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REVIEW

Translocator protein (18 kDa) (TSPO) as a therapeutic target for anxiety and neurologic disorders

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Abstract The translocator protein (18kD) (TSPO) plays a crucial role for the synthesis of neurosteroids by promoting the transport of cholesterol to the inner mitochondrial membrane, which is the rate-limiting step in neurosteroidogenesis. Neurosteroids are allosteric modulators of $GABA_A$ receptor function, which plays an important role in the pathophysiology of anxiety disorders. The TSPO ligand XBD173 enhances GABAergic neurotransmission by promoting neurosteroidogenesis without direct effects at the $GABA_A$ receptor. In humans, XBD173 shows potent antipanic efficacy without sedation and withdrawal after 7 days of treatment. XBD173 therefore appears to be a promising compound for rapid anxiolytic efficacy with a favorable side-effect profile. Furthermore, TSPO ligands show neuroprotective and antiinflammatory effects in experimental models of peripheral neuropathies and traumatic brain injury. These compounds might therefore also be valuable for the treatment of neurologic diseases with inflammation-related pathophysiology.

Keywords TSPO · Neurosteroid · Anxiety disorder · $GABA_A$ receptor · Neuroregeneration

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TSPO (18 kDa): structure, distribution, function and specificity

TSPO is localized in the outer mitochondrial membrane [1, 2]. It was formerly called the peripheral-type or mitochondrial benzodiazepine receptor because the benzodiazepine (BZD) diazepam can bind to this protein. TSPO consists of a 169-amino acid sequence arranged as a five transmembrane helix structure [3] (Fig. 1). Other specific mitochondrial proteins, such as, the voltage-dependent anion channel (VDAC) and the adenine nucleotide transporter (ANT), are associated with TSPO [4–6]. TSPO shows highest expression levels in tissues that contain steroid-synthesizing cells, for example, adrenal, gonadal and brain cells [1, 7]. Within the central nervous system (CNS), TSPO is expressed in glia, microglia [8, 9] and reactive astrocytes [10, 11]. TSPO mediates various mitochondrial functions, including cholesterol transport and steroid hormone synthesis, mitochondrial respiration, mitochondrial permeability transition pore opening, apoptosis and cell proliferation [7–9, 12–14].

The steroid biosynthesis pathway results in the formation of many steroid hormones [15–17] including neurosteroids such as allopregnanolone and allotetrahydrodeoxycorticosterone (3α, 5α-THDOC). TSPO mediates the translocation of cholesterol to the inner mitochondrial membrane, which is the rate-limiting step in the synthesis of pregnenolone, the precursor of all other neurosteroids [1, 7, 18] (Fig. 1).

The synthesis of neurosteroids is brain region specific and depends on the relative amount of TSPO as well as on the expression of specific neurosteroidogenic enzymes. The 5α-reductase and 3α-hydroxysteroid dehydrogenase, which catalyze the synthesis of allopregnanolone and 3α, 5α-THDOC (positive allosteric modulators of the $GABA_A$

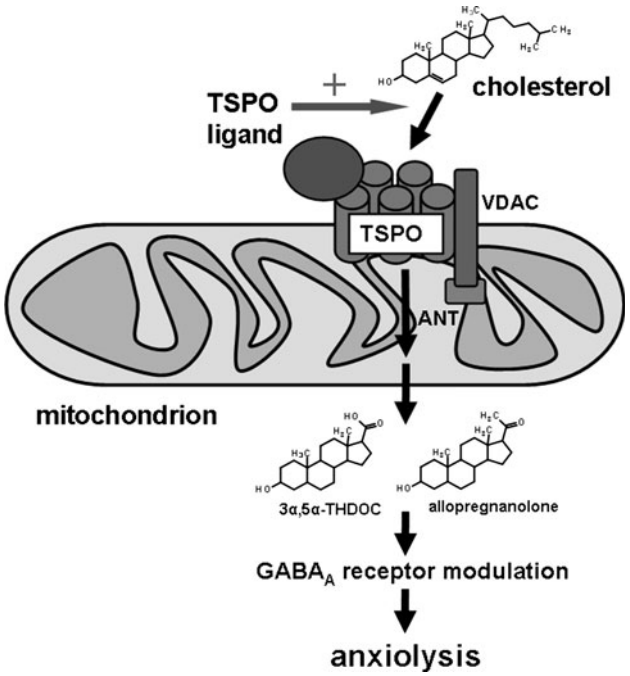

Fig. 1 Modified according to [40]. TSPO and neurosteroidogenesis. TSPO is primarily localized in the outer mitochondrial membrane; it consists of a 169-amino acid sequence arranged as a five transmembrane helix. Associated proteins are the voltage-dependent anion channel (VDAC) and the adenine nucleotide transporter (ANT). Cholesterol binds to the cytosolic carboxy terminus containing a conserved CRAC (cholesterol recognition amino acid consensus) domain; all other drug ligands bind to a region within the amino terminus. TSPO mediates the transport of cholesterol to the inner mitochondrial membrane, which is the rate-limiting step in neurosteroidogenesis. In the mitochondrial matrix, cholesterol is converted to pregnenolone and then, after diffusion into the cytoplasm, further into the neurosteroids, allopregnanolone and 3α, 5α-THDOC, which are positive allosteric $GABA_A$ receptor modulators with anxiolytic properties

receptor), have been detected in type 1 and type 2 astrocytes and oligodendrocytes [19–21] and principal output neurons, whereas these enzymes are almost absent in telencephalic or hippocampal GABAergic interneurons [22].

In psychiatric disorders, TSPO expression is reduced in peripheral blood cells of anxious subjects [23, 24], patients suffering from generalized anxiety disorder [25], social anxiety disorder [26], post-traumatic stress disorder [27] and panic disorder in the presence of adult separation anxiety disorder [28]. In schizophrenia, an association of reduced TSPO expression with anxiety, distress and aggression has been postulated [29].

Pharmacological treatment of anxiety disorders

The pharmacological treatment of anxiety disorders is still a challenge, because an anxiolytic compound without severe disadvantages has not yet been developed. BZDs exert rapid anxiolytic effects by enhancing (GABA)ergic neurotransmission [30, 31]. However, they are sedating, and their continuous use may induce tolerance effects and abuse liability [31]. Antidepressants (such as SSRIs and SNRIs) lack tolerance development and abuse liability [32], but they have a delayed onset of anxiolytic action [33].

Neurosteroids are synthesized in the brain and act as endogenous modulators of $GABA_A$ receptors [16, 34, 35]. Especially, 3α-reduced metabolites of the steroids progesterone and deoxycorticosterone are potent positive allosteric modulators of $GABA_A$ receptors even though they occupy a binding site different from that of BZDs [16, 35]. TSPO plays an important role for the synthesis of neurosteroids, thereby representing a putative novel target for anxiolytic compounds.

TSPO (18 kDa) ligands

Cholesterol, which is the substrate for the formation of neurosteroids, binds to the cytosolic carboxy terminus containing a conserved CRAC (cholesterol recognition amino acid consensus) domain [36, 37]. Currently, it is assumed that all other drug ligands bind to a region within the amino terminus [36, 38, 39].

Classical synthetic ligands of TSPO are the isoquinoline carboxamide PK 11195 and the BZD Ro5-4864 [40]. PK 11195 binds exclusively to TSPO, whereas Ro5-4864 also requires other mitochondrial protein components to reveal full binding capacity. Synthetic TSPO ligands are important tools for the scientific characterization of TSPO function, for example, as neuroimaging agents [41]. However, some TSPO ligands might also have a therapeutic potential.

Etifoxine

The first TSPO ligand that showed anxiolytic effects in a clinical trial was the benzoxazine etifoxine [42]. This compound turned out to exert anxiolytic efficacy comparable with the BZD lorazepam in patients suffering from adjustment disorders with anxiety [42]. Etifoxine enhanced tonic inhibition in hypothalamic neurons mediated by extrasynaptic $GABA_A$ receptors, an effect that could partially be inhibited by the 5α-reductase inhibitor finasteride [43]. For these reasons, an enhancement of neurosteroidogenesis appears to contribute to the anxiolytic efficacy of etifoxine [44]. However, etifoxine is also a weak direct $GABA_A$ receptor enhancer [43]. Etifoxine has been approved in France for the treatment of anxiety disorders since 1982.

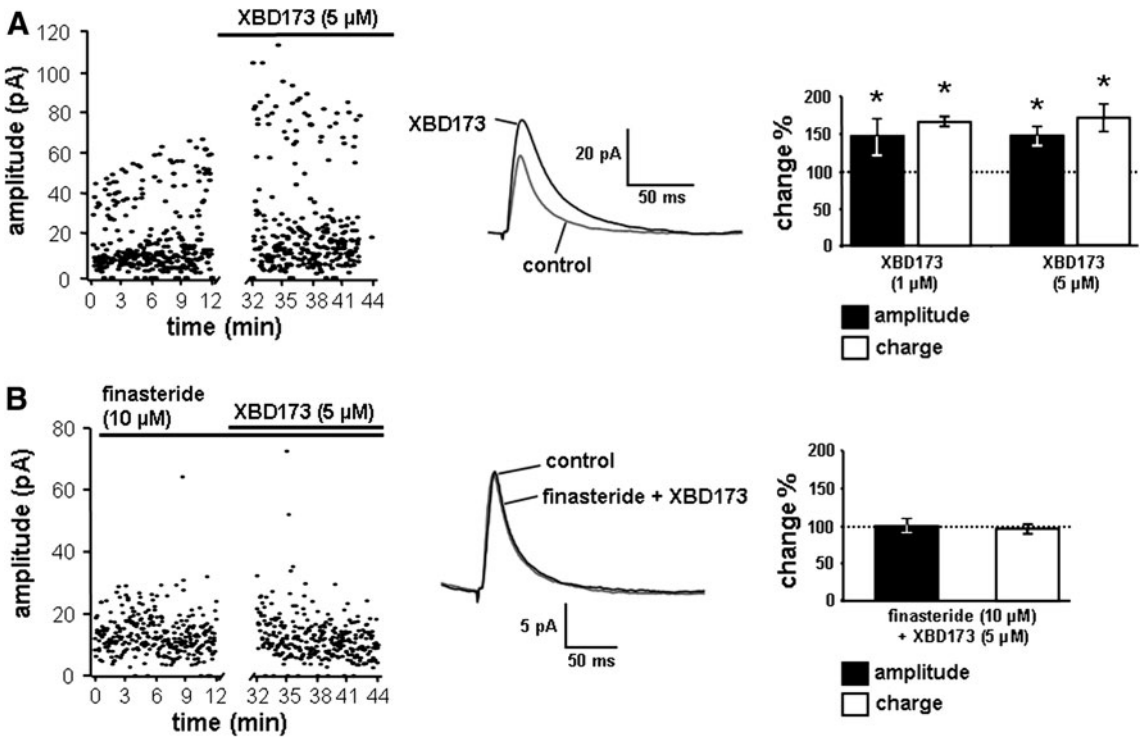

Fig. 2 Modified according to [46]. Effect of XBD173 on GABAergic neurotransmission. Whole-cell recordings and minimal stimulation were used to monitor the effect of XBD173 in mouse medial prefrontal cortex slices. The mean amplitude of all inhibitory postsynaptic currents (IPSCs) in the absence of compounds was 26.0 ± 2.7 pA (decay time constant τ: 27.8 ± 2.8 ms); the mean charge was 1.5 ± 0.7 pC (mean ± SEM of $n = 54$). Data were analyzed by the t test for paired samples, $^*P < 0.05$, as compared to control experiments. The left diagrams show individual response amplitudes during the course of one representative recording. The middle diagrams show the averaged traces from all consecutive IPSCs for control experiments and in the presence of 5 μM XBD173 or 10 μM finasteride/5 μM XBD173. The right diagrams show the averaged data of all experiments (mean ± SEM of $n = 6$–8). **a** XBD173 increases amplitude and charge of IPSCs. **b** Antagonism of the effect of XBD173 by finasteride

Xbd173

XBD173 (AC-5216, emapunil) is a phenylpurine with high and rather selective affinity to TSPO, which has recently been investigated for the treatment of anxiety disorders [45, 46]. XBD173 enhances neurosteroidogenesis in the brain, thereby exerting anxiolytic properties in animal models and in humans [46]. The amplitude and duration of GABA-mediated inhibitory postsynaptic currents (IPSCs) in mouse prefrontal cortical neurons were potentiated by XBD173, an effect that could be prevented by finasteride [46] (Fig. 2). In contrast to BZDs, XBD173 did not directly enhance $GABA_A$ receptor-mediated chloride currents [46]. XBD173 counteracted pharmacologically induced panic attacks in rodents without exerting sedative effects [46]. In healthy male volunteers, the antipanic efficacy of XBD173 was comparable to the BZD alprazolam during pharmacologically induced panic by cholecystokinin tetrapeptide (CCK-4) [46] (Fig. 3). This placebo–controlled, parallel group-proof of concept study included subjects with a sufficient panic response after CCK-4 application. Seventy-one subjects were randomized to a 7-day treatment with placebo, 10, 30 or 90 mg/day XBD173 or 2 mg/day alprazolam. At the end of the study, subjects underwent a second CCK-4 challenge. The difference in the acute panic inventory (API) (area under the time curve; AUC) between the first and the second CCK-4 challenge relative to the effects of placebo was defined as readout for anxiolytic efficacy. For both alprazolam and the highest dose of XBD173, a significant difference from placebo could be demonstrated. Interestingly, the XBD173 groups did not suffer from sedation or withdrawal symptoms after the 7-day treatment in contrast to alprazolam treated subjects.

Role of TSPO in neurologic disorders

After peripheral nervous system injuries, TSPO has been shown to be upregulated in Schwann cells, macrophages and neurons [47–49]. With regard to therapeutic efficacy, TSPO ligands seem to reveal neuroprotective effects in experimental models of peripheral neuropathies, thereby indicating a key role of TSPO in the pathophysiology also

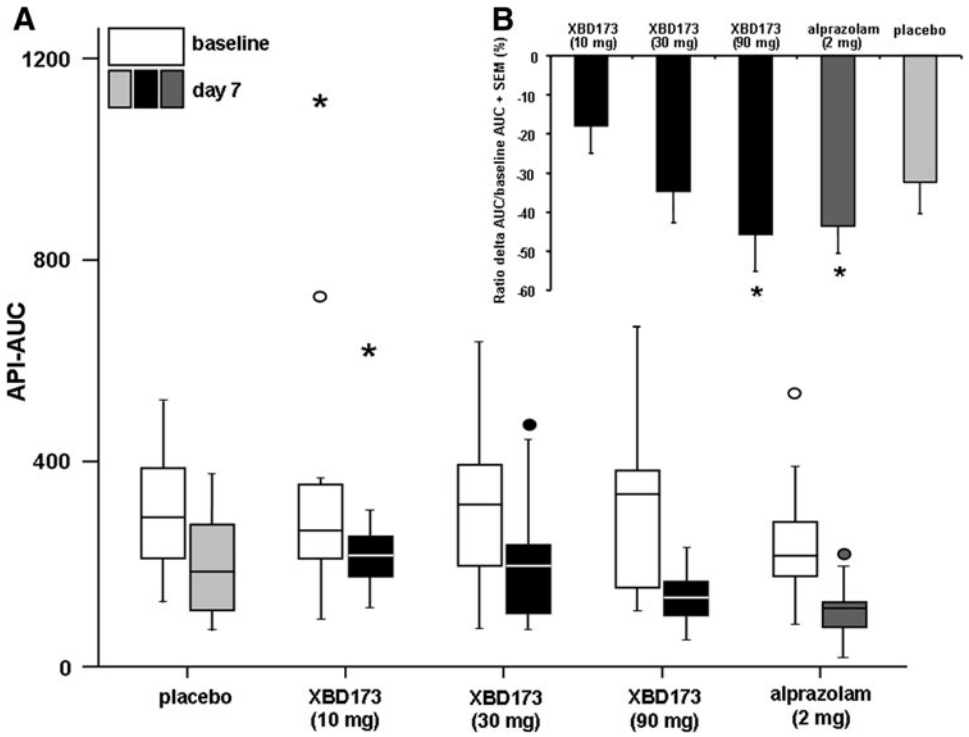

Fig. 3 Modified according to [46]. Effect of XBD173 on CCK-4 induced panic. **a** Area under the time curve (AUC) of the acute panic inventory (API) score of healthy male volunteers during a first (before treatment) and a second (after 7 days of treatment) CCK-4 challenge. *Box* plots represent the median equivalent to the 50 % percentile (*line within the boxes*), the range containing all individual values above the 25 % and below the 75 % percentile (*boxes*) and the range of individual values within 150 % above or below the difference between the 75 % and the 25 % percentile (*error bars*). *Open circles* represent outliers located more than 150 %, and *asterisks* represent extreme values located more than 300 % of the *box* height above the 75 % percentile. **b** Decrease in CCK-4 induced panic (delta API-AUC) after treatment with different dosages of XBD173, the BZD alprazolam or placebo in relation to baseline AUC (mean ± SEM). *Asterisks* indicate a significant difference from placebo (ANCOVA: 90 mg XBD173 $P < 0.036$, alprazolam $P < 0.019$)

of peripheral nervous system disorders [50–52]. Especially for the management of neuropathic pain, for example, diabetes or chemotherapy-induced pain, TSPO ligands appear to be a promising therapeutic approach. In this context, the modulation of inflammatory cytokines appears to play an important role [53]. With regard to brain damage due to cerebral infarction or injury, TSPO ligands might rather support the prevention of secondary pathophysiological consequences of such diseases [54, 55]. In neurodegenerative disorders, only few studies exist, investigating potential beneficial effects of TSPO ligands. However, there are hints that TSPO levels in astrocytes are altered in different models of neurodegeneration and Alzheimer's disease [56].

Conclusion

The need for alternative compounds with anxiolytic and neuroprotective efficacy is obvious. Potentially, the indirect modulation of $GABA_A$ receptor function via neurosteroidogenesis and the mediation of antiinflammatory effects within the CNS by TSPO ligands could be a promising approach. Nevertheless, such emerging compounds will have to prove their utility under clinical conditions.

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Conflict of interest R. Rupprecht has been on Novartis advisory boards. The clinical study on XBD173 (46) has been sponsored by Novartis, Switzerland. C. Nothdurfter, T. C. Baghai and C. Schüle declare that they have no conflict of interest.

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