

Deepen Our Understanding of Anxiety and Depression from a View of their Co-occurrence

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ABSTRACT

Anxiety and depression are two common neuropsychiatric disorders which have made great social and economic burden. Traditional studies especially animal models of these two disorders, with a relatively high probability, arbitrarily separated these two diseases from each other. In contrast, clinical studies are actually prone to treat anxiety and depression as two clinical comorbidities. A plethora of evidence from clinical studies performed on both children and adults have demonstrated the high co-occurrence probability of anxiety and depression. The evidence suggests that much more consideration pertaining to the comorbidity should be taken into account as performing studies on animal models of anxiety and depression, which then will probably be more informative for the clinical treatments. In addition, exploring potentially new brain areas with specific neural circuits and/or key neurotransmitters responsible for anxiety and depression, as well as new effective clinical treatment methods will definitely warrant the improvement of pharmacological interventions of these two neuropsychiatric disorders. Accordingly here in this mini-review, we briefly summarized the current status of anxiety and depression from a view of their co-occurrence in order to deepen our understanding of these two neuropsychiatric disorders.

INTRODUCTION

Anxiety and depression are two common neuropsychiatric disorders with a high co-occurrence [1,2], both of which have made heavy social and economic burden [3-6]. In the last few decades a wide variety of animal models emerged aiming to decipher the underlying pathophysiological mechanisms [7,8], which has greatly advanced our understanding of these two neurological disorders and, more importantly, provides some insights for clinical therapies. Studies regarding animal models of anxiety and depression are, with a relatively high probability, arbitrarily separated these two diseases from each other. For these animal models, distinct behavioral assays are usually performed to test the anxiety- and depression-like behaviors, respectively. On

the one hand, the elevated maze test and the open field test, as well the light-dark box test are commonly used to validate the anxiety-like behaviors [9,10]. On the other hand, the forced swimming test and tail suspension test, as well as the sucrose preference test are the preferred methods generally considered by researchers [11,12]. Nonetheless, actually anxiety and depression are two clinical comorbidities, and possibly each of these two disorders could potentially mirror the occurrence of the other. From this point, it will be much more meaningful and informative when considering the anxiety and depression concurrently. Here in this short review, we will briefly summarize the current status of these two neuropsychiatric disorders with an emphasis on their co-occurrence and generality to deepen our understanding from a relatively different view.

CO-OCCURRENCE OF ANXIETY AND DEPRESSION IN BOTH CHILDREN AND ADULTS

The co-occurrence of anxiety and depression is actually not a new topic, and it has been historically reported by the World Health Organization more than twenty years ago [13]. Based on this study on psychological disorders in primary health care settings at fifteen international sites, it was confirmed that, among all disorders analyzed, anxiety and depression are the most common co-occurred ones. One clinical research on 182 depressed patients aged 60 and older showed that 35% of these older patients with depression exhibited at least one lifetime anxiety disorder diagnosis, and 23% of them were diagnosed with current anxiety [14]. It is interesting and also noteworthy to mention that the co-occurrence of anxiety and depression is not only found in adults (e.g., elderly patients, as mentioned above) but also exists in children, and the co-occurrence rate is as high as around 75% [15,16]. The high rate of concurrent and sequential comorbidity of these two disorders in both children and adolescents underscores the importance and necessity of the prevention and treatment of both anxiety and depression in younger populations [17]. Moreover, a recent meta-analysis indicated that co-morbid anxiety and depression are prevalent in the antenatal periods [18]. Collectively, the evidence, more or less, suggests that much more consideration pertaining to the comorbidity should be taken into account as performing studies on animal models

of anxiety and depression, which then will probably be more informative for the clinical treatments.

POTENTIAL NEURAL SUBSTRATES INVOLVED IN THE CO-OCCURRENCE OF ANXIETY AND DEPRESSION

To maximize the efficacy of clinical treatment of both anxiety and depression, it is important and also meaningful to uncover the potentially common mechanism underlying these two neuropsychiatric disorders. Many distinct brain areas, such as the Basolateral Amygdala (BLA), have been reported to be associated with anxiety and depression in both human subjects and rodents [19-22]. One recent study demonstrated that the cross-talk between noradrenergic and cholinergic signaling in amygdala could regulate anxiety- and depression-related behaviors in mice, which was mediated by $\alpha 2A$ Adrenergic Receptors ($\alpha 2ARs$) and nAChRs (those containing the $\beta 2$ nAChR subunit) [19]. In addition, some other brain regions including the nucleus accumbens and ventral tegmental area are also involved in the pathophysiology of anxiety [23-26] and depression [26-29]. One question is raised based on these specific brain areas closely associated with the occurrence of both anxiety and depression. Do anxiety and depression share a common pathophysiological mechanism? It was documented that the concentration of Corticotropin-Releasing Factor (CRF) in the cerebrospinal fluid was increased in both anxiety and depression [30], which suggests a shared common neuroendocrinological dysregulation in these two neuropsychiatric disorders. It was further documented that if anxiety and depression coexist in a neuroendocrine continuum, it is quite possible for clinical treatments endowed with similar mechanisms of action to be performed on patients enabling symptoms of either disease [30]. Uncovering potential neural circuits or cell signaling pathway, as well as key neurotransmitters responsible for both anxiety and depression will definitely shed some lights on the pharmacological interventions of these two neuropsychiatric disorders.

PRESSING NEED TO EXPLORE NEW WAYS TO TREAT ANXIETY AND DEPRESSION CONCURRENTLY

The high co-occurrence probability of anxiety and depression emphasizes the necessity of exploring new efficacious methods for the treatment of these two neuropsychiatric disorders. The Deep Brain Stimulation (DBS) has been confirmed to be one

useful way in ameliorating the symptoms of both anxiety and depression [31,32]. One study reported that in patients suffering from resistant depression, performing DBS in nucleus accumbens decreased ratings of both anxiety and depression [33]. Some other methods, such as internet-based treatment programs and computer-based treatment for anxiety and depression [34,35], have emerged in recent years, however, the feasibility and effectiveness of these methods are still needed to be consolidated by performing much more studies.

CONCLUSION

In general, we briefly reviewed the current status of the co-occurrence of anxiety and depression based on both animal models and clinical studies, and the co-occurrence prevalence of these two disorders as well as the potential neural substrates involved in. We emphasized that anxiety and depression are two clinical comorbidities in both young children and adults, and possibly each of them could potentially mirror the occurrence of the other. It will be much more meaningful and informative when considering the anxiety and depression concurrently.

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