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Chapter I

Excitatory amino acids studied in isolated cells and culture preparations: A bridge over *in vitro* and *in vivo* experimental paradigms

Introduction

In mammals, the maturation of the central nervous system is mainly a postnatal phenomenon. Neuronal and glial growth, as well as differentiation extend to postnatal periods, with axon terminal proliferation prolonging long after birth, and probably continuing during adulthood. Different neurochemical systems follow a strictly controlled developmental pattern; by example dopamine containing pathways have a faster development than those containing noradrenaline or 5-hydroxytryptamine, and the maturation of the nigrostriatal dopamine system precedes that of mesolimbic and mesocortical systems. In the rat, cortical and hippocampal glutamatergic systems reach maturity only two to three weeks after birth. The interruption of the development of neurocircuitries by metabolic and/or vascular accidents occurring at birth, or later in life, can produce functional priming or loss of crucial neuronal components of the affected systems. This in turn would lead to re-arrangements of the unaffected neurocircuitries, preserving and/or impairing further the affected functions. These re-arrangements provide perhaps a background for functional alterations, such as those observed in psychosis and drug addiction.

Thus, there is a need for methods allowing studies of the development of the brain neurocircuitries, focusing on the plasticity of the functional phenotypes, as well as on biochemical parameters, which may disclose novel therapeutic targets.

In the present chapter, the authors were invited to discuss several models attempting to provide a bridge over *in vitro* and *in vivo* experimental paradigms. The organotypic culture model proposed by Gähwiler and collaborators (1997) appears to provide many of the requirements for such a model. Dr Jens Zimmer (University of Odense, Denmark), a pioneer in the field, presents here studies showing the excitotoxic effects of excitatory amino acids, via activation of kainate, AMPA and NMDA receptors, in hippocampal and corticostriatal slice cultures, and he discusses the possible neuroprotective effects of glutamate receptor blockers. Dr Alois Saria and collaborators (University Hospital Innsbruck, Innsbuck,

Austria) have applied the organotypic model to investigate the effects of drugs and toxins on the expression of transcription factors in isolated dorsal striatum, without dopaminergic and glutamatergic inputs, focusing of the effects of margatoxin and iberiotoxin on c-fos mRNA and c-fos like protein immunohistochemistry. At the Karolinska Institutet, Stockholm, Sweden (Herrera-Marschitz et al.), we have further developed the organotypic model to characterise the nigrostriatal and mesolimbic systems, including their corresponding cortical inputs, studying in these cultures the interactions among amino acid, dopamine, and nitric oxide containing systems.

Dr Dave Sulzer and collaborators (Columbia University, New York, NY, USA) have developed a postnatally-derived neuronal culture of midbrain dopamine neurons, and a single cell microculture model to study whether monoamine neurons may also release glutamate. They discuss the evidence from their own and other laboratories indicating that neurotransmitters may be segregated to different synapses of individual neurons, in contrast to what has been proposed by the most recent modifications of the Dale's Principle.

In the retina, glutamate is the excitatory neurotransmitter in the vertical signal transmission pathway from photoreceptors to ganglion cells. In the outer retina, glutamate is released from photoreceptors in darkness, which is modulated by light. In the inner plexiform layer, glutamate is released from on-bipolar cells in the light, while it is released from off-bipolar cells in the dark. In such a system, it is then critical to precisely control the glutamate concentration in the synaptic cleft, because it represents the light signal. The modulation of extracellular glutamate concentration is largely performed by glutamate transporters. Dr Thomas Rauen (Max-Planck Institute, Frankfurt/M, Germany) has demonstrated (Rauen et al., 1996) that glutamate transporter subtypes are differently expressed and have specific distributions in different cell types in the mammalian retina. He presents here studies identifying the major glutamate uptake sites, discussing further their possible functional roles in the mammalian retina.

While glutamate is the major excitatory neurotransmitter of the mammalian brain, GABA represents the major inhibitory system. GABA is synthesised within GABA terminals through a highly compartmentalised process in which glial-derived glutamine is a major precursor. Dr Perez de la Mora and co-workers (Aguilar-Garcia et al.) (Mexico DF, Mexico) have studied the issue of the modulation of GABA synthesis and/or release by $GABA_B$ autoreceptors, using slices, synaptosomes and prisms from hypothalamus and cerebral cortex. They conclude here that unlike GABA release, GABA synthesis is not modulated by $GABA_B$ autoreceptors.

These studies, together, demonstrate that major neurotransmission mechanisms as well as important features of neurocircuitry development can be studied *in vitro*, allowing functional and pharmacological experiments which may lead to the identification of novel pharmacological targets.

References

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