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Functional investigation of the role of tachykinins and the neurokinin 1 (NK1) receptor in anxiety and learning processes in mice

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Background: Substance P (SP) encoded by the preprotachykinin A (TAC1) gene has been shown to play an important role in higher brain functions including behaviour and learning via neurokinin 1 (NK1) receptor activation. The recently discovered TAC4 gene-derived hemokinin-1 (HK-1) is also expressed in the central nervous system with an expression pattern in the brain similar to that of SP. HK-1 is suggested to have agonistic activity on the NK1 receptors, but it might have different binding sites, receptor activation mechanisms and signal transduction pathways. Furthermore, a presumably own hemokinin receptor has also been proposed on the basis of several actions of HK-1 different from that of NK1 receptor activation. Therefore, we investigated the role of the TAC1 and TAC4 gene-derived peptides and the NK1 receptors in anxiety and learning processes using gene-deficient mice. **Methods:** Male TAC1$^{-/-}$, TAC4$^{-/-,}$ TAC1$^{-/-}$/TAC4$^{-/-}$, NK1$^{-/-}$ mice (8-12 weeks old, n=8-15/group) were investigated in comparison with their C57Bl/6 wildtypes. Anxiety was evaluated in an elevated plus maze (EPM) composed of two opposite open and closed arms with an open roof. Mice were placed into the center of the maze, facing a closed arm. The time spent on the closed arms correlating with the anxiety level is measured for a total observation time of 5 minutes. Spatial learning was evaluated in the Morris Water Maze (MWM) test. With the help of external spatial cues mice have to find a hidden 10x10 cm square plexiglas platform placed 2 cm under painted water, the latency to find this platform is measured. Negative reinforcement-induced learning was studied in a step-through avoidance test. The apparatus consists of a large, well illuminated compartment and a black-painted small closed box with a metal-grid floor to deliver a weak electric current. During conditioning, the electric stimulus was given when mice entered the dark box, 24 h and 1 week later mice were tested by determining the latency to enter the shock box. **Results:** Wiltype mice spent approximately 220 seconds in the open arms of the EPM, which was significantly shorter in the TAC1$^{-/-}$, TAC4$^{-/-}$, TAC1/4$^{-/-}$, but not in the NK1$^{-/-}$ groups compared to the wildtypes. In the MWM test wildtype animals found the platform in 2-2.5 minutes on the first day of the experiment, which reduced to 1-1.5 minutes on the third day. There was no difference in the latencies of any gene-deleted groups. During the passive avoidance test, the latency of the wildtype mice to enter the closed box after a previous electric stimulus was 3-4 minutes. It was significantly reduced in mice lacking substance P (TAC1$^{-/-}$ and TAC1/4$^{-/-}$). **Conclusion:** Both SP and HK-1 are involved in determining the anxiety level of mice, but interestingly, not through the activation of NK1 receptors. Learning in response to negative reinforcement is mediated by SP, but not HK-1 in a non NK1 receptor-mediated manner. The role of a presently not identified HK receptor can be suggested in these mechanisms. However, neither SP nor HK-1 is involved in memory processes involving spatial learning. **Funding:** SROP-4.2.1.B-10/2/KONV-2010-0002, SROP-4.2.2.B-10/1/2010-0029