Neuroscience 247 (2013) 253–272

NEUROSCIENCE FOREFRONT REVIEW

ACUTE AND CHRONIC EFFECTS OF SELECTIVE SEROTONIN REUPTAKE INHIBITOR TREATMENT ON FEAR CONDITIONING: IMPLICATIONS FOR UNDERLYING FEAR CIRCUITS

N. S. BURGHARDT [a,b] **AND E. P. BAUER** [c]*

[a] *Columbia University, Departments of Neuroscience and Psychiatry, 1051 Riverside Drive, Unit 87, New York, NY 10032, United States*

[b] *The New York State Psychiatric Institute, Division of Integrative Neuroscience, New York, NY 10032, United States*

[c] *Barnard College, Biology Department, 3009 Broadway, New York, NY 10027, United States*

Abstract—Selective serotonin reuptake inhibitors (SSRIs) are widely used for the treatment of a spectrum of anxiety disorders, yet paradoxically they may increase symptoms of anxiety when treatment is first initiated. Despite extensive research over the past 30 years focused on SSRI treatment, the precise mechanisms by which SSRIs exert these opposing acute and chronic effects on anxiety remain unknown. By testing the behavioral effects of SSRI treatment on Pavlovian fear conditioning, a well characterized model of emotional learning, we have the opportunity to identify how SSRIs affect the functioning of specific brain regions, including the amygdala, bed nucleus of the stria terminalis (BNST) and hippocampus. In this review, we first define different stages of learning involved in cued and context fear conditioning and describe the neural circuits underlying these processes. We examine the results of numerous rodent studies investigating how acute SSRI treatment modulates fear learning and relate these effects to the known functions of serotonin in specific brain regions. With these findings, we propose a model by which acute SSRI administration, by altering neural activity in the extended amygdala and hippocampus, enhances both acquisition and expression of cued fear conditioning, but impairs the expression of contextual fear conditioning. Finally, we review the literature examining the effects of chronic SSRI treatment on fear conditioning in rodents and describe how downregulation of *N*-methyl-D-aspartate (NMDA) receptors in the amygdala and hippocampus may mediate the impairments in fear learning and memory that are reported. While long-term SSRI treatment effectively reduces symptoms of anxiety, their disruptive effects on fear learning should be kept in mind when combining chronic SSRI treatment and learning-based therapies, such as cognitive behavioral therapy.

Key words: serotonin, amygdala, fear conditioning, BNST, SSRI, anxiety.

Contents

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are widely used for the treatment of a spectrum of anxiety disorders, such as panic disorder, social phobia, post-traumatic stress disorder, generalized anxiety disorder and obsessive–compulsive disorder (Sheehan et al., 1993; van der Kolk et al., 1994; Stokes and Holtz, 1997; Kent et al., 1998; Bezchlibnyk-Butler et al., 2000; Bondareff et al., 2000; Stein and Stahl, 2000; Gorman, 2003). The known pharmacological actions of SSRIs involve blocking serotonin uptake by inhibiting the serotonin transporter, leading to an increase in serotonin availability. This increase in serotonin occurs with acute administration, yet therapeutic improvements require several weeks of continuous treatment, indicating the involvement of adaptive downstream mechanisms. Despite extensive research conducted over the course

*Corresponding author. Tel: +1-212-854-2349; fax: +1-212-854-1950.
E-mail addresses: nsb2113@columbia.edu (N. S. Burghardt), ebauer@barnard.edu (E. P. Bauer).
Abbreviations: BA, basal nucleus of the amygdala; BLA, basolateral nucleus; BNST, bed nucleus of the stria terminalis; CBT, cognitive behavioral therapy; CE, central nucleus; CeL, comprised of a lateral; CeM, comprised of a medial; CS, conditioned stimulus; LA, lateral nucleus of the amygdala; LTM, long-term memory; NMDA, *N*-methyl-D-aspartate; PL, prelimbic cortex; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitor; STM, short-term memory; US, unconditioned stimulus.

0306-4522/13 $36.00
http://dx.doi.org/10.1016/j.neuroscience.2013.05.050

of the last 30 years aimed at identifying the relevant adaptive mechanisms, it is still not known how SSRIs mediate their long-term effects on anxiety.

One approach for investigating the action of SSRIs in the brain has been to test their behavioral effects on fear conditioning in animals. The advantage of using fear conditioning is that it is a model of emotional learning for which the underlying neural circuitry has been elucidated in detail. Since fear conditioning not only activates fear circuits, but also engages mechanisms involved in learning and memory, it has been possible to test how SSRI treatment affects emotion as well as different stages of learning. Over the last 17 years, numerous studies have tested the effects of SSRIs on fear conditioning in rodents, but, it has been challenging to reconcile the results. The effects of SSRI treatment seem to vary depending upon the type of fear conditioning used, the stage of learning tested, and the duration of SSRI administration. Without a clear understanding of the conditions under which SSRIs mediate their various effects, it has been difficult to use the behavioral findings as a guide for identifying relevant underlying neural structures. Here we describe the neural circuits involved in fear conditioning and review the literature describing how acute and chronic SSRI treatment modulates different aspects of fear learning in rodents. We relate these effects to the known functions of serotonin in different brain regions, propose a model in which the adaptive mechanisms within these brain regions might interact to mediate the long-term therapeutic effects of SSRI treatment, and offer recommendations for future research.

FEAR CONDITIONING AS A MODEL OF FEAR LEARNING

The benefit of using Pavlovian fear conditioning to investigate the behavioral effects of SSRI treatment in animals is that it is one of the most comprehensively studied behavioral paradigms. In classical fear conditioning, an initially neutral stimulus, such as a tone or light (conditioned stimulus; CS) is paired with a noxious stimulus, such as a brief electrical footshock (unconditioned stimulus; US). As a result of this CS–US pairing, the CS acquires aversive properties. Afterward, when presented alone, the CS elicits responses in the animal that are characteristic of fear, such as an increased heart rate, cessation of movement (freezing) and/or fear-potentiated startle (LeDoux et al., 1988; Campeau and Davis, 1995). Animals are also capable of forming configural representations of a collection of cues that form a context, which can also be associated with an aversive US to produce context fear conditioning (Selden et al., 1991; Kim et al., 1993; Maren and Fanselow, 1997).

Fear conditioning involves different stages of memory. Initial learning of the CS–US association during the training portion of fear conditioning is referred to as fear acquisition. During the 24-h period following fear acquisition, memories are thought to consolidate into stable, enduring protein-synthesis-dependent memories (McGaugh, 2000; Dudai, 2004). When the CS is later presented alone, the fear memory is retrieved, leading to expression of the conditioned fear response. If the CS is repeatedly presented in the absence of the US, there is a gradual reduction in the ability of the CS to elicit fear responses, a process called fear extinction (Quirk and Mueller, 2008). Extinction does not destroy the original fear memory, but is instead a new learning process, with accompanying stages of memory formation (Bouton et al., 2006; Ji and Maren, 2007). During extinction training, the animal learns that the CS no longer predicts the US and a reduction in fear takes place (within-session extinction). This new memory is then consolidated and recalled at a later point in time (between-session extinction, extinction retention/recall). Evidence suggests that the mechanisms underlying within-session extinction partly differ from those underlying between-session extinction (for recent reviews see Quirk and Mueller, 2008; Pape and Pare, 2010; Orsini and Maren, 2012). Both stages of fear extinction are particularly important from a therapeutic standpoint, as extinction-based cognitive behavioral therapy (CBT) is widely used to treat anxiety disorders (Barlow, 1990; Rothbaum and Schwartz, 2002). Similar to repeated exposure to the CS in absence of the US in animals, patients in exposure-based CBT systematically confront feared objects or situations in the absence of an aversive event. For example, repeated and progressively longer exposure to pictures of snakes, and then to live snakes in jars can effectively treat simple phobias to snakes. Furthermore, the partial agonist of the *N*-methyl-D-aspartate (NMDA) receptor D-cycloserine, which enhances fear extinction learning in rodents also enhances the effects of exposure therapy when treating patients with phobias, social anxiety disorder or panic disorder (Ressler et al., 2004; Hofmann et al., 2006; Otto et al., 2010).

These distinct stages of memory (acquisition, consolidation, expression, extinction learning and extinction recall) are differentially mediated by several key structures, including the amygdala, hippocampus and prefrontal cortex. Within these structures, there are unique molecular mechanisms that are known to contribute to these functions (for recent reviews see Pape and Pare, 2010; Johansen et al., 2011; Orsini and Maren, 2012). When assessing the effects of pharmacological manipulations, such as SSRI treatment, on fear conditioning, it is thus important to first identify which phases of memory formation are being affected. When a drug is given immediately before the training phase of fear conditioning and impairs both short-term (STM) and long-term memory (LTM), it is said to disrupt *acquisition* of a fear memory. When a drug is given immediately after training and impairs the formation of LTM, it is said to disrupt *consolidation*. Alternatively, if learning has already taken place and a drug is given immediately prior to testing, it can affect *expression* or *recall* of the fear memory. Similarly, if a drug is given prior to extinction training or extinction testing, it can affect the *acquisition of extinction* or the *expression*/*recall of extinction*, respectively. In this way,