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Review article

SSRIs and conditioned fear

Takeshi Inoue *, Yuji Kitaichi, Tsukasa Koyama

Department of Psychiatry, Hokkaido University Graduate School of Medicine, North 15, West 7, Kita-ku, Sapporo 060-8638, Japan

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ABSTRACT

Among drugs that act on serotonergic neurotransmission, selective serotonin (5-HT) reuptake inhibitors (SSRIs) are now the gold standard for the treatment of anxiety disorders. The precise mechanisms of the anxiolytic actions of SSRIs are unclear. We reviewed the literature related to the effects of SSRIs and the neurochemical changes of 5-HT in conditioned fear. Acute SSRIs and 5-HT_{1A} receptor agonists reduced the *acquisition* and *expression* of contextual conditioned fear. Chronic SSRI administration enhanced anxiolytic-like effects. Microinjection studies revealed the amygdala as the target brain region of both classes of serotonergic drugs, and the hippocampus as the target of 5-HT_{1A} receptor agonists. These findings highlight the contribution of post-synaptic 5-HT receptors, especially 5-HT_{1A} receptors, to the anxiolytic-like effects of serotonergic drugs. These results support the new 5-HT hypothesis of fear/anxiety: the facilitation of 5-HT neurotransmission ameliorates fear/anxiety. Furthermore, these behavioral data provide a new explanation of neurochemical adaptations to contextual conditioned fear: increased 5-HT transmission seems to decrease, not increase, fear.

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Contents

1. Introduction

Conditioned fear is based on Pavlovian aversive conditioning. A neutral stimulus (a tone, figure, light, or context) is presented with an aversive stimulus such as pain or unpleasant sounds. Repeated pairings make a neutral stimulus more aversive, representing the *acquisition* of conditioned fear. After such *acquisition*, the presentation of a neutral stimulus alone provokes the *expression* of conditioned fear,

Abbreviations: GAD, generalized anxiety disorder; 5-HT, 5-hydroxytryptamine; ITC, intercalated cell cluster; MAOI, monoamine oxidase inhibitor; NA, noradrenaline; OCD, obsessive–compulsive disorder; PD, panic disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder; SNRI, serotonin–noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

* Corresponding author at: Department of Psychiary, Hokkaiido University Graduate School of Medicine, North 15, West 7, Sapporo 060-8638, Japan. Tel.: +81 11 706 5160; fax: +81 11 706 5081.
E-mail address: tinoue@med.hokudai.ac.jp (T. Inoue).

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but repeated presentation without the aversive stimulus diminishes the effects, signifying the *extinction* of conditioned fear. Since the 1990s, several studies have elucidated the neural circuitry, neurotransmitters, and transcription factors involved in conditioned fear.

A particularly impressive experiment by Watson and Rayner (1920) demonstrated how Little Albert was made to fear a white rat paired with a loud sound, and this conditioned fear was generalized to several objects. Conditioned fear is the theoretical background of an experimental neurosis. The *extinction* process has been applied to the treatment of neurosis (now designated as anxiety disorder) as *systematic desensitization* since the 1950s by Wolpe (1969).

The psychopharmacology of anxiety disorders has advanced considerably since the 1980s; selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and serotonin (5-HT) 1A agonists are now commonly prescribed (Bandelow et al., 2008; Erikkson and Humble, 1990; Zohar and Westenberg, 2000) (Table 1). SSRIs have the broadest indications for anxiety disorders of various types (Bandelow et al., 2008). Because they do not produce dependency, cognitive impairment, or sedation like their predecessors the benzodiazepines, SSRIs are now the first-line drugs for the treatment of anxiety disorders (Bandelow et al., 2008). However, the anxiolytic mechanism of SSRIs has not been elucidated until recently. The classic hypothesis of 5-HT function in anxiety was proposed in the 1970s and posited that 5-HT systems promote anxiety and that suppression of these systems diminishes anxiety (Handley and McBlane, 1993; Traber and Glaser, 1987). However, new evidence suggests that this hypothesis is apparently contrary to the pharmacological action of SSRIs.

Since the 1990s, there have been several reports that acute treatment with SSRIs or 5-HT_{1A} agonists is anxiolytic in a conditioned fear model, although some inconsistencies exist among studies (Borsini et al., 2002; Inoue et al., 2000). It is extremely important to elucidate the mechanism of anxiolytic action because SSRIs were ineffective or anxiogenic in other animal models of anxiety (Borsini et al., 2002). Conditioned fear in rats or mice has an additional advantage in that the pharmacological action on fear can be understood in relation to neurochemical effects, which can be easily measured in this model (Inoue et al., 2000). Here, we review the behavioral pharmacology of SSRIs and other serotonergic drugs in conditioned fear and the 5-HT-related neurochemistry of conditioned fear.

2. Neural circuitry of conditioned fear and 5-HT innervation of the amygdala

Damage to various brain regions interferes with the *acquisition* and *expression* of conditioned fear. Several lesion studies have clarified the roles of specific brain regions. As reviewed by LeDoux (2000) and Davis (2002), the amygdala is critically involved in conditioned fear. Sensory inputs (e.g., tone as a conditioned stimulus) to the amygdala terminate mainly in the lateral nucleus (Fig. 1). Conditioning to the apparatus and other contextual cues that are present when the conditioned stimulus and unconditioned stimulus are paired, involves the representation of the context by the hippocampus, and communication between the basal and accessory basal nuclei of the amygdala. The central nucleus receives inputs from the lateral, basal, and accessory basal nuclei. In turn, it mediates the *expression* of conditioned fear responses elicited by both acoustic and contextual conditioned stimuli (Fig. 1) (LeDoux, 2000). The lateral, basal, and accessory basal nuclei are collectively designated as the *basolateral amygdala*. Moreover, the lateral division of the bed nucleus of the stria terminalis, which forms part of the lateral extended amygdala, receives projections from the basolateral amygdala and has direct projections to various anatomic areas that are likely involved in many symptoms of fear or anxiety. In fact, many effects previously attributed to the central nucleus might actually depend on the bed nucleus of the stria terminalis (Davis, 2002).

The *expression* of conditioned fear is mediated by the neural circuitry shown in Fig. 1 (Wilensky et al., 2006). However, repeated exposure (*expression*) to a conditioned stimulus (cue or context) causes *extinction* of conditioned fear. The ventromedial prefrontal cortex plays a critical role in this process by suppressing activity in the amygdala through inhibition of the lateral/basal nucleus neurons and/or activation of the inhibitory intercalated cell cluster (ITC) (Fig. 2) (Ehrlich et al., 2009; Izumi et al., 2011; Sotres-Bayon et al., 2006). In the *expression* of conditioned fear, glutamatergic and GABAergic neurons in the basal nucleus of the amygdala, as well as ITC GABAergic neurons, are activated during the retrieval of conditioned fear (Izumi et al., 2011).

Anatomical knowledge of the serotonergic system in the amygdala is important for understanding the effects of SSRIs on anxiety. The amygdala receives dense serotonergic innervation from the dorsal raphe nucleus (Fallon and Ciofi, 2000; Lowry et al., 2005) and contains several subtypes of 5-HT receptors (Radja et al., 1991; Wright et al., 1995). Whereas 5-HT_2 and 5-HT_3 agonists significantly increased the neuronal discharge rate in nearly all subdivisions of the amygdala, including the basal nucleus of the amygdala, a 5-HT_{1A} agonist significantly inhibited the firing rate (Stein et al., 2000). The modulatory effect of 5-HT on anxiety-related circuits has been noted. Although serotonergic drug microinjections or selective 5-HT lesions to the amygdala have been performed in several studies using various animal models, these showed conflicting results (anxiolytic vs. anxiogenic) (Lowry et al., 2005). 5-HT in the amygdala may play different roles in various animal models of anxiety (Borsini et al., 2002), suggesting that it is inappropriate to compare data between different animal models.

The amygdala is innervated by the locus coeruleus, which synthesizes the majority of the brain's noradrenaline (Mueller and Cahill, 2010). Noradrenergic neurotransmission is a possible therapeutic target of some SSRIs (paroxetine and fluoxetine) (Beyer et al., 2002; Bymaster et al., 2002). The amygdala contains α_1, α_2, β_1, and β_2 adrenoceptors (Johnson et al., 1989; Unnerstall et al., 1985), and noradrenaline enhances intrinsic excitability in the amygdala. Noradrenaline strengthens the formation, consolidation and reconsolidation of emotional memory and the consolidation of *extinction* memory partly via β-receptor activation of the basal amygdala (Mueller and Cahill, 2010).

Table 1
Summary of clinical controlled studies of anxiety disorders (Bandelow et al., 2008; Inoue et al., 2000).

	PD	GAD	SAD	PTSD	OCD
Benzodiazepine	+	+	+		
SSRI	+	+	+	+	+
SNRI	+	+	+	+	
TCA	+	+		+	+
5-HT_{1A} agonist	0	+			
5-HT_2 antagonist	0	+			
5-HTP	+				
MAOI	+		+		
β-blocker	+/0	+/0			
NA reuptake inhibitor	0				

PD, panic disorder; GAD, generalized anxiety disorder; SAD, social anxiety disorder; OCD, obsessive–compulsive disorder; PTSD, post-traumatic stress disorder; SNRI, serotonin–noradrenaline reuptake inhibitor; TCA, tricyclic antidepressant; MAOI, monoamine oxidase inhibitor; 5-HT, serotonin; NA, noradrenaline.
+, anxiolytic-like effect; 0, inactive.

3. Serotonergic neurotransmission during conditioned fear

The selective activation of dopamine metabolism by contextual conditioned fear in the antero-medial frontal cortex was first described over thirty years ago (Herman et al., 1982); fourteen years later, an *in vivo* microdialysis study revealed that the increased metabolism reflects the increased release of dopamine (Yoshioka et al., 1996). However, this regional selectivity is dependent on conditioning intensity; conditioned

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