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NEUROPHARMACOLOGY (R PI, SECTION EDITOR)

Possible Benefits of Considering Glutamate with Melatonin or Orexin or Oxytocin as a Combination Approach in the Treatment of Anxiety

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Abstract

Purpose of review Anxiety is a common neurological disorder with high prevalence and important cause of functional impairment. Related higher cost, experience of complete remission, and intolerant response to the ongoing treatment suggest an unmet need to develop novel therapeutic strategies for the treatment of anxiety. The present review has focused on the discussion of targeting of glutamate system with melatonin or orexin or oxytocin receptors as combination approach in the treatment of anxiety.

Recent findings Available evidences suggest a strong correlation between glutamate system and anxiety. Melatonin, orexin, and oxytocin receptors also showed similar correlation. Recent reports suggested the functional association between melatonin and glutamate or orexin and glutamate or oxytocin and glutamate.

Summary The novel approaches discussed in present review may avail us an efficacious and safe treatment option which can be a better or alternative option for the available anxiolytic drugs. There is a need to consider combination approach targeting melatonin or orexin or oxytocin with glutamate-related receptors in different experimental settings.

Keywords Anxiety · Glutamate · Melatonin · Orexin: Oxytocin

Introduction

Anxiety disorders are one of the most important neurological disorders. These are associated with symptoms such as fear, nervousness, apprehension, and panic and affect cardiovascular, respiratory, gastrointestinal, and nervous systems [1]. The reported lifetime prevalence of anxiety disorder was 33.7% [2]. In India, 25% of young adults were suffering from anxiety and less than 20% of these affected adults taken clinical care [3]. According to World Health Organization, related prevalence was increased worldwide almost by 50% (from 416 million to 615 million) between 1990 and 2013 [4].

Selective serotonin reuptake inhibitors (SSRI's) are considered the first line of therapy for anxiety; however they are associated with adverse drug reaction (ADR) like nervousness, sexual dysfunction, QTc prolongation, etc.[5]. Another widely prescribing class of drugs for the treatment of anxiety includes benzodiazepines (BZD). Their chronic use leads to adverse event such as physiological and psychological dependence, withdrawal syndrome, cognitive, and coordinative impairment. BZD also induces amnesia in long-term exposure [6, 7]. Nearly 58–100% of patients receiving BZD developed tolerance [8]. In addition, reduced γ-aminobutyric acid ($GABA_A$) receptor binding was seen in panic disorder [9] and posttraumatic stress disorder [10]. These factors might have contributed to the BZD insensitivity. Higher cost and experience of complete remission with partial and intolerant response to the ongoing treatment [11] suggest the unmet need in the treatment of anxiety disorders [12]. The present review has emphasized on the possible role of glutamate with melatonin or orexin or oxytocin as novel combination approaches in the management of anxiety disorders.

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Glutamate and Anxiety

Glutamate, being excitatory neurotransmitter, is known for its role in pathology of anxiety [13]. Zeredo et al. [14•] reported hypofunction of glutamatergic system that regulates high-trait

anxiety through hippocampal – area 25 circuit in primates. The need to consider the dietary glutamate as treatment option in psychiatric disorders has been emphasized by Kraal et al.[15•]. The related *N*-methyl-d-aspartate (NMDA) receptor subtypes are particularly important in anxiety disorders [16]. NR2A and NR2B, subunits of NMDA receptors, are highly expressed in the brain regions that play important role in anxiety and depression [17, 18]. Ketamine, phencyclidine, and memantine are non-competitive antagonist of NMDA receptors. Ketamine has a property of producing dissociative anesthesia. Related research studies showed benefits of using low dose of ketamine to reduce symptoms of depression and anxiety disorders [19, 20]. It binds to ionic channel of NMDA receptor and also interacts with voltage-dependent Ca^{2+} channels [21]. It blocks entry of Ca^{2+} into neurons and has fast onset [22]. Interestingly, lower doses of ketamine and other NMDA receptor antagonists have been associated with neuroprotection and neurotrophic effects [23]. Experimental studies have reported increased levels of brain-derived neurotrophic factor (BDNF) in hippocampi of rats after ketamine treatment. As it did not produce tolerance effect at higher dose (10 and 15 mg/kg) with chronic exposure, it could be a good option in treatment of depressive and anxiety disorders [24]. Lur et al. [25••] recently showed ketamine-induced inhibition of glutamatergic transmission and related co-relation with α-adrenergic receptors and $GABA_B$ receptors [26]. Apart from ketamine, propofol is another short-acting anesthetic drug, widely used for surgical anesthesia. The mechanism of action of propofol is through interaction of both GABA and NMDA receptors. The sub-anesthetic dose (40 mg/kg) of propofol has anxiolytic effect in animal models of anxiety such as elevated plus maze and Vogel-type conflict test [27, 28]. These evidences suggest importance of considering antagonist of glutamate and related NMDA receptors with GABAergic action in the treatment of anxiety.

Zoicas and Kornhuber [29••] emphasized consideration of selective targeting of metabotropic glutamate receptors in psychiatric disorders including anxiety. Metabotropic glutamate receptors such as group III, i.e., mGlu4 and mGlu8 can also be a good target for anxiety. These are G-protein-coupled receptors and modulate both GABAergic and glutaminergic neurotransmission [30]. Experimental studies showed anxiolytic effect of mGlu4 allosteric agonist PHCCC and the mGlu4/6/7/8 receptor agonist (1S,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylicacid (ACPT-1) after injection into basolateral amygdala [31, 32]. As per recent report, mGlu5 receptors also contribute in anxiety [33••]. Targeting these specific receptors may help to widen the therapeutic options.

Melatonin and Anxiety

Insomnia is frequent in people with anxiety and depression. It is generally accepted that sleep deprivation is associated with pathological anxiety-like behavior in human [34, 35]. One of the promising hypotheses for mechanism of action of antidepressant and anxiolytics is based on pathological effect of circadian abnormality [36]. Melatonin is endogenous neurohormone produced in pineal gland. It controls various physiological processes such as circadian rhythms, mood regulation, sleep, anxiety, cardiac function, etc. Melatonin type 1 (MT1) and type 2 (MT2) receptors are present in suprachiasmatic nucleus (SCN), paraventricular nucleus, and supraoptic nucleus and control neural activity. Knockdown of a clock gene selectively in the SCN leads to disruption of circadian rhythm, and it was associated with helplessness and anxiety-like behavior in mice [37]. Most of neurons which express MT2 receptors are GABAergic. It has been reported that melatonin administration increases level of GABA in hypothalamus, cerebellum, and cerebral cortex [38].

A recent report [39••] suggested melatonin benefits with safe exogenous administration as an adjuvant therapy in neonates. Another recent clinical study reported consideration of melatonin as an alternative to benzodiazepines [40••]. Pretreatment with melatonin helped in reducing anxiety also reduced the dose of anesthetic agent in patients undergoing surgery [41••, 42]. Agomelatine, a recently developed drug, has slight different mechanism of action that of other melatonergic drugs. It is MT1 and MT2 receptor agonist and 5HT2c receptor antagonist. Agomelatine and melatonin perfusions evoked similar amplitudes of suppression of SCN neuronal firing, but agomelatine caused long-lasting suppressions [43]. Rainer et al. [37] concluded that 28-day treatment of agomelatine (10 mg/kg) showed anxiolytic effect in C57BL/6Ntac mice which was comparable to fluoxetine. There was also neurogenic effect in which agomelatine facilitated maturation [37]. Novel MT2 selective partial agonist UCM765 showed anxiolytic activity at 20 mg/kg in rats [44]. According to a double-blinded clinical trial having 227 generalized anxiety disorder, patients treated with agomelatine showed decrease in risk of relapses than patient treated with placebo. Percentage of relapse was 19.5% versus 30.7%, respectively [45, 46]. However in open label long-term clinical trial studies, anxiolytic properties of melatonin showed low sedation and less potential of abuse which may offer optimal therapeutic outcome over the GABAergic compounds particularly for mild level of anxiety [47]. Agomelatine has beneficial outcome in anxiety disorder. Still it is not approved in any country for the treatment anxiety. Its use is off-label [44]. As its low risk of side effect has well established in clinical trials, melatonin and its analogue might become a better option to treat anxiety in future.

Targeting Melatonin and Glutamate Together

Recently, Shah et al. [48] showed benefits of melatonin in ischemia-induced glutamatergic impairment. Zhang et al.

[49] and Evely et al. [50••] showed correlation between melatonin release and glutamatergic inputs. Glutamate also modulates melatonin synthesis from pineal gland [51]. Melatonin is well-known for its anxiolytic activity and GABA-related inhibitory effect [52]. Mammalian pineal gland produces melatonin from serotonin through enzyme serotonin N-acetyltransferase [53]. This process of synthesis is inhibited by the glutamate. The process involves paracrine interaction between pinealocytes and astrocytes. NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and mGlu1/5 receptors present on the astrocytes get activated by binding of glutamate that released by stress and increases intracellular Ca^{+2} which further release soluble tumor necrosis factor-α (TNF-α) from astrocytes. Available reports [54, 55] state that TNF-α reduces serotonin content and aralkylamine N-acetyltransferase (AANAT) mRNA expression which results depletion of N-acetylserotonin, a precursor of melatonin. Released soluble factor alone or in association with AMPA, glutamate binds to the receptors on the pinealocytes. Activation of these receptors causes reduction in cyclic adenosine monophosphate (cAMP) which inhibits serotonin N-acetyltransferase, the enzyme responsible for production of melatonin. Finally there is depletion in melatonin synthesis [51]. Inhibition of the pathway mentioned in Fig. 1 may increase the melatonin levels and give additional benefits in anxiety. Therefore, targeting specific receptors such as MT2 and mGlu4/6/7/8 receptor in combination can be a novel therapeutic option for treatment of anxiety in future.

Correlation of Orexin with Glutamate-Related Receptors

Orexin A and B are neuropeptides produced by the neurons localized in lateral and posterior hypothalamus. These peptides are involved in physiological conditions such as blood pressure, body temperature, and sleep-waking cycle, which are also related to anxiety disorder. Orexinergic neurons are projected to bed nucleus of stria terminalis. This region has strong correlation with anxiety. Orexin peptides bind with orexin receptor 1 (OX1) and orexin receptor 2 (OX2). Injection of orexin in different regions of brain resulted in increased anxiety in light-dark box and elevated plus maze test [56–58]. Orexin produced its long-lasting effect of increasing neuronal excitability via increasing number of NMDA receptors in cell membrane (Fig. 2) and makes neurons highly responsive to glutamate for several hours [61]. Particularly, the involvement of glutamatergic transmission in the orexin A-induced anxiogenic effect is also known [59].

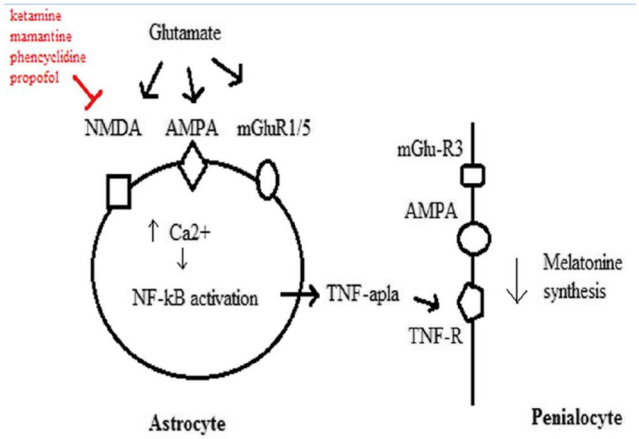

Fig. 1 Modulation of melatonin synthesis through glutamate neurotransmission [51]

OX1 receptor antagonist-treated and orexin-deficient rats showed less response to anxiogenic stimuli activated by orexin neurons [62, 63]. Exposure of SB-334867, an OX1 antagonist, attenuated anxiety in rats. Vanderhaven et al. [64] provided behavioral as well as neuroanatomical evidence regarding the role the orexin-dependent anxiety effect [64]. A recent report suggested role of OX1 receptor in arousal and panic-related anxiety through HCRTR1 rs2271933 T allele [65••]. Orexin neurons can be an interesting novel target for treatment of anxiety-related behavior [66••]. Grafe et al. [67••] reported importance of considering inhibition of orexin as an important target in stress-related disorders. In addition to antagonism of OX1 receptor, consideration of agonist OX2 receptor as novel target is important in anxiety treatment [68••, 69••]. Staton et al. [68••] showed resilience in anxiety after stimulation of OX2 receptor. Grafe and Bhatnagar [70••] recently reviewed clinical studies related to orexin and emphasized on the need to have clinical studies focusing measurement of orexin functions in psychiatric illness. Interestingly, there is a synergistic interaction between orexin and glutamate, particularly in ventral tegmental area and resultant increased dopamine levels through potentiating response to glutamate input [71]. These recent outcome suggests a need of further assessment considering OX1 and OX2 as novel targets along with glutamate-related receptors.

Correlation of Oxytocin and Glutamate-Related Receptors

Oxytocin is a hypothalamic neuropeptide. Role of oxytocin in social behaviors is well documented [72–74, 75••]. Preclinical [60] and clinical studies [76••] have showed its involvement in the pathophysiology of anxiety [72]. Several brain regions have been involved in anxiolytic action of oxytocin [74, 77]. Oxytocin (OT) acts through OT receptors (OTR) which are highly expressed in medial prefrontal cortex (mPFC) and central nucleus of amygdala [78]. Availability of OTR on GABAergic interneurons in cortex induces increase in GABA levels [79]. Interaction of OT with GABA, particularly through extrasynaptic $GABA_A$, attenuates anxiety [80].

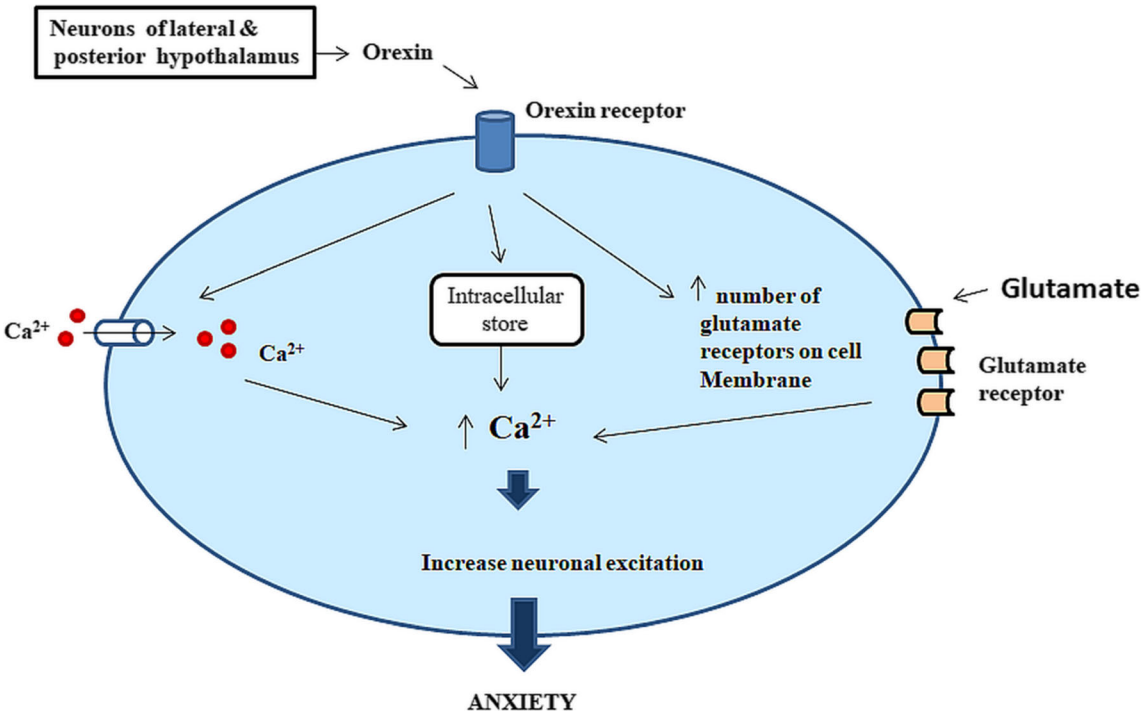

Fig. 2 Correlation of orexin and glutamate [59, 60]

Sabihi et al. [74] showed the anxiolytic effect of OT through increasing GABAergic neuronal activation (Fig. 3). Another pathway through which OT showed anxiolytic activity is related to the suppression of release of adrenocorticotropic hormone (ACTH) [82]. Release of ACTH is induced by physiological and psychological stress. OT is synchronically released in the paraventricular nucleus of the hypothalamus. It reduces the hypothalamic pituitary adrenal (HPA) axis activity, ACTH, and corticotropin-releasing factor (CRF) [83], which are implicated in anxiety. Intranasal administration of oxytocin benefited patients with anxiety disorders [60, 72, 84].

OT attenuated the release of glutamate and increased extracellular GABA in medial prefrontal cortex and dorsal hippocampus of mice [85]. Expression of OT receptors by glutamatergic prefrontal cortical neurons was responsible for social recognition [86••]. A recent clinical study showed significant difference in anxiety score between pre-intranasal administered OT-treated group and placebo group [87••]. Davies et al. [87••] also illustrated the link between GABA interneurons, glutamate pyramidal cells, and midbrain dopamine neurons through hippocampus and striatum regions of brain. Therefore, in addition to the consideration of OTR as a novel

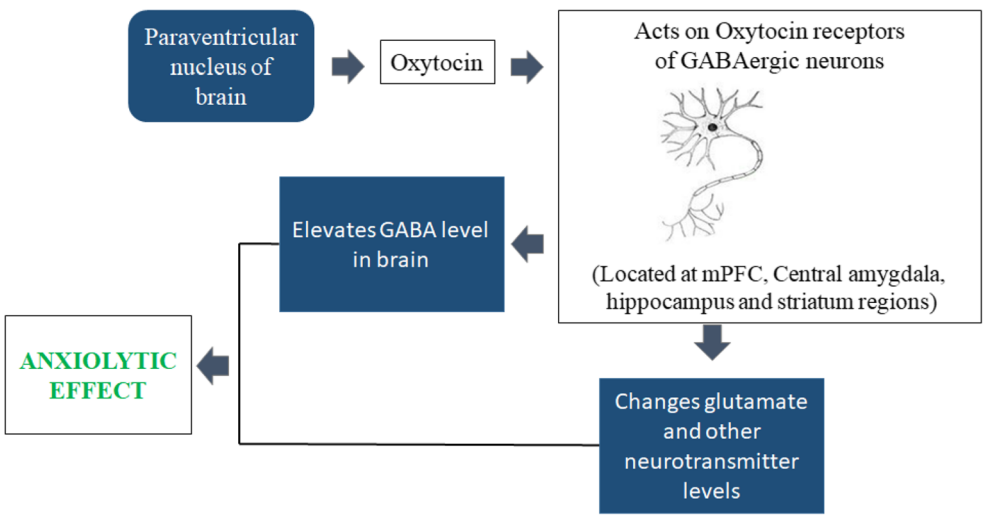

Figure 3. Correlation of oxytocin and GABA [80, 81]

target, a combination treatment focusing on balance between OTR, glutamate, and GABA may help in achieving better efficacy and safety in the treatment of anxiety.

Conclusion

Higher side effects, lower efficacy, and tolerance of available anxiolytic drugs indicate an unmet need in the treatment of anxiety. Targeting MT2 or OX1/OX2 or OT and glutamate-related receptors together need to be assessed in different experimental settings as a future endeavor. This can be considered with the use of either combination of drugs or using a new drug molecule targeting two receptor systems. Consideration of more than two targets can also be an option. These newer therapeutic approaches may provide better treatment options, enhance compliance, and increase quality of life of patients.

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Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

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•• Of major importance

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