatic therapy – be achieved? How can it be beneficial in such conditions? How can we go about investigating its effect? Schizophrenia may serve as an example.

Etiology and pathogenesis of *schizophrenic psychosis* is still obscure despite general agreement on the significance of a genetic predisposition (Woods, 1998; Lieberman, 1999; Isohanni et al., 2000). There is strong evidence for a number of co-factors (e. g., neurotrauma, drug abuse) that influence manifestation and course of the disease (Freed, 1975; Schneier and Siris, 1987; Thurm and Haefner, 1987; McAllister, 1992) (Fig. 1). The molecular and cellular mechanisms, however, are far from being understood. Imbalance of neurotransmitters, particularly of the dopaminergic system, accounting for the often dramatic clinical features, has been uncovered and is successfully repressed by dopamine antagonists (Carlsson, 1988; Schwartz et al., 2000). Other neurotransmitter systems are affected as well (Schwartz et al., 2000). Imbalance is caused by profound neuronal dysfunction due to neurodevelopmental/neurodegenera-

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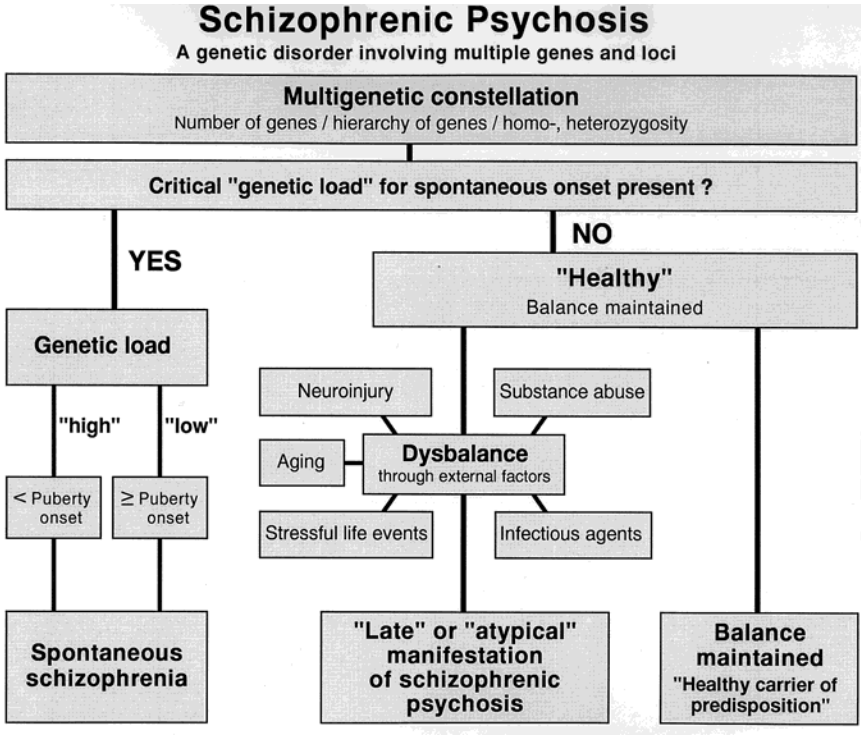

Fig. 1 A schematic presentation of the complexity of etiology/pathogenesis of schizophrenic psychosis. Identification of risk factors, both genetic and environmental, may instruct in the future starting neuroprotective treatment.

tive dysregulation and is also detectable in less spectacular and therefore initially often ignored symptoms (Woods, 1998; Velakoulis et al., 2000). In fact, a remarkable worsening of cognitive/mental performance can be observed as early as during the first episode of the psychosis (McCarley et al., 1999; Velakoulis et al., 2000), supporting the concept of a major neuronal damage occuring at that time. During consecutive psychotic episodes, a stable or slowly progressing course of the disease has been reported (Woods, 1998). This urges the early application of neuroprotective strategies as an "add-on therapy" to the predominantly symptomatic neuroleptic treatment of schizophrenic psychosis. In this regard, the value of preclinical studies is limited. There are no satisfying animal models and existing ones, at best, cover certain aspects of the disease. Therefore, an introduction of promising concepts directly into treatment of humans appears justified. In Göttingen, a neuroprotective approach to the treatment of schizophrenic psychosis using erythropoietin (EPO) as the "experimental add-on therapy" to a standardized neuroleptic regimen is presently in preparation. EPO can influence apoptosis, metabolic state of neurons and synaptic connections/axonal sprouting (Campana et al., 1998; Sirén et al., 2001, see also Sirén and Ehrenreich in this issue). Prophylactic application of EPO in persons at risk to develop a psychosis (e. g., high genetic load, neurotrauma, psychotrauma, etc.) or in a presumable prodromal phase will also have to be considered for future studies.

Neuroprotection – what means do we have?

Despite promising preclinical studies, hardly any concept of neuroprotection has been convincingly efficient in man thus far (De Keyser et al., 1999). It is important to understand why these strategies have failed in man. Animal models are limited in their power to imitate the clinical situation in respect to heterogeneity of population, risk-factors and complicating diseases. The lack of beneficial effects in many clinical trials can be attributed to methodological problems in respect to selection of patients and a non-sufficient adherence to inclusion/exclusion criteria. Protocol violations, control of therapeutic time window, dosage, duration and safety/potential toxicity of treatments have created major problems (Windisch et al., 1998; De Keyser et al., 1999).

Imitation of brain endogenous protective mechanisms may be the key to future successful approaches to neuroprotection. Thus, a major aim of neuroscience research in this respect has to be to increase the understanding of endogenous mechanisms of protection, defense against and response to damage, adaptation to and coping with new situations. Activation/mimicry of endogenous mechanisms can be expected to be efficient and well tolerated. An example of endogenous neuroprotection is the development of relative ischemic tolerance in response to repeated transient ischemic events (Kitagawa et al., 1990; Barone et al., 1998). Preconditioning obviously (re)activates silent genetic programs of cellular defense/survival strategies thereby leading to a modulation of neuronal tissue vulnerability (Barone et al., 1998; Liu et al., 2000, Kietzmann et al. and Kuhn et al.

in this issue). Another example of endogenous neuroprotection may be adult neurogenesis upon physical exercise (van Praag et al., 1999). In fact, this phenomenon may also explain how alterations in behavior or even psychotherapy can exert actions at a cellular level associated with a gain of brain function. Inactivity, in contrast, has long been known to lead to a loss of function ("use it or lose it"). Lack of input to the sensory cortex upon amputation of a finger in monkeys results in restructuring of the cortex (Merzenich et al., 1984; Manger et al., 1996).

Taken together, the mechanisms of endogenous neuroprotection appear to be multifaceted and may essentially range from 1) stimulation of adult neurogenesis (Kuhn et al. in this issue) to 2) modulation of intercellular communication/brain metabolism (Kirchhoff et al. in this issue), 3) adult reactivation of neuroprotective programs, relevant during embryogenesis (Kietzmann et al. in this issue), and 4) expression of direct neuroprotective/neurotrophic factors, e. g., erythropoietin (Sirén and Ehrenreich in this issue).

The reviews in this special issue cover the present knowledge on these "hot topics" of neuroscience research harbouring future neuroprotective potential. In addition, a visionary view of the respective field is provided in each article.

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