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Serotonin and Anxiety

Neuroanatomical, Pharmacological, and Functional Aspects

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Caio Maximino
Instituto de Ciencias Biologicas
Universidade Federal do Para
R. Augusto Correa 01
Belem 66085-110
Brazil

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To Monica Gomes Lima, for putting up with my own anxieties during writing

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Contents

1 Introduction 1
1.1 Anxiety and Risk Assessment 2
1.2 Fear/panic and the Cerebral Aversive System 5
1.3 "Coping" Styles, Stress Reactivity, and the Active–Passive Continuum 6
References 8

2 Serotonin in the Nervous System of Vertebrates 15
2.1 Synthesis and Metabolism of Serotonin. 15
2.2 Transport of Serotonin: SERT and Uptake$_2$ 18
2.3 Serotonin Receptors 22
2.3.1 5-HT1A Receptors 23
2.3.2 5-HT$_{1B}$ Receptors 25
2.3.3 5-HT$_{2C}$ Receptors 26
References 27

3 Nodal Structures in Anxiety-Like and Panic-Like Responses 37
3.1 Nodal Structures Regulating Anxiety: The Behavioral Inhibition System 37
3.2 "Limbic" Portions of the Medial Prefrontal Cortex 37
3.3 The Extended Amygdala 40
3.4 The Ventral Hippocampus 42
3.5 The Lateral Habenula 46
3.6 Nodal Structures Regulating Panic: The Cerebral Aversive System 47
3.7 The Central Amygdala 48
3.8 The Medial Hypothalamic Defense System 51
3.9 The Mesopontine Rostromedial Tegmental Nucleus 53
3.10 The Periaqueductal Gray Area 53
3.11 Locus Coeruleus 57
References 60

4 The Deakin–Graeff Hypothesis 79
4.1 Destruction or Blockade of DRN Neurons is Anxiolytic and Panicogenic 80
4.2 The Defensive Context for Increased Serotonin Release 81
References 82

5 Topographic Organization of DRN 87
5.1 The Dorsal Portion of the DRN is Part of a Mesocorticolimbic System Involved in Anxiety-Like Responses 87
5.2 The Caudal Portion of the DRN is Highly Responsive to Stress-Related Peptides 91
5.3 The Lateral Wings of the DRN are Involved in Panic-Like Responses 93
References 96

6 General Conclusions 105
References 106

Index 109

Chapter 1
Introduction

Along with benzodiazepines, drugs targeting the serotonergic system represent the major class of anxiolytic drugs. Among available serotonergic drugs, selective serotonin reuptake inhibitors still represent the most prescribed treatment for anxiety disorders, even though they are associated with low efficacy in a considerable proportion of patients, a delayed onset of therapeutic action, and diverse collateral effects which reduce tolerance (e.g., sexual dysfunction, weight changes). There is considerable debate regarding the true contribution of serotonin or serotonin receptors to the therapeutic action of these drugs [1, 2], given that the acute increase in 5-HT concentrations in the synapse are not temporally correlated with the onset of therapeutic action.

The richness of the serotonergic system is reflected in the great quantity of receptor subtypes found in the brain [3]. This diversity underlines the possibility of different roles for each receptor subtype, and therefore to the potential for the production of more specific anxiolytic drugs. Nonetheless, efforts in the production of such drugs have resulted in disappointment [2]: with the exception of buspirone, a partial agonist at 5-HT_{1A} receptors that was introduced in the treatment of generalized anxiety disorder in 1985, no other anxiolytic agent targeting serotonin receptors produced robust clinical efficacy [4].

A distinction between anxiety and fear has been drawn on the basis of pharmacological dissociability (Table 1.1 [4–12]), neuroanatomical basis [8, 10, 13], and on its relation to stressor controllability [14, 15] and/or predictability [16–21]. These criteria are, of course, not mutually exclusive. In this book, we follow an integrated approach which considers defensive responses (A) as functions of discreteness of ambiguity of threat, defensive distance/predatory imminence continuum, and presence of particular environmental affordances [22, 23]; (B) controlled by different levels of a hierarchically organized behavioral inhibition system (anxiety-like responses) or cerebral aversive system (fear-like responses) [10]; and (C) differentially modulated by serotonergic neurotransmission [24] (Table 1.2).

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Table 1.1 Various classes of drugs vary in clinical efficacy in the treatment of anxiety disorders

Disorder	BZD	Triazolo	Bus	Imi	Clom	MAOi	SSRI	SARI	β
GAD	↓	↓	↓	↓	↓	0	↓	↓	0
Panic	0	↓	0	↓	↓↓	↓	↓	?	0
PTSD	0	?	0	↓	?	↓	↓	?	?
Simple phobia	0	?	?	0	?	(↓)	(↓)	?	0
Social anxiety	↓	(↓)	(↓)	0	(↓)	↓	↓	↓	↓
OCD	0	0	(↓)	(↓)	↓↓	(↓)	↓↓	↓	0

BZD benzodiazepine, *Triazolo* triazolo-benzodiazepines, *Bus* buspirone, *Imi* imipramine, *Clom* clomipramine, *MAOi* monoamine oxidase inhibitor, *SSRI* selective serotonin reuptake inhibitor, *SARI* serotonin antagonist and reuptake inhibitor, β β-adrenoceptor antagonist
Symbols ↓ symptom decrease, ↓↓ major symptom decrease, (↓) contradictory or insufficient findings, 0: no clinical efficacy, ?: clinical efficacy not assayed
Adapted from Refs. [4–12]

1.1 Anxiety and Risk Assessment

Anxiety is a state of "action readiness" associated with unpredictable or uncontrollable aversive stimuli [14, 16–21, 25]. "Readiness" here implies preparedness for action *if* and *when* appropriate conditions (affordances) arise [26, 27]. In a situation of uncertain or merely probable risk (called "pre-encounter environment" by Fanselow and colleagues [23, 28]), behavioral adjustments grouped under the general category of "risk assessment" are made. Risk assessment is a collection of adjustments that is involved in detection and analysis of threat stimuli and the context in which it occurs [29]. Thus, animals will shift attention from ongoing motivated behavior toward detecting and/or responding to potential predators. In situations of uncertainty regarding risk, animals adopt a baseline of "apprehension", leading to the selection of vigilant behaviors [22, 29–33]. In such situations, animals also tend to "overestimate" the actual level of threat; this "cognitive bias" [34] leads animals to inhibit ongoing behavior and flee, hide or freeze if any signal of risk is detected. Depending on environmental affordances, animals tend to retreat to protected areas [35], resort to thigmotaxis ("wall-hugging") [36] and scototaxis ("dark preference") [37], and establish "home bases" to which they constantly return after exploring the environment [38].

An important environmental configuration which leads to risk assessment behavior is novelty. Montgomery [39] proposed that novel environments evoke both exploratory drives and fear, producing an approach-avoidance conflict. Importantly, novelty is a situation of potential risk, and exploratory behavior is adjusted accordingly. This is explored in diverse behavioral models of anxiety, in which the forced exposure to novelty leads to risk assessment behavior and adjustments of exploration (thigmotaxis, scototaxis, refuge use, home base behavior). In totally novel environments, anxiolytic drugs increase exploratory behavior, particularly of aversive portions of the apparatuses (e.g., open arms of an elevated plus-maze, lit chamber of a light/dark box, center of an open-field) [40].

Table 1.2 Stimulus control of defensive behavior, in relation to threat source, associated level in the predatory imminence continuum, and environmental affordances

Source of threat	Predatory imminence	Affordance	Behavior	Neuroanatomy
Uncertain	Pre-encounter		Risk assessment	Medial prefrontal cortex Septo-hippocampal system Extended amygdala Lateral habenula
		Walls, refuges	Adjustment of exploratory behavior	Cingulate cortex Septo-hippocampal system Extended amygdala Lateral habenula
			Cognitive bias	Septo-hippocampal system Extended amygdala Lateral habenula
			Behavioral activation	Mesolimbic dopaminergic system
			Attention/arousal	Cortico-coerulear projection
Discrete	Post-encounter	Escape route available	Flight	Medial hypothalamic defense system Dorsal PAG RMTg
		No escape route	Freezing	PAG RMTg
		Conspecifics nearby	Alarm call/USV	Dorsal PAG
		Hiding places available	Hiding	
			Neurovegetative adjustments	LH PVN
	Circa-strike		Defensive fight	
			Analgesia	PAG
	Predator contact		Startle	Elementary startle circuit
			Tonic immobility	Ventral PAG

Also marked are the brain regions most likely to be involved in the control of such behavior
LH lateral hypothalamus, *PAG* periaqueductal gray area, *PVN* paraventricular nucleus, *RMTg* rostromedial tegmental area, *USV* ultrasonic vocalization
Adapted from Refs. [8, 10, 13–23, 25, 28]

In situations where animals are allowed to freely *choose* between a novel and a familiar environment, nonetheless, they tend to prefer novelty [41], and this preference is reversed by anxiolytic drugs [42–44]. Likewise, if an animal is re-exposed to the elevated plus-maze 24 h after the first exposure ("trial 2"), time spent in the open arms is further decreased, and response to anxiolytic drugs

(5-HT_{1A}R agonists, benzodiazepines) is eliminated; this "one-trial tolerance" effect has been proposed as a model of simple phobia [45]. Interestingly, administration of D-cycloserine, a partial agonist at the $glycine_B$ site of the NMDA receptor, at the end of trial 1 potentiates the increase in open arm avoidance, without reverting the effect on benzodiazepine efficacy [46].

Anxiety-like behavior can also be observed in the home cage after the administration of anxiogenic drugs, including benzodiazepine inverse agonists and antagonists, caffeine, yohimbine, corticotropin releasing factor (CRF), and *m*-chlorophenyl piperazine (mCPP). After administration of such drugs, animals engage in spontaneous non-ambulatory motor activity (SNAMA, part of the class of risk assessment behavior), including visual scanning of the environment, head movements associated with sniffing, and shifts in body position, for up to 90 min. [47, 48].

Anxiety-like behavior either at novel environments or at the home cage can be increased by stressful manipulations [49]. This "fear potentiation" reflects an enhanced anxiety *state* in face of an allostatic situation, and can last from 90 min to 3 weeks, depending on the stressor used (immobilization, electrical shocks, exposure to predators or partial predator stimuli, social defeat, etc.). In these cases, enhanced secretion of corticosteroids by the adrenal glands facilitates the expression of CRF in the central amygdala and bed nucleus of the stria terminalis, leading to increased anxiety, increased norepinephrine release in the locus coeruleus, and increases in the extracellular concentrations of serotonin in limbic regions. It has been suggested that, while short-term effects of mild stressors can model acute allostatic situations, the long lasting effects of predator exposure on defensive behavior is a good model of post-traumatic stress disorder [50].

A manipulation which induces long-term increases in anxiety-like behavior is acute uncontrollable stress, producing effects that last up to 24–72 h [14, 16, 17, 51–55]. When animals are exposed to electric shocks which are contingent to escape responses, they quickly develop "active coping" behavior; if, however, electric shocks are not contingent to escape (i.e., they are inescapable or uncontrollable), these animals develop "passive coping" behavior, freezing rather than attempting to escape [54, 56]; show higher corticosteroid release than animals which have been exposed to escapable shock [57]; and show facilitated conditioning of fear and impairment of escape [58] and increased anxiety in an elevated plus-maze [57]. This sensitized state has been termed "learned helplessness" by earlier theorists, and the lack of control over the aversive event has been proposed as an important component of anxiety disorders [59–61]. Similar effects are observed in animals which have been exposed to chronic unpredictable stress (CUS [62, 63], but the effects of this latter manipulation on anxiety-like behavior are controversial (e.g., effects on the EPM or LD test are not always observed [64, 65]) and are not immediate, with a delay of about a week for onset [65].