International Journal of Veterinary Science and Medicine 5 (2017) 98–104

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Contents lists available at ScienceDirect

International Journal of Veterinary Science and Medicine

journal homepage: www.elsevier.com/locate/ijvsm
www.vet.cu.edu.eg

Review Article

Describing some behavioural animal models of anxiety and their mechanistics with special reference to oxidative stress and oxytocin relevance

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ARTICLE INFO

Article history:
Received 15 May 2017
Revised 14 August 2017
Accepted 29 August 2017
Available online 7 November 2017

Keywords:
Anxiety
Elevated plus maze
Neuropsychiatric diseases
Rat
Social defeat stress
Zebrafish

ABSTRACT

It is now generally accepted that animal studies are playing an important role in the understanding of anxiety disorders, since they contribute to the current knowledge regarding the mechanisms and possible therapeutic approaches in anxiety. In the present review we will detail some essential aspects of behavioral animal models of anxiety related to social defeat paradigm, elevated plus maze, elevated zero or T maze, light/dark box, social interaction test or tests based on predator models, considering the latest theories and methodological approaches in this area of research, as well as our previous studies focusing on anxiety manifestations in a variety of species including rats, zebrafish, dogs and pigs. Moreover, in this context, we will focus on the recent theories concerning oxidative stress, as well as importance of oxytocin administration (especially the intranasal route). This could be important considering that these two factors are currently being investigated as possible mechanisms (oxidative stress status) and related therapeutic target (both intranasal oxytocin and antioxidants) in the pathology of the anxiety disorders.

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Peer review under responsibility of Faculty of Veterinary Medicine, Cairo University.
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https://doi.org/10.1016/j.ijvsm.2017.08.003
2314-4599/

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1. Introduction

Anxiety disorders are clusters of psychiatric disorders that are mainly described by excessive and unjustified fear, somatic symptoms, and related behavioral responses (escape, avoidance or assurance behaviors) [1]. It is important to mention the fact that animal models will never be perfectly replicating the complex human neuro-psycho-pathology. Still, they have a fundamental relevance in studying neuropsychiatric disorders, considering important physiological and anatomical similarities between humans and animals [2].

Thus, animal models studies are mainly based on the physiological, anatomical, and genetic structural similarities between human and animals [3]. Moreover, animal models have many positive characteristics including, the fact that they are easy to obtain, maintain, handle, relatively inexpensive, and exhibit increased reproducibility, as compared to the clinical studies [4,5].

Considering these advantages, many rodent models of anxiety disorders have been developed and extensively used to study changes in animal behavior after exposing them to various types of stressors. Models of rodents (rat and mouse) [6] are the most commonly used models in neuropsychiatric studies, although other species of animal models have been described in neuropsychiatry research including primates [7], fish [8] or birds [9].

Studying the mechanisms of mental disorders such as anxiety on animal models is often questioned in terms of equivalence. However, as mentioned above, many evidences of similarities between rodents and human exist starting with the organization of nervous and endocrine systems [10,11]. Additionally, aspects regarding equivalences in terms of basic cognitive process and behaviors related to anxiety such as conditional learning, anticipation of danger, avoidance, freezing, and escape are important as survival mechanisms [12,13].

Concerning the validity type of the animal models, there are mainly three classes of models: 1- a correlation model with a predictive validity, implying that the model is sensitive to pharmacological agents [12], 2- an isomorphic model sustained by a face validity that implies an equivalence between behavioral responses in human and animals [13], and 3- a homologous model based on a construct validity that speculate similar etiology for a certain disorder between humans and animals [14]. By detailing, it is generally accepted now that especially for the rodent models of psychiatric and neurological diseases, there should be firstly a clear resemblance to the classical human symptoms (the so-called face validity), an additional resemblance to the main mechanisms of the disease (e.g. construct validity) and an identifiable response to the drugs that are generally working in humans (predictive validity), as described by Crawley in 2004 [15].

Considering all the aforementioned aspects, we will summarize both the current knowledge and our previous experience in animal models of anxiety, by focusing on various species such as rats, zebrafish, dogs, and pigs, as well as describing the relevance of oxidative stress in this context. Additionally, we will briefly describe the possible relevance of the oxytocin administration in this context, considering its increased relevance in this area of research in the last couple of years.

2. Some common tests of anxiety and their associated mechanisms

2.1. Social defeat stress

An important model in studying anxiety disorders relies on social defeat stress. Social defeat paradigm was used in large number of models that studied depressive [16,17] and anxiety disorders [18,19]. In this way, social defeat model is based on an interaction of the experimental animal with specific stimuli that the animal considers dangerous, without the possibility of escaping from the situation [20]. A model of social defeat is thus created by the exposure of the animal to an aggressive-type interaction that the animal considers dangerous. The classical experimental settings involve a short interaction with another larger individual, which is more aggressive, inducing a relation of coordination-submission [21].

Also, the model of social defeat could be a one-time confrontation with the threat or may be designed as chronic repeated exposures. Generally, exposure to repeated obligatory social stress (chronic stress) is fairly used in depression model, while acute exposure (acute stress) is rather investigated for anxiety disturbances [17,22].

In addition, several methods [23–25] have been described and used for study anxiety and stress related disorders that are generally divided into conditioned [26] and unconditioned methods [23,24]. The most common unconditioned tests are exploration-based models including elevated plus-maze, elevated zero maze, elevated T-maze, and the light/dark box or social interaction test [24,25], and also tests based on predator models (e.g. including cat exposure or rat exposure) [23].

2.2. Elevated plus maze

Elevated plus-maze is considered an important test that evaluates anxiety behavior by counting the number of entries in the open-arms [27]. The preference for the closed arms is a sign of need for security and reveals anxiety traits. The measure for anxiety is calculated by counting the number of open-arm entries and the number of closed-arm entries expressed as a percentage of the total number of arm entries and the period of time spent on the open arms [14]. In fact, this behavioral test has more sophisticated concerns, as additional anxiety-related behaviors are evaluated including head dipping in open-arms (sticking the head below the level of the maze and towards the floor), protected stretch-attend postures (stretching) in the closed arms (the animal stretches with the forepaws while maintaining the hind paws in the same place and then retracts to the original position), and grooming (cleaning of any part of the body with the paws and/or the mouth) [27]. Our team was the first; to the best of our knowledge; to show that the intra-cerebro-ventricular administration of a drug such as angiotensin-(1-7) could result in anxiolytic-like behavior, 3 weeks after neurosurgery, when administrated 8 consecutive days, 0.1 mg/kg body weight, as demonstrated by the significant increase in the time spent in the open arms of the elevated plus maze and increased head-dipping behavior in the open arms, as well as decreased stretching in closed arms [27]. Even more, one