The studies performed in laboratory animals and psychiatric patients suggest a possible role of limbic system-associated membrane protein (LAMP) in the mechanisms of psychiatric disorders. Stressful manipulations and genetic invalidation have revealed a role of the Lsamp gene in the regulation of anxiety in rodents. Besides that, Lsamp-deficient mice display reduced aggressiveness and impaired adaptation in novel and stressful environments. The behavioral effects of amphetamine were blunted in genetically modified mice. Recent pharmacological and biochemical studies point toward altered function of GABA-, 5-hydroxytryptamine-, and dopaminergic systems in Lsamp-deficient mice. Moreover, we found an association between the gene polymorphisms of LSAMP and major depressive disorder (MDD). Patients suffering from MDD had significantly increased ratio between risk and protective haplotypes of the LSAMP gene compared to healthy volunteers. However, the impact of these haplotypes for the function of LAMP is not clear and remains to be elucidated in future studies.

Keywords: limbic system-associated membrane protein, dopamine, GABA, 5-hydroxytryptamine, anxiety, genetic polymorphisms, major depressive disorder, panic disorder

INTRODUCTION

The limbic system-associated membrane protein (LSAMP) gene gives rise to LAMP, which is a 64- to 68-kDa heavily glycosylated protein, structurally characterized by three immunoglobulin (Ig) domains (Pimenta et al., 1996). LAMP protein is expressed on the surface of somata and proximal dendrites of neurons (Zacco et al., 1990) where it integrates via glycosyl-phosphatidyl-inositol (GPI) anchor (Pimenta et al., 1996). LAMP protein has been shown to be specific to the cortical and sub-cortical limbic-associated regions (e.g., perirhinal cortex, cingulate cortex, amygdala, hippocampus, and striatum) of the developing and adult brain (Levitt, 1984; Horton and Levitt, 1988; Pimenta et al., 1996; Reinoso et al., 1996). Despite the name, LAMP is not expressed only in the limbic-associated areas, but also less intensely in the midbrain and hindbrain regions (Reinoso et al., 1996). A 99% amino acid sequence identity between human and rodent LAMP (Pimenta et al., 1996) indicates strong phylogenetic conservation of the protein structure and associated functional properties. Several cell culture experiments suggest that LAMP mediates axon targeting and growth in the brain (Keller et al., 1989; Pimenta et al., 1995; Mann et al., 1998; Gil et al., 2002).

FUNCTIONAL STUDIES DEMONSTRATING A ROLE OF THE Lsamp GENE IN THE REGULATION OF EMOTIONAL BEHAVIOR

The first evidence for a role of the Lsamp gene in the regulation of emotional behavior came from a study where male Wistar rats were selected according to their exploratory behavior in the elevated plus-maze model of anxiety. Animals with lower exploratory activity had elevated levels of the Lsamp transcript in the periaqueductal gray (Nelovkov et al., 2003). In the same rats, an increase of Lsamp gene expression was also noticed in the amygdala, but not in the frontal cortex (Nelovkov et al., 2006). Exposure of rats to cat odor, another model of anxiety in rodents, also increased the expression of Lsamp transcript in the amygdala (Koks et al., 2004). These findings were extended by Altman et al. (2010) demonstrating that the transcript for Lsamp was more expressed in the raphe, hippocampus, and frontal cortex of rats displaying reduced exploratory activity in the motility box. Lamprecht et al. (2009) established that fear conditioning caused changes in the Lsamp transcript expression in the amygdala of rats. Altogether, rodent studies indicate that increased level of the Lsamp transcript in several brain areas is related with increased anxiety, thereby supporting the role of LAMP in the regulation of emotional behavior.
that the motor stimulant effect of amphetamine was significantly reduced in Lsamp-deficient mice, whereas the reduced anxiety as well as the increased anxiolytic effect of diazepam is stronger in Lsamp-deficient mice. This could be a possible reason for the reduced expression of dopamine transporter, a major target of amphetamine administration (Innos et al., 2013). Altogether, our recent pharmacological studies point toward changes in the function of GABA-, 5-HT-, and dopaminergic systems in Lsamp-deficient mice.

### In conclusion

In order to study the impact of environmental manipulations on the phenotype, we exposed male Lsamp-deficient mice to environmental enrichment (EE), a technique that has often been shown to abolish phenotypic deviations in knockout mice, and to social isolation, a stressful manipulation, after which all the mice were tested in a behavioral battery. EE abolished differences between the genotypes in body weight and anxiety and amplified the differences in swimming speed and anogenital sniffing. EE and isolation failed to modify the results as compared to standard housing in whisker trimming, locomotor activity, marble burying, and corticosterone levels. In conclusion, Lsamp-deficient mice were less sensitive to isolation stress than their wild-type littermates. Lack of LAMP protein seemingly leads to a deterioration in the ability to adapt to novel stressful environments and stimuli (Innos et al., 2012).
There is also a shift in the expression of GABA\(_A\) receptor subunits in favor of alpha2. This could be a reason for the reduced anxiety and increased anxiety-induced expression of dopamine in Lsamp-deficient mice (Innos et al., 2011). Furthermore, the adaptation of Lsamp-deficient mice is impaired in novel and stressful environments and they display reduced aggressiveness. Also, their response to the behavioral effects of amphetamine is blunted (Innos et al., 2013). These behavioral effects are most likely related to changes in the function of the 5-HT-ergic system in Lsamp-deficient mice. Besides that we found a relation between gene polymorphisms of the LSAMP gene and MDD (Koids et al., 2012). Patients suffering from MDD have significantly increased ratio between the risk haplotypes for the function of LAMP is not clear and remains to be elucidated in future studies.

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