Neurexan: The Bioregulatory Approach to the Treatment of Stress and Stress-related Disorders—Preclinical and Clinical Considerations

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In modern life, chronic stress becomes a main culprit of many mental and somatic disorders. The therapy for chronic stress often requires a multidisciplinary approach because drug therapies are often unsatisfactory and are associated with adverse effects that impair the possibilities of long-term treatment. In addition, recent research on stress and stress-related disorders revealed the high complexity of neurotransmitter physiology, implicating multiple possible targets for treatment. However, this complexity probably impairs the success of treatment with selectively acting pharmaceuticals that are developed to target specific metabolic pathways. Therefore, it is more and more apparent that regulating transmitter balance may be a promising extension of available treatments. Neurexan, a natural compound medicinal product, seems to be a potential therapeutic option. The medication has been studied in clinical trials and seems to be effective in the treatment of stress and stress-related complaints, such as sleep disturbance, nervousness, restlessness, difficulties with concentration, forgetfulness, and nocturnal anxiety. In preclinical studies, an affinity of Neurexan to the central γ-aminobutyric acid (GABA) benzodiazepine receptor was observed. From these results, the peripheral benzodiazepine receptor system also could be a target of the medication, generating neuroactive steroids known to be highly potent allostatic modulators of the GABA signaling pathway. Both receptors are fundamentally involved in the mediation of the stress response. Based on the results from preclinical and clinical studies performed with Neurexan and knowledge about stress, this study will try to contribute to a better understanding of the potential implication of Neurexan in the treatment of stress and stress-related disorders. (*Altern Ther Health Med.* 2011;17(2 Suppl):S32-S40.)

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From an evolutionary viewpoint, stress is important for the development of successful strategies for animals and humans to cope with the demands of life. If an individual is able to meet the challenges of life, then acute stress seems not to be harmful and physiological balance can be maintained. However, if "overwhelming" tasks last too long, then stress becomes deleterious and increases an individual's vulnerability to mental and somatic disorders. Based on this distinction, good stress is termed *eustress* and bad stress is termed *distress*. In modern life, work can become a source of distress for a variety of reasons. Feelings of inadequate control over one's work, frustrated hopes and expectations, and losing life's meaning seem to be independent causes of chronic exhaustion and can lead to so-called burnout. Nearly 30% of the adults in Western countries are affected by burnout.[1,2]

In recent years, research on stress has considerably enhanced the understanding of the underlying pathophysiology. Many mediators and neurotransmitters that are directly associated with the stress response can be identified. Examples include corticotropin-releasing factor, corticosteroids, oxytocin, prolactin and vasopressin, serotonin, norepinephrine, dopamine, vasoactive intestinal polypeptide, neuropeptide Y, cholecystokinin, substance P, nitric oxide, proinflammatory mediators, γ-aminobutyric acid (GABA), and neuroactive steroids. These mediators and neurotransmitters play a key role in the overall balance between neuronal excitation and inhibition.[3]

Because of the complexity of the pathophysiology of stress, the focus on more or less selective pathophysiological targets, as is the case in treatment with benzodiazepines (eg, diazepam and lorazepam) and selective serotonin reuptake inhibitors (SSRIs; eg, citalopram, fluoxetine, and paroxetine), is often suboptimal with heterogeneous outcomes.[4,5]

Therefore, it is suggested that a multitarget bioregulatory approach may expand the existing treatment possibilities. Bioregulation aims at homeostasis that is "the coordinated physiological reaction which maintains most of the steady states in the body."[6] This integrates the mind and the body, and it is assumed that nearly all naturopathic treatments affect the body holistically.[7] Complex homeopathic preparations seem to act both on a low substantial level and on an energetic level because of the succussion procedure of the diluted constituents during the manufacturing process. This may explain the observed modulating effect on homeostasis. Therefore, bioregulatory medicine seems to be especially useful in functional disorders of the mind and body.[8]

Neurexan, a complex homeopathic medicinal product, is effective in fostering mental balance during stress and associated complaints (eg, nervousness, restlessness, and sleeplessness). Based on the results of preclinical and clinical research on

Neurexan and knowledge about the pathophysiology of stress, this study will discuss the hypothetical mode of action of this medication and the possible clinical implications for the treatment of stress and stress-related disorders.

STRESS AND STRESS-RELATED DISORDERS

From a scientific viewpoint, stress is generally described as a state of bodily or mental tension resulting from factors that tend to alter an existing equilibrium.[9] This definition can lead back to Hans Selye, who defined stress as "the non-specific response of the body to any demand" leading to perturbations of physiological and psychological homeostasis.[10] Selye observed that the body develops a nonspecific response to stressors when their action is prolonged. This was termed *general adaptation syndrome* and involved the following triphasic response[11]:

1. The "alarm reaction": Acute stress is characterized by an activation of the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic nervous system, with elevated levels of cortisol, epinephrine, and norepinephrine. The physiological adaptation (eg, an increase in blood pressure, heart and breathing rates, glucose level, and oxygen consumption) allows the body to act according to the archetypical "fight-and-flight" behavior. After a stressful event, a sufficient recovery restores the body to the basic level.

2. The "stage of resistance": In the case of permanent stress with insufficient recovery from stressful events, the organism progressively loses the natural capacity to regulate stress response and to recover to the normal level again. Persistent changes of physiological parameters affected in acute stress cause a pathological adaptation in the attempt of the organism to obtain an optimal adaptation to chronic stress. Disorders, such as hypertension, metabolic syndrome, gastrointestinal dysfunction, and headache, develop.

3. The "stage of exhaustion": In the case of persistent stress, the signs and symptoms of the alert and resistance phase become irreversible, characterized by the loss of acquired adaptation. Chronic mental and somatic diseases are the consequences. Impaired sleep, concentration, and memory and mood disorders become more and more prominent and are a characteristic feature of exhaustion and burnout.

From an evolutionary viewpoint, stressful situations should adapt the body to excessive physical demands ("fight-or-flight" response) that are necessary for survival. However, in modern life, both fight and flight are typically not options and no adequate demand for such physiological and metabolic adaptations exists. Therefore, chronic stress becomes deleterious. An example of the serious consequences of chronic stress is burnout syndrome. The term *burnout* was coined in 1974 by the psychoanalyst Herbert Freudenberger and originally related to people working in highly engaged social jobs (eg, teachers, nurses, and physicians) with increased risk for chronic exhaustion and illness. Meanwhile, burnout can affect nearly all social groups irrespective of occupation. Burnout is mainly regarded as the result of chronic stress that has not been successfully treated.[12] The complete syndrome is an end stage of chronic distress.

In addition to the subjective feeling of excessive demands and exhaustion, chronic stress induces many objective comorbidities, such as a decline in memory and cognition and sleep disturbances.[13] In addition, chronic distress is a considerable risk factor for the development of anxiety and depressive disorders.[14] Stressful events often precede the onset of depression, and stress also has been associated with the severity of the illness.[15] In addition, recent depressive and anxious symptoms predict stress response in humans.[16] Thus, the connection between chronic stress, insomnia, and mental disorders has the feature of a vicious circle and can explain, at least in part, the development of burnout syndrome.

Clinically, burnout syndrome is characterized by emotional exhaustion, depersonalization, physical fatigue, and cognitive weariness. This is accompanied by reduced personal accomplishment and satisfaction in performance, a sense of inadequacy, memory problems, loss of social contacts, and depressed mood.[12] The risk for drug or alcohol dependency is increased, and the immunocompromised body is susceptible to infections and a proinflammatory state. Also, insomnia impairs recovery, leading to dramatic consequences for mental and somatic health. Patients are susceptible to major depression, cardiovascular or gastrointestinal diseases, and even cancer.[17] In half of the participants with job-related burnout, some depressive disorders can be determined. The risk of depressive disorders is greater when burnout is severe.[1]

Chronic stress and burnout are linked to ill health. Although virtually all organs are affected by the exposure to exhaustive stress, the cardiovascular, neuroendocrine, immunological, and gastrointestinal systems are the first to experience functional changes. In Japan, sudden death caused by occupational overload is called *karoshi* and is related to chronic stress and burnout.[18]

From a physiological viewpoint in the case of chronic stress, the body, little by little, loses the capability to regulate the stress response. This also means that, in times without an acute stressful event, the physiological balance (allostasis) is not recovered again. Therefore, chronic distress and burnout can be viewed as a long-lasting overactive stress system with a loss of self-regulation.[13] This loss of acquired adaptation provokes an allostatic load that can accelerate disease processes.

The term *allostatic load* was coined in 1993 by Bruce McEwen and Elliot Stellar as a multisystem summary indicator that refers to the physiological risk of chronic stress response.[19] Allostatic load comprises the following parameters indicative of being relevant disease mediators: cortisol, epinephrine and norepinephrine, dehydroepiandosterone (DHEA) sulfate, waist-to-hip ratio, glycosylated hemoglobin, high-density lipoprotein,

total cholesterol to high-density lipoprotein ratio, systolic and diastolic blood pressures, tumor necrosis factor α, C-reactive protein, fibrinogen, d-dimer (ie, decomposition product of fibrin), percentage of body fat, triglycerides, and glucose.[20] In addition, mental disorders often associated with chronic stress, such as depression, are related to chemical imbalances in the central nervous system (CNS) that constitute a special form of allostatic load.[21]

The loss of allostasis, with changes toward allostatic load, and the development of diseases involve a complex interaction of neural, neuroendocrine, and neuroendocrine-immune mechanisms, with dysbalanced HPA axis activation as a central mechanism. For stress regulation and treatment options, two targets are especially important: the GABAergic system, acting via GABA, and the peripheral benzodiazepine receptor (PBR) pathway, generating neuroactive steroids known to be highly potent allostatic modulators of the GABA signaling pathway.

THERAPEUTIC TARGETS FOR THE TREATMENT OF STRESS AND STRESS-RELATED DISORDERS

The first target is GABA, the principal inhibitory neurotransmitter in the brain. It plays a key role in the overall balance between neuronal excitation and inhibition. In the mammalian brain, as many as one third of all synapses are GABAergic.[22] GABA is synthesized in presynaptic neurons and stored in synaptic vesicles. On neuronal activation, GABA is released into the synaptic cleft, where it activates postsynaptic GABA receptors and reduces the excitability of the neurons.[22-24]

Excessive GABAergic signaling results in sedation, whereas the mildest attenuation of GABAergic signaling results in arousal, anxiety, restlessness, and insomnia. Therefore, GABA is essentially involved in the regulation of sleep. Dysfunction also has been demonstrated in psychiatric disorders, such as anxiety and depression.[25] The GABAergic system is also considered one of the major neuronal mechanisms that underlies learning and memory.[26] The GABAergic system plays a central role in homeostasis during stress; the inhibitory role of GABA on the HPA axis is well established.[27] GABA is known to inhibit the release of corticotropin-releasing hormone from the hypothalamus, followed by reduced secretion of adrenocorticotropin from the pituitary gland and, subsequently, glucocorticoids from the adrenal gland.[28,29]

Normally, the HPA axis is under autoregulatory control, and an increase of cortisol will negatively affect feedback and dampen HPA axis activity.[9] Disruption of this homeostatic mechanism may play an etiopathogenic role in disorders related to stress and is often associated with increased adrenal glucocorticoid output.[30] Intensive stress and a prolonged increase in corticosterone levels attenuate GABAergic control because of altered GABA(A) benzodiazepine binding density.[31] This impairs the inhibitory activity of GABA on HPA axis activation and can deplete resources. Although acute stress causes hypercortisolism, long-standing strain on the HPA axis may lead to hypocortisolism.[32] Therefore, for cortisol levels, the clinical findings in burnout and stress-related disorders are often inconsistent. Elevations in the levels of circulating glucocorticoids are often seen in depressive disorders[33]; in patients with chronic exhaustive conditions, such as chronic fatigue syndrome and vital exhaustion, hypocortisolism is a prominent feature.[34,35]

Benzodiazepines are widely used in the treatment of stress and stress-related disorders. These medications target the central benzodiazepine receptor, which is a component of the GABA(A) receptor distinct from the GABA binding site.[36] Receptor agonists, such as benzodiazepines and some natural compounds, only potentiate the effects of GABA and cannot directly activate the receptor. They enhance the effect of GABA by lowering the concentration of GABA required to open the GABA(A) channel, thus augmenting its inhibitory effects.[25] Flumazenil, an antagonist at the GABA(A) benzodiazepine binding site, displaces benzodiazepines from this receptor and is clinically used to neutralize the sedative effects of these drugs. In receptor-binding studies, Neurexan could displace flumazenil from the receptor, suggesting that enhanced GABA signaling is a mode of action of this natural compound medication.[37] This could reconstitute the GABAergic control in the stress response.

Additional targets of Neurexan may be the modulation of neuroactive steroids. Neuroactive steroids serve as endogenous homeostatic mechanisms, restoring both normal GABAergic activity and HPA axis function after acute stress.[38] They are involved in various neurological disorders (eg, anxiety and mood disorders) and psychotic, childhood, eating, dementia, stress, and postpartum disorders.[39,40] Neuroactive steroids (eg, allopregnenolone) are pregnane steroids and are among the most potent allosteric modulators of the GABA(A) receptor. They are active in nanomolar concentrations[41] and play a role in the fine-tuning of CNS functioning by targeting the activity of GABAergic and glutamatergic transmissions.[40] Thus, both inhibitory (GABA) and excitatory (*N*-methyl-D-aspartate) receptor functions are modulated.[42,43]

Neuroactive steroids can be synthesized by PBR-dependent pathways.[44,45] This receptor was first described in 1977 as a binding site for the benzodiazepine diazepam in tissues outside the CNS.[46] Meanwhile, it is known that PBRs are also present in the brain and are found in almost all peripheral tissues. They are highly expressed in tissues involved in steroid synthesis, and their levels of expression in normal tissues are correlated with the amount of mitochondria in the cell.[47] The PBR binds cholesterol and mediates its transport from the outer to the inner mitochondrial membranes, where it is converted into pregnenolone and neuroactive steroids (eg, allopregnenolone and DHEA).[48,49] Neuroactive steroids can easily diffuse across the blood-brain barrier to modulate neural activity.[39] However, PBR ligand signaling also affects peripheral tissues. Peripheral benzodiazepine receptor binding sites are particularly dense in peripheral organs that are highly activated during stress, such as the adrenal gland and the heart. Based on the control of steroid synthesis, a compound or medication with affinity to PBR may improve regeneration and energy supply and offer tissue protection.[50]

Experimental results suggest that PBR plays an important role in physiological adaptation to stress, anxiety, and depression[51] and that PBR ligands could especially prevent psychiatric

disorders that arise from a stress-induced imbalance of CNS function.[39] Several stress systems, such as the HPA axis, the sympathetic nervous system, the renin-angiotensin axis, and the neuroendocrine-immune axis, seem to be regulated by PBR.[52] Mechanisms of action that may play a role are the control of steroid genesis, immunomodulation, and modulation of mitochondrial respiration.[50,53]

The ability of both exogenous and endogenous PBR ligands to regulate steroid production supports the view that this site may be integral to an organism's response to stress.[54,55] In addition to benzodiazepines, many endogenous (eg, cholesterol) and exogenous (eg, some flavonoids) natural compounds are known to exhibit affinity to PBRs.[56] In addition, flumazenil is also able to occupy the receptor and, like benzodiazepines, was shown to exert metabolic effects in peripheral tissues.[57] This led back to the affinity of the medications to PBR.[58,59] Because Neurexan was able to displace flumazenil in receptor-binding studies,[37] it seems probable that this medication also mediates part of its effects by binding to the PBR and neuroactive steroid signaling.

Medications acting directly as PBR ligands, such as benzodiazepines, induce the formation of neuroactive steroids, which are potent modulators of the GABA(A) receptor.[60] In contrast, SSRIs act, as part of their mode of action, on an enzyme of the neurosteroidogenic pathway.[61] Consequently, both treatments, recommended for the therapy of stress-related complaints, increase the neuroactive steroid level.[62,63] Natural PBR ligands that increase the levels of neuroactive steroids, with a better safety profile than conventional medications, would be a valuable therapeutic extension in indications for which coping with stress is required.

NEUREXAN: A BIOREGULATORY COMPLEX MEDICATION FOR THE TREATMENT OF STRESS

Neurexan is a complex homeopathic preparation that contains a combination of diluted components. The constituents are *Passiflora incarnata* (white sarsaparilla) D2, *Avena sativa* (common oats) D2, *Coffea arabica* (coffee tree) D12, and *Zincum isovalerianicum* (valerianate of zinc) D4.[64] All components are listed in the *German Homeopathic Pharmacopoeia*.[65] Neurexan is used for the treatment of stress-related disorders, such as nervousness and sleep disturbances. The recommended daily dose is one tablet taken three times. In cases of acute disorders, the administration of one tablet every 30 to 60 minutes is recommended for temporary symptomatic relief, up to a maximum of 12 tablets daily.

In an in vitro study, the affinity of Neurexan to different receptors (GABA[A], GABA[A]-benzodiazepine binding site, and serotonin transporter) was tested using established receptor-binding assays. The results revealed that Neurexan has an affinity to the GABA(A)-benzodiazepine binding site of the GABA receptor, displacing approximately 50% of flumazenil (a receptor antagonist used in receptor-binding studies). (On the GABA receptor, half the maximal inhibitory concentration for a reconstituted formulation was 25 µg/mL.) The affinity to other receptors or enzymes tested (GABA[A], serotonin, and monoamine oxidase A) was low and did not show significant binding. These data suggest that the clinical efficacy is at least partially mediated via the GABA(A)-benzodiazepine binding site.[37]

In a randomized, placebo-controlled, double-blind study, neurophysiological methods were used to determine the effects of Neurexan on psychophysiological condition. To investigate the effect of Neurexan during mental strain, healthy volunteers (N = 30) were exposed to a stressful situation. For intraindividual comparison, a crossover design was used. After the administration of Neurexan (four tablets each) or placebo, participants of the study were exposed to a mental arithmetic stress test. The reward (financial compensation) was dependent on the test results, enhancing psychological pressure. During the test procedure, an electroencephalogram (EEG) was recorded. The psychological strains of the participants were assessed with the Profile of Mood States score. Under the treatment of Neurexan, the α, β, and δ frequencies were modulated. Compared with the results after placebo administration, Neurexan significantly reduced the increase in the α power caused by the circadian rhythm. Also, the increase of β waves during the mental stress test was significantly reduced after Neurexan administration ($P < .05$). In addition, treatment with Neurexan caused a significant reduction of δ waves compared with placebo. This may be indicative of a modulatory effect of the medication on the parasympathetic nervous system. When the Profile of Mood States subscores (ie, "displeasure," "drive," "fatigue," and "depressiveness") were examined, displeasure was more reduced in the verum group. The results of the arithmetic test showed no relevant difference between both treatments. Therefore, impairment of mental power after the administration of Neurexan can be excluded. In conclusion, the reduced power of the β waves during the stress test can be interpreted as emotional stabilization as the result of treatment with Neurexan, indicating improvement in coping with stress.[66]

In an observational study, patients with sleep disturbances were allocated to therapy with Neurexan (n = 156) or a commercial variety of valerian (n = 164). The duration of therapy under study conditions was 28 days. The dosage schedule was set up by a physician. All patients in the Neurexan group received the regular dose of one to three tablets a day. In 22% of the population, additional tablets were taken at bedtime. Based on the sleep diaries of patients, sleep latency was comparably reduced from baseline by both treatments. However, the improvement in sleep duration was significantly in favor of Neurexan within the first 2 weeks of the study. The time to improvement was mostly in the range of 3 to 7 days. On day 28, the quality of sleep was comparably improved in both groups. However, significantly more patients reported lack of daytime fatigue with Neurexan than with valerian ($P < .05$ for the comparison). In addition, a slight reduction in mean blood pressure was observed in both groups during therapy. The overall effectiveness was rated as "very high" or "high" in more than 80% of patients. Overall tolerance was excellent in both groups. The data suggest that Neurexan has a similar efficacy to valerian.[67]

In another noninterventional observational study, the effectiveness of Neurexan was compared with that of different valerian-based preparations for the treatment of nervousness and restlessness. The choice and doses of study therapies were at the respective physician's discretion. The planned treatment duration was 2 weeks. The assessment of efficacy was based on the ratings (from 0 [asymptomatic] to 3 [severe]) of a summary score and on subscores at the end of the study (eg, nervousness or restlessness, excitability or jitteriness, sleep disturbance, hyperactivity, fitful sleep, nocturnal anxiety, forgetfulness or difficulties with concentration, fatigue, listlessness, moroseness, gastrointestinal disturbance, headache or pressure, and overall disease severity). In the final evaluation, 777 patients (553 receiving Neurexan and 224 receiving valerian) were included. In the Neurexan group, 42.9% of the patients received more than three tablets a day, 49.6% of the patients were treated with three tablets, and only 6% received less than three tablets per day. When the clinical parameters were studied, an overall significant effect of Neurexan could be observed ($P < .001$). Concomitant medications with psychotropic drugs were rare (0.5%-1.0%) and are not considered to have a relevant impact on the study results. The results suggest that Neurexan is an effective and well-tolerated treatment for conditions associated with nervousness and restlessness.[68]

DISCUSSION

Neurexan has been authorized to be marketed for the treatment of stress-related disorders, such as nervousness and sleep disturbances. The mode of action of complex homeopathic medications is still debatable. Like the use of highly complex composed plant extracts in phytotherapy, complex homeopathic medications are also a multicomponent therapy, suggesting a multitargeted approach with both treatments. In addition, the results of preclinical findings from both ultra low–diluted homeopathic preparations and phytotherapeutic extracts (eg, *Passiflora* species) suggest that at the level of cellular signaling there are, at least in part, some similarities between the two treatment concepts (eg, GABA[A] benzodiazepine receptor signaling).[37,69] This could also be an explanation for the frequently observed comparability in the claimed clinical indications of plant-derived preparations in phytotherapy and homeopathy. Therefore, profiling of the single constituents of Neurexan might provide new insights into the possible mode of action of this medication.

Passiflora incarnata: Possible Contributions to the Efficacy of Neurexan

In homeopathy and phytotherapy, *P incarnata* is traditionally used for comparable indications (eg, insomnia, anxiety, restlessness, neuralgia, nervous tachycardia, and spasmodic disorders) and seems to be particularly useful for nervous disorders.[70,71]

These indications could be confirmed in animal studies[72,73] with drug extracts, thereby showing anxiolytic, sleep-inducing, and anticonvulsant activity. A reduction of the craving for alcohol and nicotine was also shown.[74] After short-term administration of the extract, a selective effect on reducing anxiety without the unwanted adverse effect of sedation was observed.[75] The anxiolytic efficacy was also proved in a randomized, double-blind clinical study.[76]

One of the constituents of *Passiflora* extracts is chrysin, a compound that is a ligand of the benzodiazepine receptors, both central (competitive mechanism) and peripheral (mixed-type mechanism).[73] The mode of action of the extract at the central nervous level seems to be related to the GABAergic and opioid systems because the antagonists flumazenil and naloxone could suppress them. In addition to enhancement of GABAergic activity, attenuation of glutamatergic activity is discussed.[77] In comparison, Neurexan has a proven affinity to the GABA(A) benzodiazepine receptor. To our knowledge, the activity on the opioid and glutamatergic system has not been evaluated.

Avena sativa: Possible Contributions to the Efficacy of Neurexan

In homeopathy, *A sativa* is the best tonic for treating debility after exhaustive diseases. It is indicated in insomnia after worry and mental exertion and in patients when exhaustion aggravates insomnia. In addition, it is used in cases of addiction to help the patients overcome drug and alcohol abuse.[71] These indications correlate with use in traditional phytotherapy, and the latter was also seen in a small human study.[78] In animal studies, sedative, antiseizure, and antiaddiction (nicotine and morphine) activities were demonstrated.[79] Investigations on the mode of action in in vitro models are lacking. However, data from studies in animals and humans strongly suggest that the CNS is a target of the constituents of *A sativa*.

Coffea arabica: Possible Contributions to the Efficacy of Neurexan

In homeopathy, *C arabica* (*Coffea cruda*) is specially indicated in conditions associated with nervousness and extreme sensitiveness. This includes hyperactivity of the mind and body, sleeplessness, great nervous agitation and restlessness, neuralgia in various parts, intolerance of pain, nervous palpitations, and convulsions. The sleep is superficial, and the patients easily wake up with the slightest noise.[71] Results from animal studies performed with *C cruda*, 30 L, also suggest that the diluted preparation modifies sleep pattern and increases sleep intensity. In the EEG, an enhancement in slow δ activity was demonstrated by trend.[80,81]

Extracts from *Coffea* are not used in modern phytotherapy. However, the mode of action of caffeine is well understood. An important target of caffeine is the adenosine receptor, where it acts as a competent nonselective antagonist of adenosine A(1) and A(2A) receptors in the brain.[82] The promotion of wakefulness by caffeine was proposed to be mediated by antagonizing adenosine receptor function because, during prolonged intervals of wakefulness, the adenosine levels increase in the brain to promote sleep. Adenosine receptors in the brain modulate acetylcholine release and dopamine transmission. They affect many brain functions, such as behavioral arousal, EEG δ power, and

sleep.[83] The modulation of EEG slow δ activity by diluted *Coffea*[80] supports the view that homeopathic *Coffea* preparations can act via adenosine signaling pathways.

Neurexan contains *C arabica* in a higher dilution (D12) than the other constituents. Based on the principle of homeopathy *similia similibus curentur*, it can be suggested that *Coffea* as a more highly diluted remedy can exert clinically the opposite effect of substantial doses of *Coffea* extract or caffeine. This assumption is in agreement with the indications claimed for *Coffea* in homeopathy and the experience from therapy with more highly diluted *Coffea* preparations. The mode of action of such more highly diluted *Coffea* in part functionally resembles that of adenosine or adenosine agonists at the cerebral adenosine receptors, with reference to sleep-promoting, anxiolytic, and antidepressive properties. In contrast, it has been reported that caffeine, an adenosine antagonist, can worsen anxiety and psychosis in affected people and can cause these mood disorders in otherwise healthy people after high caffeine intake.[84] The possible impact of Neurexan on the adenosine signaling pathways should be addressed in further research.

Zincum isovalerianicum: Possible Contributions to the Efficacy of Neurexan

Neurexan contains *Z isovalerianicum* (D4). *Zincum valerianicum* or *Z isovalerianicum* is a synthetic compound prepared from zinc oxide and valeric acid, a short carbonic acid derived from *Valeriana officinalis*. However, the content of valeric acid does not correlate with the pharmacological effects of valerian. Therefore, it is expected that this zincum preparation resembles more zincum (metallicum) than valerian. The constituent is used in low dilutions, with the main indications being irritable sleep disturbances with "restless legs" and neuralgia.[65]

In homeopathy, *Z valerianicum* is a favorite medicine to treat hypochondria with groundless fear. Exhaustion, tiredness, and weakness associated with excitement and agitation are typical symptoms. Patients are oversensitive, nervous, and sleepless; they often exhibit fidgety feet. The results of a retrospective study[85] confirm the possible usefulness of this remedy in patients with restless legs syndrome. It is also recommended for the treatment of different painful afflictions, such as neuralgia,[71] which underlines its specific affinity to the brain and nerves. Because of the calming effect, homeopathic zincum is also called "metallic opium." Although the patients experience drowsiness by day, they cannot sleep at night. The wake-sleep cycle is inverted.[86]

Zinc is extremely important for brain physiology and neurotransmitter balance.[87,88] For the possible mode of action of homeopathic remedies, it is suggested that ultra low–diluted compounds that are relevant for cellular biochemistry can stimulate the physiological functions and the cellular metabolism in tissues with a functional imbalance. Examples include sulfur, ferrum, and endogenous cellular compounds (eg, Ubichinon and the Krebs cycle intermediate biocatalyst used in bioregulatory medicine).[8] From this viewpoint, the role of zinc in neurophysiology can add some aspects to the hypothetical mode of action of ultra low–diluted zinc-containing compounds and can support the claimed indications of Neurexan.

In the CNS, zinc acts as a neuromodulator of both excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmission and seems to have a considerable role in stress response.[89] Most zinc-enriched neurons are inhibitory (GABAergic), especially in the spinal cord, and a direct modulation of GABA receptors by zinc may occur.[90] This could be an explanation for the calming effect of homeopathic zinc preparations on the motoric activity of the lower extremities, as the clinical experience in patients with restless legs suggests.[85]

Studies in animals and humans demonstrated that zinc deficiency is associated with depression and that treatment with zinc leads to antidepressant-like activity, especially in combination with antidepressant medications.[91] In addition, anxiety, anhedonia, and lethargy are characteristic mood disorders in those with zinc deficiency and are often associated with depressive disorders.[92] Animal models suggest that a direct or indirect activation of adenosine receptors may contribute to the antidepressantlike effect of zinc.[93] From the hypothetical viewpoint, better use of zinc at the receptor site by homeopathic lower-diluted zinc preparations could complement the functional adenosine agonistic activity of more highly diluted *Coffea*. Such a coordinated stimulation of adenosine signaling could also contribute to the calming activity of Neurexan.

Comparability of Neurexan and Valerian in Clinical Trials

Neurexan has shown comparable efficacy in clinical trials with valerian[67] and valerian-based preparations,[68] although there seems to be a tendency for the superiority of Neurexan in the indications investigated.[68]

Valerian is recommended for the treatment of restlessness and insomnia. However, in experimental studies and clinical trials,[94,95] sedating properties of common valerian extract preparations were found only inconsistently. Several observations indicate the putative efficacy of valerian extracts in the treatment of anxiety and stress-related symptoms and also a diminished response to mental stress under laboratory conditions.[96] This suggests that the claimed sedating properties of valerian may be more related to the anxiolytic or antidepressant effects of the extracts. This could also apply to the sleep-promoting activity of Neurexan. However, preclinical studies with valerenic acid, a single compound of valerian extract, revealed considerable sedative effects (eg, a prolongation of pentobarbital-induced sleeping time in animals).[97] This could explain why, compared with Neurexan in the valerian group, a "hangover"-like effect was more often reported.[67]

Neurexan: A Partial Agonist Acting Through a GABAergic "Bystander Reaction"

Like Neurexan, valerian extract interacts with the benzodiazepine site of GABA(A) receptors in a manner consistent with the known in vivo effects.[98] However, Neurexan seems to have more features of a partial agonist at the receptor without a relevant

affinity to the α1-subunit, which is responsible for the sedative effects of the benzodiazepine or nonbenzodiazepine hypnotic agents that preferentially bind to the α1-receptors (eg, zaleplon [Sonata]). Partial agonists show only partial efficacy in relation to a full agonist. Therefore, they may be capable of enough potentiation of GABA to reduce anxiety but not enough to cause sedation or amnesia. Thus, they could prove to be anxiolytic but not sedative, with a markedly reduced risk of dependence and interaction with alcohol, which would have enormous potential clinical advantages.[99] By targeting the GABA(A) benzodiazepine receptor, Neurexan seems to act as an allosteric modulator and facilitate the binding of GABA at its receptor. This is comparable to a "GABAergic bystander reaction" because endogenous GABA is necessary for signaling. Several conventional psychotropic drugs have a direct action on the receptor responsible for the toxicity of these drugs.

The assumption that Neurexan has similarities with a partial agonist not occupying the GABA(A) receptor α1-subunit, is also clinically supported by the results of arithmetic stress tests. No decline in concentration has been found. In addition, also from the results of EEG studies, no sedative effect was recognizable after the administration of Neurexan. Changes in the EEG suggest that, in addition to GABA, other neurotransmitters are relevant for the mode of action of Neurexan (eg, serotonin).[66] Independent of the exact knowledge about the neurotransmitters involved, the changes in the EEG recordings suggest a more balanced mood under stressful conditions, without impairment of mental function after the administration of Neurexan. Moreover, a possible modulation of both the central receptor and the PBR by Neurexan could not only explain the clinical efficacy of the medication but could also imply an important perspective for a holistic therapeutic approach in the prophylaxis and treatment of stress and stress-related disorders. However, this expected efficacy needs to be confirmed in further basic research and scientific approaches.

Because of its clinical efficacy and convincing safety profile, Neurexan seems to be a valuable extension of the available therapeutic opportunities in the treatment of stress and stress-related disorders. Drug safety is as equally important as drug efficacy. In contrast to conventional medications, treatment with Neurexan is not associated with adverse effects. Therefore, Neurexan seems to expand the possibilities of treatment in patients with stress and stress-related disorders. However, prevention is better than cure. Therefore, at early signs of overloading, therapy with Neurexan should be started to avoid the development of burnout.

CONCLUSIONS

The results from preclinical and clinical studies performed with Neurexan provide a convincing profile for the clinical application of this complex medication in stress and stress-related disorders, such as nervousness, restlessness, and sleep disturbances.

In the brain, GABA is the principal inhibitory neurotransmitter. By targeting the GABA(A) benzodiazepine receptor, Neurexan could attenuate one of the most important pathways of stress response, the HPA axis. Normally, the HPA axis is delicately controlled by an autoregulatory feedback system. However, in cases of chronic stress, the body, little by little, loses the capacity to regulate the stress response. This means that in times without an acute stressful event, the normal level is not recovered again. Therefore, chronic stress and burnout can be viewed as a chronically overactive stress system with a loss of self-regulation. This loss of adaptation provokes an "allostatic load" (eg, elevated levels of cortisol, epinephrine, cholesterol, glucose, and proinflammatory mediators), all known to be relevant disease mediators. Therefore, chronic stress virtually affects the whole body and is a considerable risk factor for cardiovascular diseases, immune dysfunction, diabetes mellitus, and sexual disorders.

In addition to the affinity to the central-type GABA(A) benzodiazepine receptor, Neurexan probably also occupies the peripheral type of the benzodiazepine receptor. Ligands of the benzodiazepine receptor type stimulate the synthesis of neuroactive steroids, which are powerful modulators of the GABA(A) receptor function but also seem to protect peripheral tissues, such as the heart, from stress-induced damage. In addition, neuroactive steroids appear to be especially important in the pathophysiology and treatment of many psychiatric disorders, such as anxiety and depression. There is evidence that the PBR system serves as an endogenous homeostatic mechanism, restoring both normal GABAergic and HPA function in cases of acute and chronic stress.

Clinically, Neurexan seems to function as a partial agonist at the GABA(A) receptor because it lacks a direct sedative effect. This belief is supported by the results of arithmetic stress tests, in which no decline in concentration was found. In addition, from the results of EEG studies, no sedative effect was recognizable after the administration of Neurexan. Partial agonists reduce anxiety but do not cause sedation or amnesia. Therefore, it seems likely that the calming and sleep-promoting effects of Neurexan in stress can mainly lead back to a mood-stabilizing, anxiolytic, or possibly antidepressive effect. EEG recordings support this view, suggesting a more balanced mood under stressful conditions without impairment of mental function.

In conclusion, all preclinical and clinical data indicate that Neurexan is a valuable medication for the prophylaxis and treatment of stress and stress-related disorders.

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