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Which molecules regulate synaptic brain asymmetries?

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Cerebral specialization between the left and right hemisphere is a fundamental concept in neuroscience. Left–right brain asymmetries of macroscopic structures or functions in human brain are well characterized (Toga & Thompson, 2003). For example, the left hemisphere is dominant for language and logical processing, whereas the right hemisphere prevails in spatial cognition. The brain is also lateralized for several behavioural functions in non-human animals (Walker, 1980). For example, the activation of the left hemisphere is dominant in songbirds and primates in response to visual or auditory stimuli, whereas the right hemisphere leads in space and emotion processing in rodents and chick, respectively. Recently, an intriguing lateralization of emotional processing has been observed in the mouse suggesting that only the right, but not the left, anterior cingulate cortex encodes fear learning (Kim *et al.* 2012).

In contrast to the knowledge of brain lateralization at the macroscopic level, virtually nothing was known about brain left–right asymmetries at microscopic levels involving molecules, synapses and neurons. A breakthrough occurred 10 years ago when the groups of Ito and Shigemoto reported an unexpected molecular difference at excitatory synapses of the left and right mouse hippocampus. They found that the synaptic distribution of one of the four *N*-methyl-D-aspartate (NMDA) receptor GluN2 subunits, namely the GluRε2 (GluN2B), is asymmetrical between the left and right (L–R) and between the apical and basal dendrites of CA1 pyramidal neurons (Kawakami *et al.* 2003; Fig. 1*A*). Presynaptic axons from the left CA3 pyramidal neurons form ε2-dominant synapses on the apical dendrites of post-synaptic pyramidal neurons in both left and right hippocampus. Conversely, presynaptic axons from the right CA3 pyramidal neurons form ε2-dominant synapses on the basal dendrites of postsynaptic pyramidal neurons in both left and right hippocampus. Subsequently, they demonstrated that such functional asymmetry has structural correlates: GluRε2-dominant synapses are often found on small thin dendritic spines whereas GluRε2 non-dominant synapses are present on large mushroom-type spines (Shinohara *et al.* 2008). Furthermore, this molecular asymmetry is target specific, namely it does not occur in excitatory synapses on interneurons (Wu *et al.* 2005). It also has functional consequences since spike-timing-dependent long-term potentiation (LTP) induced by optogenetic stimulation of afferent fibres from the left CA3, targeting GluN2B-dominant spines in the apical dendrites, is larger than LTP at GluN2B non-dominant spines targeted by afferents from the right CA3 (Kohl *et al.* 2011).

In spite of this progress, many questions remained to be answered, and in particular it was not known what molecules regulate the generation of the L–R and apical–basal asymmetries. In this issue of *The Journal of Physiology*, Kawahara *et al.* (2013) identify the major histocompatibility complex class I (MHCI) as key molecules involved in the regulation of the asymmetry of NMDA receptors at hippocampal synapses.

The authors started off by using the β2-microglobulin (β2m)-deficient mouse that lacks cell surface expression of MHCI. To reveal molecular asymmetries, as in their previous papers, they tested the inhibitory effect of Ro 25-6981, a highly potent and selective blocker of NMDA receptors containing the GluRε2 (GluN2B) subunit, on NMDA-excitatory postsynaptic currents (EPSCs) evoked by the stimulation either of the stratum radiatum or the stratum oriens to activate apical or basal synapses, respectively. As in their previous papers, to selectively stimulate Schaffer collaterals, originating in ipsilateral CA3 pyramidal cells, they cut the commissural fibres coming from contralateral CA3 pyramidal neurons. This was needed since commissural fibres are intermingled with Schaffer fibres, and also excite CA1 pyramidal neurons. In control experiments, they also tested the hippocampus of the

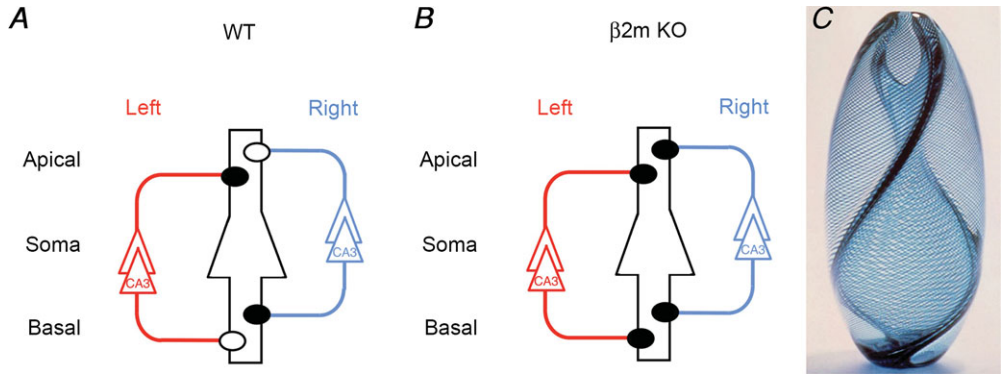

Figure 1. Hippocampal asymmetry in wild-type (WT, *A*) or β2m knockout (KO, *B*) mice
Left and right CA3 pyramidal neurons and their axons are labelled red and blue, respectively. A postsynaptic CA1 pyramidal neuron is shown in the centre (black). Filled and open circles show 'ε2-dominant' and 'ε2-non-dominant' synapses, respectively. Apical, apical dendrites; Basal, basal dendrites. Reproduced from Kawahara *et al*. (2013). *C*, glass vase by glass master Lino Tagliapietra. Taken from http://www.linotagliapietra.com.

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iv mouse that possess a spontaneous mutation in a gene encoding the motor protein Left-right dynein. These mice display normal apical–basal asymmetry but lack L–R asymmetry (Kawakami *et al.* 2008). Strikingly, they observed neither L–R asymmetry nor apical–basal asymmetry in the β2m-deficient synapses (Fig. 1*B*). Furthermore, commissural–CA3 synapses of wild-type mice were preferentially ε2-dominant on the left side, but this asymmetry was not present in the β2m-deficient mice. Consistent with their main findings, the authors also observed a lack of asymmetries in the frequency dependency of synaptic plasticity and in morphological aspects of dendritic spines in the β2m-deficient mice. Further experiments indicated that NMDA-EPSC sensitivity to Ro 25-6981 was similar in β2m-deficient and in GluRε2-dominant synapses, and that β2m proteins were expressed by hippocampal synapses in control mice.

This paper is the first attempt to dissect out the cellular processes that generate molecular asymmetries in the brain. However, the exact role of MHCI molecules in this process is still unclear. As the authors pointed out, their work does not allow one to distinguish whether the lack of asymmetries in the β2m-deficient mouse is due to a specific effect on circuit asymmetries or a consequence of generalized failure of synapse maturation caused by MHCI deficiency. Immune molecules, including MHCI proteins, play an important role in the formation and plasticity of glutamatergic synapses (Fourgeaud & Boulanger, 2010). Therefore, the lack of synaptic asymmetries could simply be due to abnormal synaptic development. Moreover, the role of other synapse-associated molecules, such as those involved in the target recognition between pre- and postsynaptic neurons during synapse formation, remains to be investigated.

The study of brain asymmetry is a fascinating topic and has an intrinsic aesthetic value. Not surprisingly, symmetry and asymmetry capture the attention of artists too. For example, the mirror-image asymmetry for NMDA receptors expressed by CA1 hippocampal neurons can be detected in the main motif of the work of art shown in Fig. 1*C*.

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Additional information

Competing interests

None.

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