Possible modulation of neurobehavioural patterns by anxiolytics drugs

Zaved Ahmed Khan ,FICER (Corresponding Author)
Assistant Professor
Medical Biotechnology Division
School of Biosciences and Technology,
VIT University,
Vellore-632014
TN, India

Dr Asit Ranjan Ghosh
Professor
Medical Biotechnology Division
School of Biosciences and Technology,
VIT University,
Vellore-632014
TN, India

ABSTRACT

Stress is very common and affects as many as one in eight every people in their teen years. Depression, which is common form of stress related disorder affects people of every color, race, economic status, or age. However, it does seem to affect more females than males during adolescence and adulthood. Stress affects mind, body, and behavior in many ways. The signs and symptoms of stress vary from person to person, but all have the potential to harm our health, emotional wellbeing, and relationships with others. The stress response of the body is meant to protect and support us in maintaining stability. Our body is constantly adjusting to its surroundings. When a physical or mental event threatens this equilibrium, we react to it. Anxiety is characterized by a persistent and disproportionate fear unrelated to any genuine risk. It can increase to an extent that may interfere with even normal routine of life and person may feel apprehensive regarding happenings of normal things in life. The present paper discusses anti-anxiety potential of 15 anxiolytics with emphasis on their pre-clinical and clinical reports.majority of drugs have been found to be acting through modulation of serotonin and gamma butyric acid (GABA) neurotransmitters.

Keywords: anxiolytics, depressants, GABA, serotonin

INTRODUCTION

Stress is simply a fact of the natural forces from the outside world affecting the individual. The individual responds to stress in ways that affect him as well as his environment. Hence, all living creatures are in a constant interchange with their surroundings (the ecosystem), both physically as well as behaviorally. This interplay of forces or energy is of course present in the relationships between all matter in the universe, both living and non living. However, there are critical differences in the methods in which the different living creatures relate to their environment. These differences have far-reaching consequences to their survival. Because of the overabundance of stress in our modern lives. The cultural, social economical values has changes with time and so do the ability to cope with stress.Our ancestors responded to stressful ordeals in the fashion which is quite different and destructive Millions of years later, when we face a situation that we perceive as challenging, our body automatically goes into an overdrive, engaging the stress response to succumb it. Immediately, we release the same hormones that enabled prehistoric humans to move and think faster, hit harder, see better and hear more acutely since our experience of stress is generally related to how we respond to an event, not to the event itself. In practice, the biological concept of stress carries a more general connotation. Perhaps the most useful definition

of biological stress is an adverse force or influence that tends to inhibit normal systems from functioning. The psychological and environmental stimuli can influence health and diseases. Stress is a term used to describe such an adverse force that can disrupt the physiological environment. Stress is the outcome of interaction between the stressor and the stressed and it ranges from the cellular and organic to the molecular level [1]. Anxiety disorders comprise clinical conditions of Generalized Anxiety Disorder, Panic Disorder, Post-traumatic Stress Disorder, Social Anxiety Disorder and Phobia . Monoamines (dopamine , noradrenaline and serotonin) ,neuropeptides (galanin, neuropeptide Y, arginine vasopressin, tackykinin and substance P), neurosteroids and cytokines have been observed to play a modulators role in anxiety states. Among therapeutic regimens, benzodiazepines and serotonin modulators remain the mainstay of pharmacological treatment of anxiety disorders. However, in the light of their adverse effects and dependence potential, search for novel pharmacotherapy for anxiety is in fast progress. There has been effort to develop anxiolytics from medicinal plants [2, 3]. In this review paper information on drugs that have been explored for their potential anti-anxiety profile using pharmacologically validated animal models has been compiled and discussed.

ANXIOLYTICS BENZODIAZEPINE: ALPRAZOLAM:

Also known under the trade names Xanax, Xanor and Niravam, is a short-acting drug of the benzodiazepine class used to treat moderate to severe anxiety disorders, panic attacks, and as an adjunctive treatment for anxiety associated with moderate depression. Alprazolam is potentially an addictive drug and long term use of alprazolam may cause a physical dependence to develop and benzodiazepine withdrawal syndrome to appear during discontinuation.

MODE OF ACTION:

Alprazolam is a triazolobenzodiazepine [4], that is, a benzodiazepine with a triazolo-ring attached to its structure. Benzodiazepines produce a variety of therapeutic and adverse effects by binding to the benzodiazepine site on the GABAA and modulating the function of the GABA receptor, the most prolific inhibitory receptor within the brain.

SIDE EFFECTS:

These may include[5] euphoria, drowsiness,decreased inhibitions, no fear of danger (increased risk taking behavior) ,depressed mood with thoughts of suicide or self harm or elevated mood and confidence,hallucinations ,agitation ,feeling dizziness, light headed or fainting,urinating less than usual or not at all,headache, fatigue, joint pain and unusual weakness (flu like symptoms),speech problems,short term memory loss and impairment of memory functions.

BROMAZEPAM:

Marketed under brand names Calmepam, Compendium, Creosedin, Durazanil, Lectopam, Lexaurin, Lexilium, Lexomil, Lexotan, Lexotanil, Normoc, Novepam, Somalium, Lexatinis, a potent benzodiazepine derivative drug, developed in 1970s [6]. It has mainly anxiolytic and at higher doses also sedative, hypnotic and skeletal muscle relaxant properties.

MODE OF ACTION:

Its molecular structure is composed of a diazepine connected to a benzene ring and a pyridine ring, the benzene ring having a bromine atom attached to it. It is at is a 1,4-benzodiazepine, which means that the nitrogens on the seven-sided diazepine ring are in the 1 and 4 positions. Bromazepam binds to the GABA receptor GABAA, causing a conformational change and increasing inhibitory effects of GABA. Other neurotransmitters are not influenced. Bromazepam is intermediate-short acting benzodiazepine and is lipophilic, is metabolised hepatically via oxidative pathways [7].

It does not possess any antidepressant or antipsychotic qualities[8]. After night time administration of bromazepam a highly significant reduction of gastric acid secretion occurs during sleep followed by a highly significant

rebound in gastric acid production the following day[9]. Bromazepam alters electrical status of the brain causing an increased beta activity and a decrease in alpha activity in the EEG recordings[10,11].

SIDE EFFECTS:

There is decrease in libido and drowsiness [12],altered skin conduction [13], induce extreme alterations in memory such as anterograde amnesia and amnesic automatism [14],impaired memory, processing of sensory data and psychomotor performance [15].

Chlordiazepoxide:

Is a sedative/hypnotic drug which is a benzodiazepine derivative and is marketed under the trade name Librium. It has a medium to long half life but its active metabolite has a very long half life. Chlordiazepoxide has amnestic, anxiolytic, hypnotic and skeletal muscle relaxant properties[16].

MODE OF ACTION:

Chlordiazepoxide acts on benzodiazepine subreceptors of the main GABAA receptor and this results in an increased binding of the inhibitory neurotransmitter GABA to the GABAA receptor thereby producing inhibitory effects on the central nervous system and body similar to the effects of other benzodiazepines[17]. Chlordiazepoxide is anticonvulsant[18]. There is preferential storage of chlordiazepoxide in some organs including the heart of the neonate.chlordiazepoxide rapidly crosses the placenta and also is excreted in breast milk [19]. Chlordiazepoxide also decreases prolactin release in rats[20]. Benzodiazepines act via micro-molar benzodiazepine binding sites as Ca2+ channel blockers and significantly inhibit depolarization-sensitive Calcium uptake in animal nerve terminal preparations[21]. Chlordiazepoxide inhibits acetylcholine release in mouse hippocampal synaptosomes in vivo. This has been found by measuring sodium-dependent high affinity choline uptake in vitro after pretreatment of the mice in vivo with chlordiazepoxide.

SIDE EFFECTS:

These include constipation ,drowsiness, fainting ,liver problems, lack of muscle coordination, minor menstrual irregularities, nausea.

Clonazepam:

Marketed by Roche under the trade-names Klonopin, Rivotril, Ravotril or Rivatril is a drug which is a benzodiazepine derivative. It is a highly potent anticonvulsant, muscle relaxant and anxiolytic[22]. Clonazepam is a chlorinated derivative of nitrazepam [23] and a nitrobenzodiazepine like nitrazepam [24].

MODE OF ACTION:

Clonazepam's primary mechanism of action is via modulating GABA function in the brain, via the benzodiazepine receptor which in turn leads to enhanced GABAergic inhibition of neuronal firing. In addition clonazepam decreases the utilization of 5-HT (serotonin) by neurons and has been shown to bind tightly to central type benzodiazepine receptors [24]. Because of its strong anxiolytic and anticonvulsant properties, it is said to be among the class of "highly potent" benzodiazepines. The anticonvulsant properties of benzodiazepines are due to enhancement of synaptic GABA responses and inhibition of sustained high frequency repetitive firing[25].

Benzodiazepines, including clonazepam, bind to mouse glial cell membranes with high affinity[26,27]. Clonazepam decreases release of acetylcholine in cat brain [28] and decreases prolactin release [29]. Benzodiazepines inhibit cold-induced thyroid stimulating hormone (also known as TSH or thyrotropin) release [30]. Benzodiazepines acted via micromolar benzodiazepine binding sites as Ca2+ channel blockers and significantly inhibit depolarization-sensitive calcium uptake in experimentation on rat brain cell components. This has been conjectured as a mechanism for high-dose effects on seizures in the study [31].

Clonazepam exerts its action by binding to the benzodiazepine site of the GABA receptors, which causes an enhancement of the electric effect of GABA binding on neurons. This results in an inhibition of synaptic transmission across the central nervous system[32]. Benzodiazepines, however, do not have any effect on the levels of GABA in the brain [33]. Clonazepam has no effect on GABA levels and has no effect on gamma-aminobutyric acid transaminase. Clonazepam does however affect glutamate decarboxylase activity. It differs insofar from other anticonvulsant drugs it was compared to in a study [34].

SIDE EFFECTS:

There is drowsiness, impairment of cognition and judgment[35],irritability and aggression [36],psychomotor agitation[37],lack of motivation [38],impaired motor function.

Diazepam:

First marketed as Valium, is a benzodiazepine derivative drug. It possesses anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnestic properties. It is commonly used for treating anxiety, insomnia, seizures, alcohol withdrawal, and muscle spasms. It may also be used before certain medical procedures (such as endoscopies) to reduce tension and anxiety, and in some surgical procedures to induce amnesia.

MODE OF ACTION:

Diazepam has no effect on GABA levels and no effect on glutamate decarboxylase activity but has a slight effect on gamma-aminobutyric acid transaminase activity. It differs insofar from some other anticonvulsive drugs it was compared with [39]Benzodiazepines act via micromolar benzodiazepine binding sites as Ca2+ channel blockers and significantly inhibit depolarization-sensitive Calcium uptake in rat nerve cell preparations [40]. Diazepam affects the emotional-motivational component of the pain experience, but not the sensory discriminative component or the central control of pain [41]. Diazepam inhibits acetylcholine release in mouse hippocampal synaptosomes. This has been found by measuring sodium-dependent high affinity choline uptake in mouse brain cells in vitro, after pretreatment of the mice with diazepam in vivo. This may play a role in explaining diazepam's anticonvulsant properties[42]. Diazepam binds with high affinity to glial cells in animal cell cultures [43].

Diazepam is a benzodiazepine that binds to a specific subunit on the GABAA receptor at a site that is distinct from the binding site of the endogenous GABA molecule [44]

SIDE EFFECTS:

There is suppression of REM sleep, impaired motor function, impaired learning, anterograde amnesia (especially pronounced in higher doses) and cognitive deficits [45].

Lorazepam:

Also known as Ativan or Temestais it is a benzodiazepine drug with short to medium duration of action. It has all five intrinsic benzodiazepine effects: anxiolytic, amnesic, sedative/hypnotic, anticonvulsant and muscle relaxant, to different extent. It is a powerful anxiolyte.

MODE OF ACTION:

Relative to other benzodiazepines, lorazepam is thought to have high affinity for GABA receptors [46], which may also explain its marked amnesic effect. The main pharmacological effects of lorazepam are the enhancement of GABA at the GABAA receptor [47]. Benzodiazepine drugs including lorazepam increase the inhibitory processes in the cerebral cortex[48].

Medazepam:

Medazepam is a drug which is a benzodiazepine derivative. It possesses anxiolytic, anticonvulsant, sedative and

skeletal muscle relaxant properties. It is known by the following brand names: Nobrium, Rudotel, Raporan,Ansilan. Medazepam is a long acting benzodiazepine drug. The half life of medazepam is 36 - 200 hours .

MODE OF ACTION:

Benzodiazepine drugs including medazepam increase the inhibitory processes in the cerebral cortex by allosteric modulation of the GABA receptor [49]. Benzodiazepines may also act via micromolar benzodiazepine binding sites as Ca2+ channel blockers and significantly inhibited depolarization-sensitive calcium uptake in experiments with cell components from rat brains.

Oxazepam:

Oxazepam (marketed under brand names Alepam, Alopam, Murelax, Opamox, Oxascand, Serax, Serepax, Seresta, Sobril, Vaben) is a drug which is a benzodiazepine derivative. It has moderate anxiolytic, anticonvulsant, sedative and skeletal muscle relaxant properties compared to other benzodiazepines.

MODE OF ACTION:

Oxazepam is an intermediate acting benzodiazepine. Oxazepam acts on benzodiazepine receptors resulting in increased effect of GABA to the GABAA receptor which results in inhibitory effects on the central nervous system[50] The half-life of oxazepam is 4-15 hours[51]. Oxazepam has been shown to suppress cortisol levels [52].

SIDE EFFECTS:

The side effects of oxazepam are similar in nature to those of other benzodiazepines.

BARBITALS:

Amobarbital:

Amobarbital (formerly known as amylobarbitone) is a drug that is a barbiturate derivative. It has sedative-hypnotic and analgesic properties. It is a white crystalline powder with no odor and a slightly bitter taste. If amobarbital is taken for extended periods of time, physical and psychological dependence can develop.

MODE OF ACTION:

Amobarbital works by activating GABAA receptors, which decreases input resistance, depresses burst and tonic firing, especially in ventrobasal and intralaminar neurons, while at the same time increasing burst duration and mean conductance at individual chloride channels; this increases both the amplitude and decay time of inhibitory postsynaptic currents [53].

Methohexital:

Methohexital (marketed under the brand name Brevital) is a drug which is a barbiturate derivative. It is classified as short-acting, and has a rapid onset of action. It is similar in its effects to sodium thiopental, a drug with which it competed in the market for anaesthetics.

MODE OF ACTION:

Methohexital binds to a distinct site which is associated with Cl^- ionophores at GABAA receptors. This increases the length of time which the Cl^- ionopores are open, thus causing an inhibitory effect.Metabolism of methohexital is primarily hepatic (i.e., taking place in the liver) via demethylation and oxidation. Side-chain oxidation is the primary means of metabolism involved in the termination of the drug's biological activity.

Etazolate:

Etazolate is a pyrazolopyridine derivative drug[54], which acts as an anxiolytic[60].It has several mechanisms of action, acting as an adenosine antagonist(, a subtype-selective GABAA receptor partial agonist, and a phosphodiesterase inhibitor selective for the PDE4 subtype[55].

Etifoxine:

Etifoxine (INN, also known as etafenoxine; trade name Stresam) is an anxiolytic and anticonvulsant drug. It is used in anxiety disorders and to promote peripheral nerve healing [56]. It has similar effects to benzodiazepine drugs, but is structurally distinct and so is classed as a nonbenzodiazepine anxiolytic[57]It is more effective than lorazepam as an anxiolytic, and has less side effects [58].

MODE OF ACTION:

Unlike benzodiazepines, etifoxine appears to produce its anxiolytic effects by binding to β2 and β3 subunits of the GABAA receptor complex, and so is acting at a different target site to benzodiazepines, although the physiological effect that is produced is similar to that of benzodiazepines[59]. This difference in binding means that etifoxine can be used alongside benzodiazepines to potentiate their effects without competing for binding sites [60], however it also means that the effects of etifoxine are not reversed by the benzodiazepine antagonist flumazenil [67].

Saredutant:

Saredutant, or SR 48968, is a neurokinin-2 receptor antagonist drug being developed as an antidepressant and anxiolytic by Sanofi-Aventis. Its mechanism of action is different from antidepressants currently available on the market. It works by blocking the effects of Neurokinin A at the NK2 receptor.

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