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DISSERTATION SUMMARY

Use of pseudorabies virus to delineate plastic neuronal circuits in the brain: opportunities and limitations, and possible background

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It has earlier been demonstrated that strain Bartha (PRV-Ba), an attenuated pseudorabies virus (PRV) live vaccine virus, is suitable as a retrograde tracing tool for revealing neural circuitries. Although fewer studies have employed intracerebral injections of the virus, available evidence suggests that this experimental approach is also an effective means of defining multisynaptic circuits. We tested whether this method based on the use of this virus is sensitive enough to detect fine plastic changes induced in the central nervous system (CNS).

A number of publications have demonstrated that oestrogen induces plastic alterations in the synaptic connections in the CNS. We examined that neuronal infectivity and the spreading of PRV through the synapses in the CNS are influenced by the oestrogen levels. The arcuate nucleus and the subfornical organ were chosen as models for analysis; the neurons in both structures possess oestrogen receptors and are mutually connected. Our results demonstrate that transneuronal PRV labelling depends on the effects of oestrogen on certain CNS structures and connections (Horváth et al. 2002).

In adult mammals, the somatotopic representation map of the muscle system in the motor cortex is not stable, but may be modified within hours to days after peripheral facial nerve injury. In particular, we have previously demonstrated an facial nerve injury (N7x)-induced early disinhibition of the commissural connections between the primary motor cortices (MIs) by intracortical microstimulation of the facial muscle representation field. In our second experiment, unilateral N7x was found to influence the transcallosal spread of PRV-Ba from the affected (left) primary motor cortex (MI) to the contralateral MI of rats (Horváth et al.).

To explain these results, it should be taken into account that the entry of alpha herpes viruses into the cells usually requires multiple interactions between the viral envelope and the cell surface proteins. At least two groups (HSPGs and nectins) of these cell surface glycoproteins are known to play roles in these processes (Mettenleiter 2000). It should also be taken into account that HSPGs and nectins participate in the development and plasticity in adulthood of tissues of neuroepithelial origin (Mizoguhi et al. 2002; Rauvala and Peng 1997). We have shown here that oestrogen level and N7x does not affect the entry of PRV, but increases the efficiency of its cell-to-cell spread. Thus, the infection pattern does not appear to be related to cellular components (HSPGs) involved in the attachment of the virus, but rather to cellular components located at the synaptic region of the membrane of post-synaptic neurons.

Nectin-1 and nectin-2, components of a novel cell-cell adhesion system, and localized within the cadherin-catenin system at cell-cell adhesive junctions, have been shown to play important parts in synapse formation (Mizoguhi et al. 2002). In ep-ithelial cells, dissociation of the cell junctions releases nectin-1 to serve more efficiently as an entry receptor. Sakisaka and coworkers (2001) have reported that the interaction of nectin-1a with afadin does not affect the entry of HSV-1, but increases the efficiency of the cell-cell spread of that virus. The mechanism by which oestrogen level and N7x increases the efficiency of cell-cell spread of PRV in the cortical network *in vivo* remains to be elucidated, but one possible explanation will be discussed.

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