Recent developments in potential anxiolytic agents targeting GABAA/BzR complex or the translocator protein (18kDa) (TSPO).

Abstract:
Anxiety disorders are frequent and disabling disorders. For short-term treatment, benzodiazepines are useful due to their rapid onset of anxiolytic action. However, these compounds have sedative properties and may induce tolerance, abuse liability and withdrawal symptoms. First-line choices for the long-term treatment are selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors. The major disadvantage of these compounds is their delayed onset of action. It is obvious that there is a need for novel pharmacological approaches that combine a rapid anxiolytic efficacy with the lack of tolerance induction, abuse liability and withdrawal symptoms. A very important target for the development of such compounds is the -amino-butyric-acid (GABA)A receptor. Subtype specific benzodiazepines are being developed, but also phytotherapeutic agents experience a renaissance as GABA receptor modulators. On the other hand, GABA related compounds, e.g. tiagabine, did not show pronounced anxiolytic efficacy. Neuroactive steroids such as allopregnanolone and tetrahydrodeoxycorticosterone (THDOC) are potent modulators of GABAA receptors. To date synthetic neuroactive steroids could not be established in the treatment of anxiety disorders. Regarding endogenous neurosteroidogenesis, recently the translocator protein (18kDa) (TSPO) has been identified as a potential target.
novel target. TSPO is supposed to play an important role for the synthesis of neuroactive steroids. TSPO ligands may promote the synthesis of neuroactive steroids via induction of cholesterol translocation to the inner mitochondrial membrane. First clinical studies revealed promising results. In this review, we discuss putative compounds affecting the GABAergic system which may provide the basis for fast acting anxiolytics with a favorable side effect profile.