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three-dimensional (3D) reconstruction (26) of a trajectory containing both helical swimming and a clearly recognizable sharp turning event (Fig. 4B). Analysis of hundreds of sharp turns from 3D trajectories (24) yields the probability distribution of their angular speeds (Fig. 4C) and duration (Fig. 4D). The range of angular speeds is consistent with an estimate derived from the average frequency difference during asynchronous beating periods and the average angular rotation of the cell body per flagellar beat (24). The distribution of durations of turns is nearly identical to that of drifts (Fig. 4D) and incompatible with that of slips, the only other observed behavior that could lead to turns in the dark. These results indicate that sharp turns are the direct consequence of periods of asynchronous flagellar beating. Because sharp turns are defined by angular speeds much higher than typical background rates (Fig. 4B), we choose to consider these as the only turning events, which separate straight-line free-flight segments. The probability distribution of the duration of such free flights, shown in Fig. 4E, decays exponentially with a mean of $\tau = 11.2$ s. This time scale is clearly the one inferred earlier from the macroscopic diffusion measurements. The diffusion constant D can be estimated more precisely with the well-known results from run-and-tumble random walk models (14). With the average parameters extracted from the 3D trajectories, we obtain (24) $D \cong (0.47 \pm 0.05) \times 10^{-3} \text{ cm}^2/\text{s}$, which is in very good agreement with the value estimated from the macroscopic measurements on large populations.

We have found that in the dark, *C. reinhardtii* can vary the intrinsic frequencies of its two flagella so that they alternate between synchronous and asynchronous beating, with synchrony realized through a mechanism consistent with hydrodynamic coupling. This leads to swimming trajectories with stochastically distributed sharp turns and ultimately to the diffusive behavior of a population. In contrast to previous observations on cell models (20), we showed that in each cell either flagellum can beat faster than the other. This approximate symmetry is a strong indication that the unknown regulatory system at work here is distinct from that governing phototaxis, which is based instead on opposite amplitude modulations of flagellar motion, and it shows that the idea of a well-defined intrinsic frequency difference between cis and trans flagella is incorrect. Such control mechanisms could also have a role in coordinating large numbers of cilia in simple multicellular organisms lacking a central nervous system (such as *Volvox*). Open issues include the origins of this regulation, the characteristic time scale between asynchronous intervals, and the noise of flagellar beats, along with the possible interplay of these processes with chemotaxis and phototaxis.

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Materials and Methods

Figs. S1 to S3

References

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Translocator Protein (18 kD) as Target for Anxiolytics Without Benzodiazepine-Like Side Effects

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Most antianxiety drugs (anxiolytics) work by modulating neurotransmitters in the brain. Benzodiazepines are fast and effective anxiolytic drugs; however, their long-term use is limited by the development of tolerance and withdrawal symptoms. Ligands of the translocator protein [18 kilodaltons (kD)] may promote the synthesis of endogenous neurosteroids, which also exert anxiolytic effects in animal models. Here, we found that the translocator protein (18 kD) ligand XBD173 enhanced γ -aminobutyric acid-mediated neurotransmission and counteracted induced panic attacks in rodents in the absence of sedation and tolerance development. XBD173 also exerted antipanic activity in humans and, in contrast to benzodiazepines, did not cause sedation or withdrawal symptoms. Thus, translocator protein (18 kD) ligands are promising candidates for fast-acting anxiolytic drugs with less severe side effects than benzodiazepines.

Anxiety disorders are highly prevalent disabling disorders (1) that frequently turn into chronic clinical conditions (2). Benzodiazepines such as diazepam are fast-acting and effective antianxiety agents (3–5) and the most commonly prescribed anxiolytics. However, their side effects such as sedation and, following chronic administration, development of tolerance, consecutive abuse liability, and withdrawal symptoms render their use problematic in the long-term treatment of anxiety disorders (2–4). Currently, antidepressants such as selective serotonin reuptake inhibitors are first-line treatment for most anxiety disorders. However, their anxiolytic effects occur only after several

weeks of treatment (2–4). Thus, there is need for anxiolytic agents that retain the rapid anxiolytic potential of benzodiazepines but lack their unfavorable side effects.

Neurosteroids are synthesized from cholesterol or steroidal precursors and modulate neurotransmitter receptors (6–8). Ring A-reduced neurosteroids are endogenous metabolites of the hormone progesterone and potent positive allosteric modulators of γ -aminobutyric acid type A (GABA_A) receptors, which mediate the effects of the inhibitory neurotransmitter GABA in the mammalian nervous system (6–8). They exert pronounced anxiolytic effects in animal models (9–11), and their concentrations are reduced

during panic attacks in patients with panic disorder (12, 13). Thus, neurosteroidogenic compounds might represent a previously undiscovered anxiolytic principle. The translocator protein (18 kD), formerly called peripheral or mitochondrial benzodiazepine receptor, is mainly located in the outer mitochondrial membrane and favors the transport of cholesterol to the inner mitochondrial membrane, ultimately promoting neu-

rosteroid synthesis (14, 15). Certain ligands of this protein have been shown to enhance neurosteroidogenesis in the brain (16–18) and to exert acute anxiolytic/anticonflict activity in rodent models (17–20). However, so far no data are available as to whether such compounds act as anxiolytics also in humans or whether they lack tolerance development and withdrawal effects.

XBD173 binds to the translocator protein (18 kD) with nanomolar affinity and shows negligible affinity to a broad range of neurotransmitter receptors, including GABA_A receptors (19).

At the cellular level, we examined whether XBD173 modulates the GABA-induced response in human WSS1 cells expressing rat $\alpha_1\gamma_2$ and human β_3 GABA_A receptor subunits. In contrast to diazepam, XBD173 did not enhance GABA-evoked chloride currents (fig. S1, A to C). However, in mouse neocortical slices XBD173 potentiated GABA-mediated (GABAergic) neurotransmission (Fig. 1A, fig. S2D, and table S1A), which was prevented by the 5 α -reductase in-

hibitor finasteride (Fig. 1B). This is in line with the induction of neurosteroidogenesis after XBD173 administration (fig. S1D). Thus, the enhancement of GABAergic neurotransmission by XBD173 in vivo is mediated indirectly through the generation of GABAergic neurosteroids.

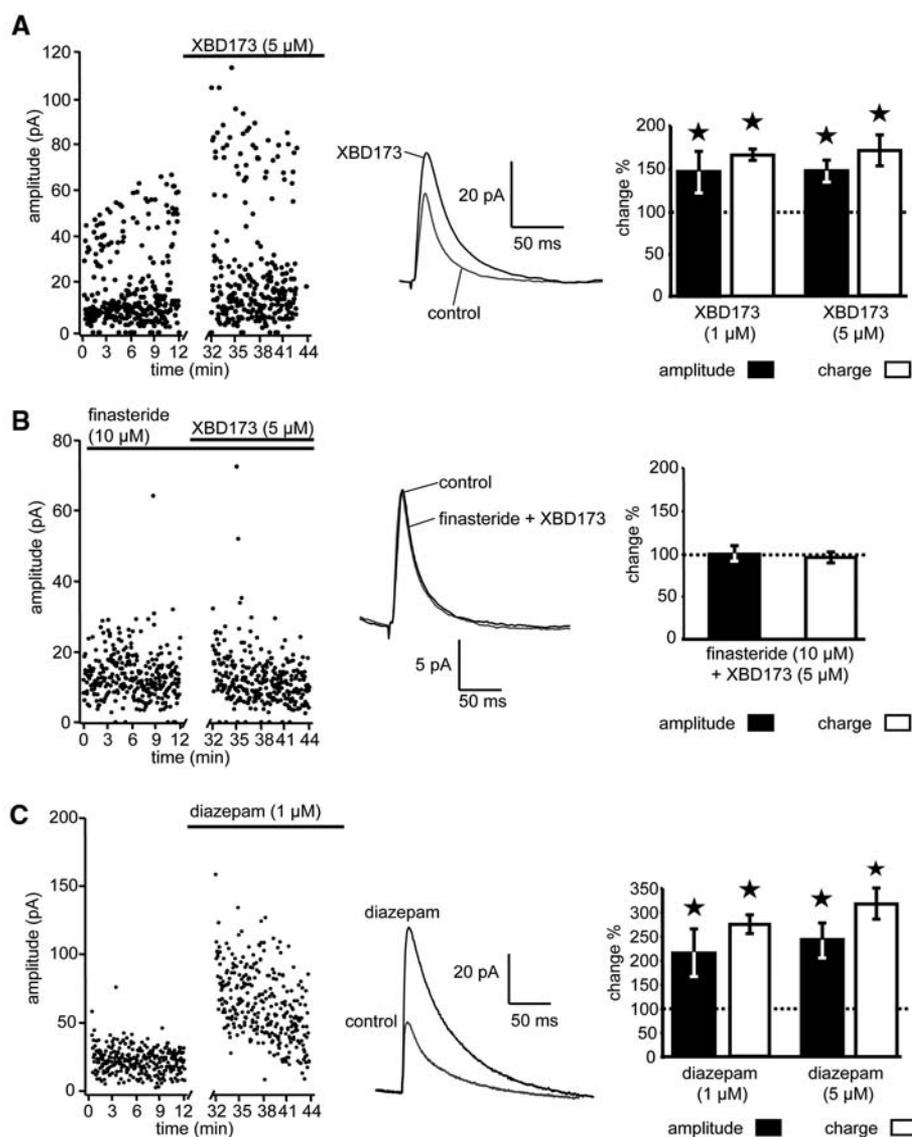
XBD173 exerted acute anxiolytic effects, which were prevented by the translocator protein (18 kD) antagonist PK11195 (fig. S3, A and B), in the social exploration test in rats and the elevated plus maze test (table S2). To address tolerance development, we administered XBD173 to rats twice daily for 5 days. Its anxiolytic activity in the social exploration test was fully retained with this subchronic administration (fig. S3A). Next, we explored whether XBD173 could counteract lactate- or cholecystinin tetrapeptide (CCK4)-induced panic in rodent paradigms, because panic-like anxiety can be experimentally induced in humans through challenge with lactate or the neuropeptide fragment CCK4 (12, 21). Both the benzodiazepine alprazolam and XBD173

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Fig. 1. Effects of XBD173 and diazepam on GABAergic neurotransmission in slices of the medial prefrontal cortex. The mean amplitude of all recorded inhibitory postsynaptic currents (IPSCs) in the absence of compounds was 26.0 ± 2.7 pA with a decay time constant (τ) of 27.8 ± 2.8 ms, and the mean charge was 1.5 ± 0.7 pC (mean \pm SEM) ($n = 54$ neurons). (A to C) (Left) Individual response amplitudes during the course of a representative experiment. (Middle) Averaged traces from all consecutive IPSCs for the control experiments and in the presence of 5 μ M XBD173, 10 μ M finasteride and 5 μ M XBD173, or 1 μ M diazepam. Compounds were applied for at least 20 min at the indicated concentrations before IPSCs were recorded. (Right) Averaged data (mean \pm SEM) of all experiments ($n = 6$ to 8 neurons). (A) Effects of XBD173. The effect of XBD173 was monitored with whole-cell recordings and minimal stimulation. XBD173 increases the amplitude and charge and prolongs the decay of GABA_A receptor-mediated synaptic transmission (table S1A). (B) Antagonism of the effects of XBD173 by finasteride. (C) Effects of diazepam. Diazepam increases the amplitude and charge of GABA_A receptor-mediated synaptic transmission. Electrophysiological data were analyzed by the *t* test for paired samples. * $P < 0.05$, as compared with control experiments.



effectively prevented panic behavior elicited by means of an infusion of sodium lactate in panic-prone rats (Fig. 2A). No sedation was observed after treatment with XBD173, whereas alprazolam caused a marked reduction in locomotor activity (fig. S4). Also, in the CCK4 challenge paradigm in rats both alprazolam (Fig. 2B) and XBD173 (Fig. 2C) clearly displayed antipanic properties. These preclinical studies suggest that XBD173 exerts rapid anxiolytic and antipanic effects with a more favorable side-effect profile than that of benzodiazepines.

Next, we investigated the anxiolytic potential of XBD173 in healthy male volunteers using the CCK4 challenge. Only subjects that showed a clear panic response to the initial CCK4 challenge entered one of the five treatment arms of the study ($n = 14$ subjects each). Out of 85 subjects, 71 healthy volunteers were randomized to treatment for 7 consecutive days with placebo, 10, 30, or 90 mg/day XBD173 or 2 mg/day alprazolam before undergoing a second CCK4 challenge. Seventy subjects completed the study (fig. S5). Both XBD173 and alprazolam were rapidly absorbed, with peak concentrations occurring within 2.5 hours after oral administration (fig. S6). For analysis of the anxiolytic potential of XBD173 and alprazolam, the difference in the acute panic inventory (API) [area under the time curve (AUC)] between the first and the second challenge with CCK4 relative to the effects of placebo served as an efficacy parameter in this exploratory analysis (Fig. 3 and fig. S5). One-way analysis of covariance (ANCOVA) revealed a significant difference from placebo in attenuating CCK4-induced anxiety after both alprazolam

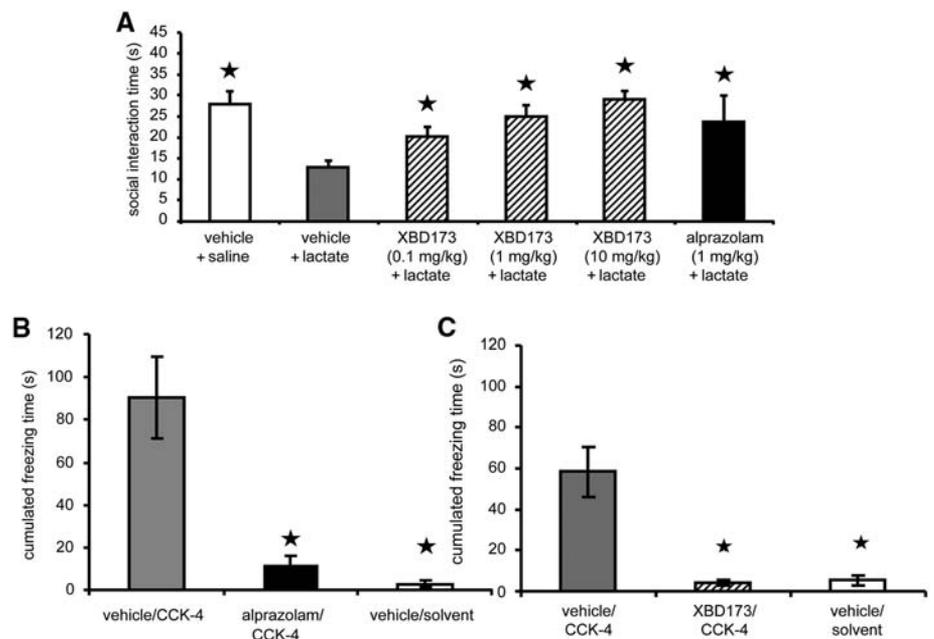
and the highest dose of XBD173 (Fig. 3). The number of side effects reported with XBD173 was comparable to the incidence in the placebo group. In contrast, a much higher incidence was reported by the alprazolam-treated group, in particular dizziness and somnolence (table S3A). Although 57% of the subjects treated with alprazolam complained of withdrawal symptoms such as sleep disturbances or restlessness, these were almost absent in the XBD173-treated groups (table S3B). No serious adverse event occurred during the entire study, and there was no need for treatment of withdrawal symptoms. Thus, this placebo-controlled parallel group study indicates that in humans XBD173 has both anxiolytic properties and clearly fewer side effects compared with benzodiazepines.

Ligands of the translocator protein (18 kD) such as XBD173 may represent a pharmacological mechanism for the treatment of anxiety disorders (13). XBD173 seems to be superior to benzodiazepines because a rapid anxiolytic activity is retained in the absence of their well-known side effects (3, 4). This fast anxiolytic effect is also superior to antidepressants, which have a considerably slower onset of action (2–4). Surprisingly, withdrawal symptoms were reported after treatment with alprazolam for only 7 days. This is remarkable because prescription of benzodiazepines is recommended for up to 4 weeks (3, 4). No withdrawal symptoms were noted in the XBD173-treated subjects in spite of an anxiolytic efficacy of the 90 mg/day dose comparable to that of alprazolam, which is in line with the lack of withdrawal-induced hypophagia after chronic administration of XBD173 in mice (13). A major

challenge in the development of anxiolytic compounds is the failure rate in clinical trials, even for those compounds with proven preclinical anxiolytic properties in commonly used animal models. The possibility of the challenge with sodium lactate or CCK4 in rats and humans (12, 22) may thus represent an advantage in a translational approach for evaluating anxiolytics. Although the CCK4 challenge was used as a surrogate marker, which does not allow us to draw firm conclusions on the efficacy of XBD173 in anxiety disorders, CCK4 fulfills the criteria for an ideal panicogenic agent (21, 23, 24), and the panic induction by CCK4 is sensitive to clinically effective anxiolytic agents, including benzodiazepines (24, 25).

Translocator protein (18 kD) ligands promote the biosynthesis of endogenous neurosteroids (17, 18, 26). An enhancement of GABAergic neurotransmission by neurosteroids probably accounts for the anxiolytic effects of XBD173 because anxiolytic effects of translocator protein (18 kD) ligands can be prevented by finasteride (26) and neurosteroidogenesis is increased after XBD173 administration. Moreover, XBD173 potentiated GABAergic neurotransmission in neocortical slices, and its GABA-enhancing potential was prevented by finasteride (13). Neurosteroids modulate GABA_A receptors via an allosteric site different from that targeted by benzodiazepines (5, 7, 27). These distinct sites of action at the GABA_A receptor might explain the lack of tolerance development and withdrawal symptoms after XBD173-induced neurosteroidogenesis. There is considerable evidence for an involvement of neurosteroids in the etiology of anxiety

Fig. 2. Effects of XBD173 or alprazolam in models for pharmacologically induced panic in rats. **(A)** Effect of an acute pretreatment (–60 min) with XBD173 (0.1, 1, or 10 mg/kg per second orally) or alprazolam (1 mg/kg intraperitoneally) on the time spent in social interaction after an intravenous infusion of a 1 M sodium lactate solution in panic-prone rats. Bars represent the mean (\pm SEM) social interaction time during 5 min after the lactate challenge ($n = 8$ rats per group). Data were analyzed by means of restricted maximum-likelihood analysis of variance (ANOVA) followed by Student's *t* test. $*P < 0.05$, as compared with rats treated with vehicle and lactate. **(B)** Effects of alprazolam on the freezing response induced by 10 mg/kg subcutaneously CCK4. Bars represent the mean (\pm SEM) of the cumulated time spent freezing between 2 and 15 min after an injection of CCK4 or solvent ($n = 11$ rats per group). Rats were subcutaneously pretreated with either vehicle or alprazolam (0.1 mg/kg) 15 min before CCK4 or solvent injection. **(C)** Effects of XBD173 on the freezing response induced by 10 mg/kg subcutaneously CCK4. Bars represent the mean (\pm SEM) of the cumulated time spent freezing between 2 and 10 min after an injection of CCK4 or solvent ($n = 10$ rats per group). Rats were orally pretreated with either vehicle or XBD173 (0.1 mg/kg) 60 min before CCK4 or solvent injection. Data were analyzed by means of Kruskal-Wallis one-way ANOVA followed by the Mann-Whitney *U* test. $*P < 0.001$, as compared with control rats treated with vehicle and CCK4.



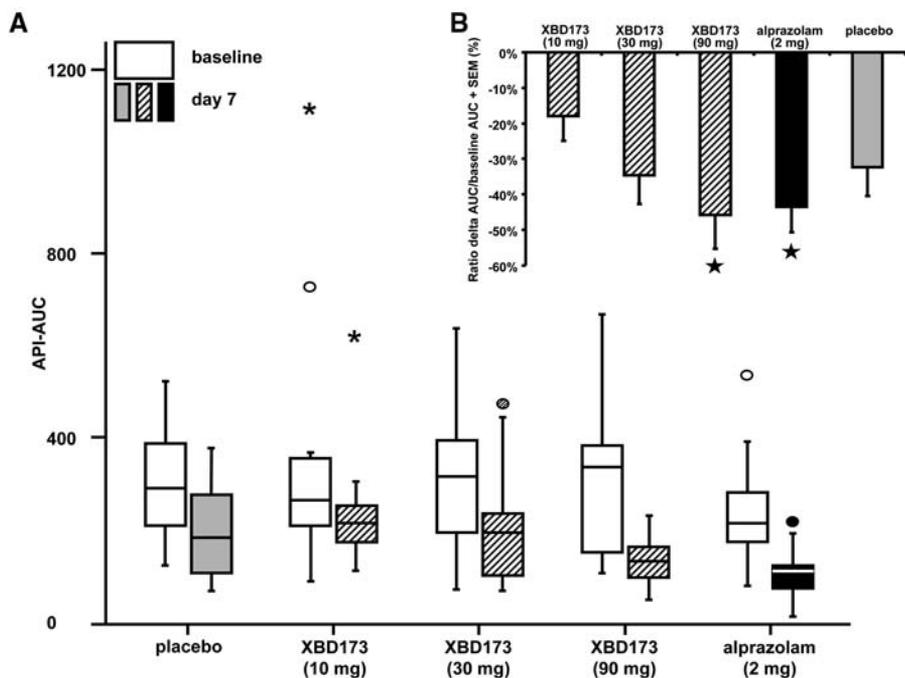


Fig. 3. Effects of XBD173 or alprazolam on CCK4-induced anxiety in healthy male volunteers. **(A)** AUC of the API score during the first and second CCK4 challenge. Boxplots represent the median equivalent to the 50th percentile (line within the boxes), the range containing all individual values above the 25th and below the 75th percentile (boxes), and the range of individual values within 150% above or below the difference between the 75th and the 25th percentile (error bars). Open circles indicate outliers located more than 150% and asterisks indicate extreme values located more than 300% of the box height above the 75th percentile. **(B)** Decrease in CCK4-induced anxiety (Δ API-AUC) after treatment with XBD173, alprazolam, or placebo in relation to baseline AUC (mean \pm SEM). Asterisks indicate a significant difference against placebo for 90 mg XBD173 ($P < 0.036$) and alprazolam ($P < 0.019$) by way of ANCOVA.

disorders. Neurosteroid homeostasis is altered (12, 13), and translocator protein (18 kD)-binding sites on platelets are reduced in panic disorder (28). Moreover, variations in the encoding gene may confer susceptibility to this disease (29).

XBD173 enhances GABAergic neurotransmission via induction of neurosteroidogenesis and shows anxiolytic efficacy in humans with a favorable side-effect profile, which suggests that the translocator protein (18 kD) represents a target for anxiolytic drug discovery.

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ERRATUM

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Reports: "Translocator protein (18 kD) as target for anxiolytics without benzodiazepine-like side effects" by R. Rupprecht *et al.* (24 July, p. 490). In the fourth line of the caption for Fig. 2, the dosage of XBD173 should be: 0.1, 1, or 10 mg/kg orally.