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REVIEW ARTICLE

Avian Models of the Neurobiology of Anxiety: A Systematic Review

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Abstract

Objective: Anxiety is partly driven by changes in neuroendocrine signaling, which continues to be an area of study. Birds are a useful model to study anxiety disorders due to their unique behaviors and social makeup, leading to several observable behaviors indicative of anxiety.

Methods: Using PRISMA guidelines, a systematic review of studies published from January 2000 to August 2022 in PubMed, PsycINFO and MedLine was conducted. Inclusion criteria included animal studies utilizing an avian model, examining the relationship between a neuroendocrine biomarker and behavioral displays of anxiety. Exclusion criteria included review articles, editorials, studies where anxiolytic drugs were used and studies where anxiety was not the primary studied behavior.

Results: 376 articles were screened. 10 papers met the review criteria. Dopamine, serotonin and glycogen synthase kinase 3β (GSK-3β) were found to be inversely related to anxiety levels. Ghrelin and γ-Aminobutyric acid type A (GABAa) were directly correlated with anxiety levels. Corticosterone correlated in a bidirectional manner depending on when a stress was applied, however, lower levels at baseline were more predictive of less anxious birds. Pituitary adenylate cyclase was shown to increase anxiety but was also time-dependent. Arginine vaso-peptide was found to reduce anxiety, but was also context-dependent. Vasointestinal Peptide had no relation to anxiety.

Conclusion: Birds display similar chemical responses to humans when anxious, and due to anxiety-related behaviors unique to birds, allow for an additional approach to the investigation of different neuroendocrine markers that are not always strongly considered when studying the neurobiology of anxiety in humans.

Introduction

Anxiety is a human emotion that arises in many situations, such as in fear or in anticipation. It serves a functional, protective role in processing a situation or environment. When pathological, such as in Generalized Anxiety Disorder (GAD), anxiety is one of the most prevalent psychiatric disorders in society with a high medical and socioeconomic cost (1). The etiology of anxiety is both biological and environmental. Recently, there has been a marked increase in understanding the neurobiology of anxiety. Research in this area can allow scientists to better understand how the

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human brain and human behavior are connected, as well as appreciate the signaling behind this common emotion and how it is induced both naturally, and artificially, through illness or drugs. Notably, this understanding can also provide insight into the pathophysiology of GAD or social anxiety and help with understanding how to diagnose and treat these conditions. Current prominent biomarkers associated with anxiety include cortisol, lysozyme, a-amylase, serotonin, Brain-Derived Serum Neurotrophic Factor (BDNF), microRNA, oxytocin and 5-Hydroxyindoleacetic acid (5-HIAA). There are several obstacles to understanding the biology of anxiety, including insufficient knowledge, variation in its presentation, and low specificity of these biomarkers, paving the way for new ways to find and assess these biomarkers [1].

Birds are an underappreciated model used in animal studies. They can assist in the study of different neuropsychiatric phenomena, particularly anxiety. Relative to rodents, there are fewer studies looking at anxiety and cognitive performance in avian models. Like other animals, birds are sensitive to stressful stimuli. They are frequently exposed to stressful situations in nature [2]. A unique bird model, the chick anxiety-depression model, has been used in several anxiety studies to illustrate that anxiety and depression are related clinical syndromes, and this model has been validated as a useful pharmacological screening assay for potential anxiolytic and antidepressant medications [3,4].

Birds are a useful model of human anxiety due to their complex social hierarchies and social units and their rich inter-personal relationships. They have many easily observable behaviors that can easily translate to an equivalent in human anxiety [5]. These avian models can assist in addressing the obstacles that currently exist when trying to understand the neurobiological basis of anxiety by allowing for additional approaches to study the condition. We conducted a review to examine literature encompassing biomarkers of anxiety in avian models and how it parallels human anxiety.

Methods

This systematic review was conducted using PRISMA guidelines. A search was completed for studies published from January 2000 to August 2022 in PubMed, PsycINFO and MedLine using the search terms ((anxiety) AND (bird OR birds OR avian)). The search criteria were intentionally left broad to prevent limiting the scope of the review to any specific neuroendocrine or biological markers. Included articles contained animal studies utilizing an avian model with the presence of a neuroendocrine compound, and consequent behavioral displays of anxiety. Exclusion criteria included review articles, opinion articles, editorials, duplicate articles and pharmacologic studies where anxiolytic drugs were the focus. Excluded studies also included those in which anxiety was not the primary condition studied, studies that focused on genetic markers of anxiety and studies that were primarily focused on animal behavior and welfare without human applications. Several articles were screened out through the title and abstract, and a select few were screened out since the author last name was "Bird". Most articles required a full review. There were no systematic reviews or meta-analyses found on our study topic.

All studies found using the search terms in the database were compiled into a list on Microsoft Excel, but only included studies were put in a table with study author/date, avian model type and characteristics, neuroendocrine marker under review and study conclusion (table 1). The sample size of the birds was included, as was the species and characterization of the sample (sex, age, captivity status, breed/strain) to help understand the population under study. The main bird species used in the studies included: domestic chickens (*Gallus gallus domesticus)*, zebra finches (*Taeniopygia guttata)*, house sparrows (*Passer domesticus)* and song sparrows (*Melospiza melodia*).

Results

376 articles resulted through the database search. 10 papers met the review criteria, covering 4 species of birds and a variety of neuroendocrine markers including: dopamine, serotonin, glycogen synthase kinase 3β (GSK-3β), ghrelin, γ-Aminobutyric acid type A (GABAa), corticosterone, pituitary adenylate cyclase, arginine vasopeptide and vasointestinal peptide (Table 1).

Table 1: The sample size of the birds.

Article	Study Design/ Details	Sample Characteristics	Test of Anxiety	Measure of Anxiety
Krause et al. 2017 [8]	Female, Three genotypes (W/W, W/D, D/D)	Chicken	Open-field, light–dark test	5-HTT (serotonin transmitter)
Gaston et al. 2017 [14]	Male and female, day-old cobb chicks	Chicks	Open Field test	Ghrelin + GABAa causing HPA axis activation, leading to increase ACTH, corticosterone and anxiety Bicuculline as a GABAa antagonist
Kelly A.M., & Goodson J.L. 2015 [5,11]	Male and female	Zebra Finches	Novelty suppression of feeding and exploration	Measure dopamine cell groups (A8-A15)
Gaston et al. 2015 [7]	Male and female, day-old cobb chicks	Chicks	Open-field test	Ghrelin and GABAa, blocked by biccuculline
Kingsbury 2013 [10]	Male and female	Finches	Familiar, Novel-familiar cage test	VIP and VIP receptors (VPAC)
Goodson J.L., Evans A.K. 2004 [11]	Male birds	Song sparrow	Nonsocial stress (capture, handling, and infusion) Social Stress	AVT (arginine vasopeptide) within the lateral septum
Carvajal et al 2009 [9]	Male and female	Chicks	Open-field study	Ghrelin
Moaraff et al. 2022 [12]	Female	Zebra finch	Familiar and novel bird test, cage center test	GSK-3β inhibition caused the treated birds to spend more time in the more middle parts of the cage compared to controls, a behaviour that might indicate anxiety.
Lattin et al. 2019 [6]	Male, captured at 3 different times of year	House sparrows	Behavioral observation (feather ruffling, beak wiping, hopping, preening)	D2 receptor binding, corticosterone serum levels
Hollosy et al. 2004 [13]	Male and female, treated in ovo in the first and second half of embryonic life (E8 and E16, respectively)	Chicks	Open-field test, novel environment	Pituitary adenylate cyclase activating polypeptide (PACAP)

Dopamine (DA)

DA plays a role in stress-associated behaviors, and decreased DA leads to increased stress-resilience. DA has been most associated with reward and addiction pathways, as well as novelty-seeking and learning. However, its function can be expanded to anxiety when viewing it from the perspective of a stressed organism associating stimuli as positive verses negative, and then responding in kind [5].

There are many DA cell groups in human and avian brains. These cells have significant overlap in projections, which can make it difficult to isolate actions to one cell group. Kelly AM, et al. [5] measured DA as a behavioral phenotype in individual DA cell groups A8-A15 in finches divided by sex (n = 80). They found that in these cell groups, which are conserved in all amniote vertebrates, there was a clear correlation with anxiety and that it varied from group to group.

Anxiety was measured via novelty suppression of feeding and exploration. The scale in which the birds' behavior was measured was developed in a previous study in which zebra finches were found to have multidimensional personality structures of behaviors in social and nonsocial contexts. The exploration of a novel environment encompassed the birds being placed in a new cage with a branch in each corner. Latency to move and areas of branches explored were recorded. For novelty-suppressed feeding, birds were placed in new cages with a novel object (ex: glove) hanging over the bird's feed area. Latency to move and latency to feed were measured.

The results of the study by Kelly AM, et al. [5] showed that cell group A8 was negatively correlated with anxiety, while group A12 was indicated in social anxiety. Group A13 was anxiolytic and did not vary between male and female specimens. Prior to this, few studies understand social behavior in A13, having predominantly linked it to paradoxical sleep in rats and migraines. Group A15 was sex-specific, and was found to cause anxiety in females and decreased anxiety in males. Previously, this group was linked to seasonal breeding and anestrus in sheep. This study was unique in looking at individual specimen's personalities and expressions of anxiety.

It was also found that female birds exposed to non-familiar birds experienced higher anxiety scores than when exposed to familiar birds. Male birds had lower anxiety scores when exposed to novel birds than when exposed to familiar birds, indicating an interesting, sex-dependent relationship.

Another study in this review that looked at the relationship between dopamine and anxiety was by Lattin CR, et al. [6]. In this study, house sparrows (n = 15) were captured at 3 different, stressful times of year--molt, breeding, and wintertime. The results showed that individual biologic variation may lead to differences in anxiety related behaviors. Larger decreases in levels of the DA D2 receptor (D2R) binding caused an increase in anxiety related behaviors 2 and 4 weeks after the specimen's capture. These behaviors included feather ruffling, beak wiping, hopping, flights, preening and feeding. Preening and feeding were inversely associated with anxiety levels.

Corticosterone

Corticosterone is a hormone that is strongly associated with the stress and anxiety response in humans and mammals. The Lattin CR, et al. [6] study, mentioned previously, also studied corticosterone in the house sparrows they had captures. They found an interesting pattern in corticosterone that has been gaining popularity in literature--house sparrows with lower baseline corticosterone levels at capture, but higher levels when stressed, exhibited less anxiety.

Serotonin (5-HT)/serotonin transporter (5-HTT)

Increased 5-HTT levels are associated with less fear in mammals, and in humans, a decrease in 5-HTT expression is associated with increased anxiety. In a study by Krause ET, et al. [8], adult chickens (n = 268) and polymorphisms in 5-HTT were studied. In this study, chickens with the D-allele possessed greater 5-HTT expression, and W-allele, or wild-type, chickens, possessed less 5-HT expression. A similar effect to humans was found with 5-HTT and anxiety in adult chickens.

There were 2 behavioral paradigms used in this study. One paradigm was the open field study, in

which a bird first explores a novel environment and is isolated, balancing the desire to make contact with another member of the species with the anxiety of avoiding contact with a predator through drawing less attention to itself and increasing arousal, attention and being more alert. Less fearful chickens are more comfortable with exploring more of the novel environment. Latency to first locomotion, the number of fields visited (the field is marked into small squares), the number of fields changes, and number of droppings were measured, as they are all indicative of fear or anxiety [7,8]. An increased number of squares crossed and an increase in escapes can be due to the chick feeling anxious and trying to establish contact with another chick [9]. The other behavioral paradigm was the light-dark test, in which an arena is half-dark and half well-lit. In chickens, an avoidance of dark areas translates to fear or anxiety related behavior. Chickens would be placed in the center of the arena and the latency to first locomotion, time spent in the light/dark area after their first movement, and the number of droppings, were measured. Locomotion is a more specific behavior for anxiety, as it is regulated by 5-HT.

The D-allele chickens, hence, increased 5-HTT expression, showed less fear and anxiety in both paradigms when compared to the W-allele chickens.

Ghrelin and GABAa

Central ghrelin has been associated with stress and anxiety in rodents and birds. mRNA for ghrelin can be seen in many parts of the brain and in rodents and chicks, is synthesized primarily in the stomach [9]. In chicks and rodents, central ghrelin causes anxiogenic behavior. In the chick forebrain, GABAa receptor modification can influence behavior. The relationship of GABAa receptors and ghrelin can be due to possible links with serotonin stimulating 5-HT synthesis and secretion. Ghrelin may also affect serotonin indirectly. GABAa receptors have been associated with the pathogenesis of many psychiatric conditions, including anxiety, depression, schizophrenia, substance abuse and epilepsy [7].

In a study by Gaston MS, et al. [7] and Carvajal P, et al. [9], ghrelin was found to be anxiogenic. In the Gaston MS, et al. [7] study, for the first time, they found that the anxiogenic behavior caused by ghrelin could be blocked by bicuculline, a GABAa receptor competitive antagonist. Gaston MS, et al. [7] also confirmed for the first time that ghrelin activated the Hypothalamic-Pituitary-Adrenal (HPA) axis, leading to increased ACTH, corticosterone and consequently, anxiety. There is already evidence in literature that Ghrelin increases corticosterone release in chicks and rodents, and that this is a summative effect. As mentioned previously, corticosterone has been associated with the stress and anxiety response.

Increased GABAa receptor density occurs in the open field test and with novelty, 2 behavioral paradigms used in the Gaston MS, et al. [7] and Carvajal P, et al. [9] study. The Gaston MS, et al. [7] study added vocalizations on as an additional variable. In the Carvajal P, et al. [9] study (n = 20), the authors found that Ghrelin increased latency to ambulate but decreased ambulation activity (to the point of no ambulation) in a dose dependent manner. There was also an increase in latency to defecate and the number of defecations, indicating anxiety. Notably, by day 2 of the experiment, chicks had a lower latency to ambulation and would require larger doses of ghrelin, indicating habituation to repeated exposure of the same stimulus and a way to reduce anxiety over time.

Carvajal P, et al. [9] discussed that in some chicks, in the open field test, chicks would sit with their eyes closed, indicative of an inhibition of the behavior response induced by the fear or anxiety of the task. This could indicate that sleep plays a role in responding to stress or anxiety. They referred to another study in which a large amount of infused ghrelin caused sleep-like behavior, and that the immobility by large doses could be a response to anxiety.

Vasointestinal Peptide (VIP) and VIP receptors (VPACr)

Kingsbury MA, et al. [10] looked at VIP and VPAC and their association with general anxiety and socially-induced anxiety. VIP is a neuropeptide most associated with prolactin release in humans and in other animal models, including birds and rodents. These markers are located diffusely in the brain in almost all areas associated with social behavior and contribute to anxiety-like responses and stress

responses. VIP is associated with aggression in birds and social recognition in rodents. Its affects are mediated through VPACr. These are found in more density in gregarious, social finches over territorial finches. It encourages social contact and a bird's desire for large groups.

For this study, two paradigms were created. In one, finches were placed in a cage in a new environment divided into zones with either 2 familiar birds or 10 familiar birds. The time the bird spent with the large group was for social contact or gregariousness. In the novel-familiar test, the birds cage sides had either 5 novel birds or 6 familiar birds, and the bird's preference for new birds was determined through time spent with them. It was found that for social anxiety, in female birds, VPACr antagonism did not affect novel-familiar social preferences in a familiar environment or produce anxiety-like behaviors. It would help with social contact and could, by extension, alleviate stress or anxiety in novel environments. It was found that VPACr antagonism decreases social contact in a new environment, and this could be indicative of endogenous VIP alleviating anxiety in new social situations.

Anxiety was also measured using latency to feed in presence of novel object and exploration of novel environment--both are considered good measures of anxiety in birds. The novel object was a purple nitrile glove. There was no difference with latency to approach the food dish in this study. Exploration of a novel environment was also used, similar to that used with chick models in aforementioned studies, and a good marker of anxiety in birds. The finches were put into a cage in a new room with 3 groups of new branches. The number of times the finch visited the branches, hop count and the number of branches touched were measured. The. There was no difference in exploration in controls and infused birds. Thus, VPAC antagonism can be indicated in social, but not general, anxiety.

Arginine Vasopeptide/Vasopressin (AVT)

The avian brain is similar to the mammal brain. Responses to stressful stimuli are regulated by evolutionary conserved brain regions in several areas in the basal forebrain, and in this study by Goodson JL, et al. [11], AVT was a marker considered in different regions. AVT in the Lateral Septum (LS) responds to stress and anxiety with an anxiolytic response. AVT/AVP is similar across birds and mammals, including locations of cell groups, sex dimorphisms and steroid sensitivities, as well as their role in stress and anxiety. In general, the LS is involved in anxiety, aggression, and social memory. It is unsure if this function is distributed throughout, or in individual neurons in early social stress or nonsocial stress. In this study, stress was synonymous with anxiety.

Goodson JL, et al. [11] looked at song sparrows under nonsocial stress (capture, handling, and infusion) and social stress. Birds were exposed to 1 of 5 conditions: saline + simulated territorial intrusion (STI, in this case, presented another male bird with a song playing), arginine vasopressin V1 antagonist (AVPa) + STI, AVP + STI + saline + empty cage and empty cage unhandled. AVPa infusions reduced or eliminated the ZENK-ir increase, a measure of stress and anxiety, which suggested that AVT would help with stress response or on a more limited role, social challenge. Specifically, they concluded that the septum AVT responds to general stress, and that this varies from songbird to songbird and can be context-dependent, such as in dawn chorus territorial singing verses a bird facing a predator. This divergence can vary on the behavior of the bird if it is more aggressive, or species dependent. This effect has also been seen in rodents.

Glycogen Synthase Kinase-3B (GSK-3B)

GSK-3B is a much conserved protein kinase that plays a role in many processes including cognition and behavior and mood. A and B isozymes are conserved in vertebrates and even fish, amphibians and reptiles, but interestingly, the A gene is not in birds. This study by Moaraf S, et al. [12] ($n = 20$) wanted to study the effects of GSK-B in isolation on zebra finches. This biomarker has been noted to have high activity in Alzheimer's disease, Parkinson's disease, bipolar disorder and schizophrenia. Inhibition of it is potentially considered therapeutic for mood disorders and stress-induced depression. Birds are a better model than mice as they are an inherent knockout, whereas knockout mice have had lethality and often do not show significant differences.

The results in Moaraf S, et al. [12] study indicated that GSK-3B affected social recognition or anxiety, in which a bird was more comfortable with moving towards a stranger bird, in a study conducted similarly to that in Goodson JL, et al. [11] study. This is unusual, as zebra finches are social birds and live in large flock's safety. GSK-3B also caused the birds to spend more time in the center of their cage as opposed to other areas, which can be another marker indicative of anxiety. This can be seen in earlier references to the open-field study, as birds, and even rodents, avoid staying in the center of a wide-open space. In this study, control birds would explore more in the beginning and then begin to stay in more restricted areas at the sides of the cage as time gradually passed, seen through decreased latency to ambulation, since they became habituated. Interestingly, they also became less indecisive with time, where they would take less time to decide where to settle.

Pituitary Adenylate Cyclase Activating Polypeptide (PACAP)

PACAP is a protein used in neurodevelopment. This study by Hollosy T, et al. [13] (n = 20) antagonized this marker during the embryonic development of chicks. PACAP is similar to VIP, and studies have shown that inhibiting VIP with an antagonist can cause neurobehavioral developmental disruption.

Hollosy T, et al. [13] found that an injection of a PACAP antagonist in the first half of development caused subtle changes. There was reduced anxiety in novel environment at 2 days post-hatch, but these effects were gone after 2 weeks. Treatment in the 2nd half of embryonic development did not show behavioral changes. PACAP content in different brain areas also did not vary between chickens, but it decreased overall with age. Open-field test was also used in this study, but additional behaviors evaluated here were number of steps, burst activity, pecking, preening, wing movement, wall runs, diagonal runs and jumping. This indicated a lack of relationship between PACAP and anxiety.

Discussion and Conclusion

Anxiety is a common expression and emotion found in humans and animals alike. When present in higher quantity or frequency, anxiety can be pathologic. In humans, diagnosing features of anxiety, or even an anxiety disorder, is based on the skills of an experienced clinician. Currently, there are no specific laboratory tests that can identify anxiety. It is based on the skills of an experienced observer. Animal models of anxiety have typically involved rodents. While there are less such studies in avian models, bird models are undervalued and serve a unique purpose and present valuable behaviors to study [5]. In this systematic review, studies that involved avian and neurobiological models of anxiety were utilized. From our research, it is evident that that birds display similar chemical responses to humans when anxious. Anxiety-related behaviors unique to birds allow for an additional approach to the investigation of different neurobiological markers that are not always strongly considered when studying the neurophysiology of anxiety in humans. There is significant overlap in birds and mammals and birds often possess longer lifespans than rodents [7]. There is also overlap in their behavioral and social expression, such as in zebra finches with a two-parent, nuclear family structure [5].

In this review, dopamine, serotonin and GSK-3β were found to be inversely related to anxiety levels. Ghrelin and GABAa were directly correlated with anxiety levels. Corticosterone correlated in a bidirectional manner depending on when a stress was applied, however, lower levels at baseline were more predictive of less anxious birds. Pituitary adenylate cyclase was shown to increase anxiety but was also time-dependent. Arginine vasopeptide was found to reduce anxiety, but was also context-dependent. Vasointestinal Peptide was not related to anxiety.

This study was valuable in considering the individual makeup of a bird, or person, when considering predisposition to anxiety. Lattin CR, et al. [6] proposed that individuals could vary in their predisposition to anxiety. As an example, they illustrated that house sparrows in the wild can abandon their nest when stressed, but some birds within the same species will not. There is evidence that this is a trait passed down from parents to offspring in these birds. They also speculated that in the future, Positron Emission Tomography (PET), as used in their study, could change the progress made

in understanding the neurobiological etiologies of behavior and stress.

In the study by Krause ET, et al. [8] it was proposed that in humans, increased expression of the 5-HTT gene is seen with a particular allele, however, in chickens, increased expression is mediated through a deletion. These are different paths towards the same outcome, which further raises the question on individual, biological variation in the development of anxiety. Furthermore, in humans, the allele associated with decreased anxiety (increased 5-HTT) occurs at a similar frequency to its alternative allele. However, this allele is decreased in chickens, causing chickens to be more fearful. This leads to discussion on the evolutionary benefits of keeping certain traits that cause increased anxiety, and how this may apply to the heritability of anxiety traits. As seen in the study by Kelly AM, et al. [5], anxiety can also be dependent on sex. Kingsbury MA, et al. [10] expands on this through discussing the various contexts and even inter-species variation in anxiety expression.

This review was limited in scope and study number and there is significant need for further studies and work in understanding the neurobiological basis of anxiety in avian models, and beyond.

Limitations

Due to the varied nature of the studies, population sample varied between studies and were not always explicitly specified. In some studies, since birds were captured from the wild, there were limitations in controlling bird characteristics and experiment sample size.

Furthermore, due to the limited number of studies on the topic of avian models of the neurobiology of anxiety, several studies were included that also encompassed additional study directions and results, in addition to anxiety. Many studies would additionally refer to anxiety or anxiety-like behaviors with words such as stress, fear and personality.

Finally, as referenced earlier, animal models can be excellent tools in studying psychology and behavior, but they also come with several limitations that prevent them being a strong replica or replacement of the uniquely complex expression of human emotion.

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