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Regulation of dorsal raphe nucleus function by serotonin autoreceptors: a behavioral perspective

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Abstract

Neurotransmission by serotonin (5-HT) is tightly regulated by several autoreceptors that fine-tune serotonergic neurotransmission through negative feedback inhibition at the cell bodies (predominantly 5-HT_{1A}) or at the axon terminals (predominantly 5-HT_{1B}); however, more subtle roles for 5-HT_{1D} and 5-HT_{2B} autoreceptors have also been detected. This review provides an overview of 5-HT autoreceptors, focusing on their contribution in animal behavioral models of stress and emotion. Experiments targeting 5-HT autoreceptors in awake, behaving animals have generally shown that increasing autoreceptor feedback is anxiolytic and rewarding, while enhanced 5-HT function is aversive and anxiogenic; however, the role of serotonergic activity in behavioral models of helplessness is more complex. The prevailing model suggests that 5-HT autoreceptors become desensitized in response to stress exposure and antidepressant administration, two seemingly opposite manipulations. Thus there are still unresolved questions regarding the role of these receptors - and serotonin in general - in normal and pathological states.

Keywords

5-HT1A; 5-HT1B; autoregulation; serotonergic

1 Introduction

The neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) influences a wide range of behavioral and physiological processes including anxiety, depression, aggression, sleep, memory, and reward (Lucki, 1998). There are at least 14 serotonin receptors in the mammalian nervous system. Some of these are expressed as autoreceptors, which we define as a receptor that is expressed within a serotonergic neuron that provides feedback in modulating the activity of that neuron. These receptors are also expressed on non-serotonergic neurons as heteroreceptors. Compelling evidence indicates that several 5-HT_1 receptors act as inhibitory autoreceptors to provide negative feedback in serotonin neurons – functioning like a thermostat, they maintain a certain homeostatic tone in serotonergic function. There is also intriguing evidence 5-HT_{2B} receptors may enhance serotonin release under specific circumstances. The goal of this review is to provide an overview of serotonin autoreceptor research from the perspective of the investigator interested in animal models of

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emotional behavior. For clarity, we shall focus on experiments in which manipulations or measurements of 5-HT receptors are restricted specifically to the autoreceptor form.

2 Molecular and pharmacological properties of 5-HT autoreceptors

For a general overview of 5-HT receptors, we refer the reader to previous reviews (Barnes and Sharp, 1999; Hannon and Hoyer, 2008; Millan *et al.*, 2008). Because there are several reviews on the pharmacology and physiology of serotonergic autoregulation (Pineyro and Blier, 1999; Stamford *et al.*, 2000), here we will limit our discussion to a simplified overview. The best established serotonin autoreceptors are all members of the 5-HT_1 family, which consists of 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}. All members of the 5-HT_1 family share high affinity for serotonin and are inhibitory in nature, coupling to Gi/o - but may also signal through additional mechanisms (Lin *et al.*, 2002). The receptor that was originally referred to as 5-HT_{1C}, which was placed in the 5-HT_1 family on the basis of its pharmacological properties, was later found to share molecular properties of the 5-HT_2 subfamily (DNA sequence, Gq coupling) and was renamed 5-HT_{2C}. The rat 5-HT_{1B} receptor was initially thought to be the rodent analogue of the human 5-$HT_{1D\beta}$ receptor (Hoyer and Middlemiss, 1989); however, it is now clear that both 5-HT_{1B} and 5-HT_{1D} receptors exist in every species examined and have very similar pharmacology.

The predominant somatodendritic autoreceptor is 5-HT_{1A}. Activation of somatodendritic 5-HT_{1A} autoreceptors leads to inhibition of action potentials via opening of potassium channels in a Gi/o-dependent manner (Bayliss *et al.*, 1997; Innis and Aghajanian, 1987; Katayama *et al.*, 1997; Penington *et al.*, 1993). A recent report suggests that 5-HT_{1A} autoreceptors may display agonist-directed trafficking to activate multiple signal transduction pathways (Valdizan *et al.*, 2010). Terminal autoregulation occurs primarily via 5-HT_{1B} autoreceptors, which are located on serotonergic axons adjacent to terminals (Riad *et al.*, 2000). Activation of 5-HT_{1B} autoreceptors reduces extracellular 5-HT concentrations in terminal regions; experiments designed to isolate mechanistic components of this have shown that 5-HT_{1B} autoreceptor activation directly inhibits release (Hjorth and Tao, 1991) and synthesis of 5-HT (Hjorth *et al.*, 1995) while simultaneously enhancing reuptake via the serotonin transporter (Daws *et al.*, 2000) (Hagan *et al*, submitted). Though their contribution is relatively minor, there is evidence that 5-HT_{1D} autoreceptors contribute to autoinhibition of 5-HT function at terminals and possibly also dendrites (Pineyro and Blier, 1996; Pineyro *et al.*, 1995; Trillat *et al.*, 1997) – see also (Stamford *et al.*, 2000).

While less data have been reported on the 5-HT_{2B} receptor acting as an autoreceptor, it is reported to co-express and interact with 5-HT_{1B} receptors (Janoshazi *et al.*, 2007). There is recent evidence that 5-HT_{2B} autoreceptors facilitate the effects of 3,4-methylenedioxymethamphetamine (MDMA), a drug that stimulates 5-HT release via its actions on serotonin transporter (Gudelsky and Yamamoto, 2008), increases locomotion, and induces conditioned-place preference and psychomotor sensitization (Cole and Sumnall, 2003; Kalivas *et al.*, 1998). Disruption of 5-HT_{2B} function via antagonism or genetic knockout blocks the effects of MDMA on serotonin release and behavior (Doly *et al.*, 2009; Doly *et al.*, 2008). In cultured serotonergic-like cells and primary neuron cultures, 5-HT_{2B} receptor activation phosphorylates the serotonin transporter and inhibits its function – an effect that would oppose the effects of 5-$HT_{1B/1D}$ autoreceptors (Launay *et al.*, 2006). More data will be needed to fully understand the functional role of 5-HT_{2B} autoreceptors in regulating 5-HT function. There is little or no support for any serotonin receptors ranging from 5-$HT_{3–7}$ to act as autoreceptors, and the contributions of 5-HT_{1E} and 5-HT_{1F} receptors to physiology and behavior in general are not well understood. Because the current bulk of evidence implicates 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} as the predominant 5-HT autoreceptors, they will be the focus of this review.

3 Neuroanatomy of 5-HT autoreceptors and heteroreceptors

The 5-HT autoreceptors and heteroreceptors have distinct anatomical distributions in the brain. Autoreceptors, by definition, are expressed on serotonergic neurons residing in the midbrain raphe nuclei. The dorsal raphe nucleus (DRN) is the largest of these nuclei, containing approximately half of the brain's serotonergic neurons (Jacobs and Azmitia, 1992). The DRN accounts for the majority of ascending serotonergic projections, and is the focus of this review. Within the DRN, the majority of cells expressing 5-HT_{1A} and 5-HT_{1B} receptors are serotonergic, demonstrated by the fact that chemical lesions of serotonergic neurons destroy the majority of 5-HT_{1A} binding (Verge *et al.*, 1986), 5-HT_{1A} mRNA (Miquel *et al.*, 1992), and 5-HT_{1B} mRNA (Doucet *et al.*, 1995; Neumaier *et al.*, 1996b) within the DRN. Double-label immunohistochemistry and in situ hybridization studies show that virtually all serotonergic neurons in the DRN express 5-HT_{1A} (Day *et al.*, 2004; Sotelo *et al.*, 1990). The distribution of 5-HT_{1A} and 5-HT_{1B} mRNA densities throughout the DRN generally mirror expression of Tph2 and SERT, with peak expression of all four genes found in ventromedial DRN at mid-rostral levels (Clark *et al.*, 2006). One study utilizing systemic 5-HT_{1A} antagonist administration and Fos immunohistochemistry suggests that basal 5-HT_{1A}-mediated inhibition of DRN neurons is greatest in the lateral wings and ventral caudal subregions (Commons, 2008). Expression of 5-HT_{1A} and 5-HT_{1B} receptors in the DRN is not purely limited to serotonergic neurons. There is expression of 5-HT_{1A} in a modest number of GABAergic neurons throughout the rostrocaudal axis of the DRN (Beck *et al.*, 2004; Day *et al.*, 2004). Furthermore, at extreme caudal portions of the rat DRN (−8.5 to −9.0 bregma), there are dorsolateral "extra DRN wings" which are non-serotonergic but positive for both 5-HT_{1A} and 5-HT_{1B} mRNA (Clark *et al.*, 2006).

Because 5-HT_{1A} receptors are located on cell bodies and dendrites, there is close concordance between the distribution of 5-HT_{1A} binding sites and mRNA throughout the brain (Chalmers and Watson, 1991; Pompeiano *et al.*, 1992). 5-HT_{1A} heteroreceptors are expressed widely, with most prominent expression in hippocampus (CA1, CA3, dentate gyrus), septum, and entorhinal cortex. On the other hand, because 5-HT_{1B} and 5-HT_{1D} receptors are trafficked to axon terminals, the distributions of their binding sites and mRNA do not correspond (Sari, 2004). Because each of these receptors is expressed as autoreceptors on terminals that are intermingled throughout the brain with terminals containing heteroreceptors, one cannot distinguish auto- versus heteroreceptor subtypes in autoradiograms. Furthermore, the large majority of total brain 5-HT_{1B} binding reflects heteroreceptors, since lesions of serotonergic neurons do not decrease 5-HT_{1B} binding throughout the brain (Compan *et al.*, 1998; Manrique *et al.*, 1993; Offord *et al.*, 1988; Pranzatelli *et al.*, 1996; Sexton *et al.*, 1999; Sijbesma *et al.*, 1991; Verge *et al.*, 1986). With those caveats in mind, 5-HT_{1B} binding, likely to predominantly represent 5-HT_{1B} heteroreceptors, is reported throughout the brain with most prominent expression in the globus pallidus and substantia nigra (Bruinvels *et al.*, 1993; Pazos and Palacios, 1985; Verge *et al.*, 1986; Waeber *et al.*, 1989). These data are corroborated by more recent immunohistochemical studies with antibodies demonstrated to show specificity for 5-HT_{1B} receptors (Langlois *et al.*, 1995; Sari *et al.*, 1997; Sari *et al.*, 1999). 5-HT_{1B} heteroreceptor mRNA is expressed in a wide range of brain areas, particularly the hippocampus (CA1), caudate/putamen, and cortex (Bruinvels *et al.*, 1994; Voigt *et al.*, 1991); in each of these cases it is possible to associate the 5-HT_{1B} mRNA with different neuron types based on their anatomical localization. 5-HT_{1D} heteroreceptor mRNA, which appears to be expressed at lower densities in the brain, is found primarily in caudate/putamen and cortex (Bruinvels *et al.*, 1994). Binding sites for 5-HT_{1D}, while dramatically less prevalent than 5-HT_{1B}, are most prominent in the globus pallidus and substantia nigra.

4 Methodology for studying 5-HT autoreceptors

A complication in studying autoreceptors is the fact that all genes encoding 5-HT autoreceptors are also expressed in the brain as heteroreceptors. A given environmental stimulus that alters expression and/or function of one population may not affect the other, and the interpretation of an experiment can depend critically on knowing which receptor population was affected. For example, functional desensitization of 5-HT_{1A} autoreceptors would result in greater serotonergic cell body activity and release, and consequently greater activation of all postsynaptic 5-HT receptors - including 5-HT_{1A} heteroreceptors. In contrast, desensitization of 5-HT_{1A} heteroreceptors would not have any direct effect on the function of 5-HT neurons or activity at other postsynaptic 5-HT receptors. In studying serotonergic autoregulation it is important to employ methods that allow for the differentiation between 5-HT auto- and heteroreceptors. We will discuss this issue with respect to experimental designs employing measurement and manipulation of 5-HT autoreceptors.

4.1 Measurement

Measurements of 5-HT autoreceptor function were employed initially in experiments characterizing the basic physiology of these receptors. In later work, the effects of various environmental and chemical stimuli on 5-HT autoreceptor function were measured. Because 5-HT_{1A} autoreceptors are located somatodendritically, autoreceptor function can be measured by recording electrophysiological responses on raphe neurons, or by infusing 5-HT_{1A} ligands into the raphe nuclei and measuring electrophysiological or neurochemical responses. Because 5-HT_{1B} and 5-HT_{1D} autoreceptors are located axonally, alternative strategies are used. Activity of these receptors can be studied by applying drugs and measuring 5-HT efflux, which tends to select for serotonergic terminals and 5-HT autoreceptors. Because some downstream effectors of 5-HT_{1B} and 5-HT_{1D} autoreceptors – serotonin transporter and tryptophan hydroxylase – are only expressed in serotonergic terminals, they also provide measurement targets that selectively isolate the function of 5-HT autoreceptors. Additionally, behavioral pharmacology can be used to study autoreceptor function indirectly by measuring behaviors influenced by autoreceptor function, although it can be difficult to parse the effects of autoreceptors vs. heteroreceptors in some cases.

4.2 Manipulation

A straightforward way of selectively activating 5-HT_{1A} autoreceptors is by infusing 5-HT_{1A} ligands directly into the DRN, which results in decreased spike rate of serotonergic DRN neurons (Blier *et al.*, 1989) and reduced 5-HT release in terminal regions (Bonvento *et al.*, 1992; Hjorth and Sharp, 1991; Hutson *et al.*, 1989). A second, less selective, method of pharmacologically manipulating 5-HT_{1A} autoreceptors is by systemically injecting agonists/antagonists at low doses, which preferentially activate autoreceptors (Blier *et al.*, 1993; Hjorth and Magnusson, 1988; Kennett *et al.*, 1987; Sprouse and Aghajanian, 1988). Because this method is less selective for autoreceptors than intra-DRN infusions, results from these types of experiments will be presented in this review only when there is additional evidence demonstrating that the effects of systemic drug injections are autoreceptor-mediated.

Because 5-HT_{1B} protein is transported to axon terminals, selectively manipulating 5-HT_{1B} autoreceptors is technically challenging. Our laboratory has developed a system to overexpress 5-HT_{1B} autoreceptors using herpes simplex virus that is stereotaxically injected in the DRN. These transgenic receptors are transported to axon terminals like endogenous 5-HT_{1B} autoreceptors and possess normal 5-HT_{1B}-like function (Clark *et al.*, 2002; Clark *et al.*, 2004; Riegert *et al.*, 2008). Similar to 5-HT_{1A}, 5-HT_{1B} autoreceptors are preferentially activated at lower doses of agonists than 5-HT_{1B} heteroreceptors (Sarhan and Fillion, 1999),

and systemic injections of 5-HT_{1B} agonists at low doses may activate 5-HT_{1B} autoreceptors with partial selectivity.

Both 5-HT_{1A} and 5-HT_{1B} receptors have been "knocked out" using traditional mouse genetic strategies (Gardier *et al.*, 2009). In both cases a single gene encodes both autoreceptors and heteroreceptors, making it difficult to know what aspects of behavioral phenotype to attribute to the loss of autoreceptors versus heteroreceptors. Further complicating matters, certain aspects of these phenotypes are mediated by developmental effects (Castanon *et al.*, 2000; Gross *et al.*, 2002). Because of these ambiguities, we will provide only limited discussion of traditional knock-out literature. Newer mouse genetics strategies allow for autoreceptor/heteroreceptor specificity and temporal control, providing an important new avenue for study of serotonin autoreceptors (Gross *et al.*, 2002; Richardson-Jones *et al.*, 2010).

5 Influence of 5-HT autoreceptors on behavior in unstressed, drug-free animals

5.1 Conditioned preference/aversion

Several studies have used conditioned place preference/aversion to show that 5-HT autoreceptor activation is itself inherently rewarding. Systemic injections of a 5-HT_{1A} agonist show biphasic effects, with rats showing a serotonin-dependent (autoreceptor-mediated) preference for chambers paired with low doses and a serotonin-independent (heteroreceptor-mediated) avoidance of chambers paired with high doses (Papp and Willner, 1991). Further demonstrating that the rewarding aspects are mediated by autoreceptors, animals show a conditioned place preference for local infusion of 5-HT_{1A} agonist into the DRN (Fletcher *et al.*, 1993). Animals do not show a preference for low doses of systemic 5-HT_{1B} agonists, although they do show aversion to high doses (Cervo *et al.*, 2002; De Vry *et al.*, 2000). Collectively these results suggest that acute inhibition of the DRN via 5-HT_{1A} autoreceptors is rewarding, whereas stimulation of 5-HT_{1A} and 5-HT_{1B} heteroreceptors is aversive. This conclusion is consistent with pharmacological studies using acute administration of a serotonin-specific reuptake inhibitor or monoamine oxidase inhibitor to enhance 5-HT function, which rodents find aversive (Berendsen and Broekkamp, 1994; Buresova and Bures, 1987; Gommans *et al.*, 1998; Prendergast *et al.*, 1996) - but see (Olivier *et al.*, 1999; Subhan *et al.*, 2000). The idea of serotonin as an aversive signal has been further explored in "opponent process" theory (Boureau and Dayan, 2011; Cools *et al.*, 2011; Daw *et al.*, 2002).

5.2 Anxiety and conditioned fear

Stimulation of 5-HT autoreceptors is anxiolytic in a variety of tests. Intra-DRN infusions of a 5-HT_{1A} agonist are anxiolytic in the light-dark box (Romaniuk *et al.*, 2001), social interaction test (Higgins *et al.*, 1992; Hogg *et al.*, 1994), punished drinking (Higgins *et al.*, 1988), inhibitory avoidance (Graeff *et al.*, 1998) and shock-induced ultrasonic vocalization (Remy *et al.*, 1996). Similarly, intra-MRN infusion of 5-HT_{1A} agonist is anxiolytic in the elevated plus maze (De Almeida *et al.*, 1998) and social interaction test (File *et al.*, 1996; Picazo *et al.*, 1995). Underscoring the difference between 5-HT_{1A} autoreceptors and heteroreceptors, stimulation of 5-HT_{1A} heteroreceptors in medial septum and dorsal hippocampus is anxiogenic (De Almeida *et al.*, 1998; File *et al.*, 1996). 5-HT_{1A} knockout mice – which lack 5-HT_{1A} auto- and heteroreceptors - display heightened anxiety in the open field test, elevated plus maze, elevated zero maze, and novelty-suppressed feeding (Gross *et al.*, 2000; Heisler *et al.*, 1998; Parks *et al.*, 1998; Ramboz *et al.*, 1998). Using inducible knockout and tissue-specific rescue, it was demonstrated that these anxiety effects are due to lack of forebrain 5-HT_{1A} heteroreceptors during early development (Gross *et al.*,

2002). Similarly, mice with inducible suppression of 5-HT_{1A} autoreceptor expression display normal anxiety in the open field test and elevated plus maze; however, data presented suggest that these mice may be more anxious than control mice in tests of novelty-suppressed feeding (Richardson-Jones *et al.*, 2010). Collectively, mouse genetics literature does not strongly support a role for 5-HT_{1A} autoreceptor function in regulating anxiety in the adult mouse – a conclusion that is inconsistent with the behavioral pharmacology literature presented above. One possibility for this discrepancy is that knocking out 5-HT_{1A} autoreceptors results in compensatory changes in other aspects of serotonergic function that may undermine the primary effects of the genetic deletion (Ase *et al.*, 2000, 2001; Ramboz *et al.*, 1998). However there may also be limitations to the behavioral pharmacology literature, such as unexpected effects of 5-HT_{1A} agonists infused into the DRN, potentially inhibiting nonserotonergic projection neurons or interneurons.

Overexpression of DRN 5-HT_{1B} autoreceptors in unstressed rats reduces anxiety in the open field test and reduces measures of conditioned fear in both contextual fear conditioning and fear-potentiated startle (Clark *et al.*, 2002; Clark *et al.*, 2004; McDevitt *et al.*, 2011). Systemic administration of the selective 5-HT_{1B} agonist 5-propoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-pyrrolo[3,2-*b*]pyridine hydrochloride (CP-94,253) has a U-shaped dose-response on conditioned fear, with low doses (1 mg/kg) reducing fear similarly to 5-HT_{1B} autoreceptor overexpression and higher having no effect at 3 mg/kg (McDevitt *et al.*, 2011) and enhancing fear at 5 mg/kg (unpublished observations). These results suggest that activation of 5-HT_{1B} heteroreceptors may be anxiogenic. Indeed, rats show conditioned aversion (referenced earlier) and increased anxiety in the elevated plus maze with systemic administration of this drug at 3 mg/kg or higher doses, but not at 1 mg/kg (Lin and Parsons, 2002). We have observed that endogenous expression levels of 5-HT_{1B} autoreceptor mRNA in the rat DRN correlate inversely with anxiety (Hiroi and Neumaier, 2009; Kaiyala *et al.*, 2003). Conclusions from traditional knockout experiments are again inconsistent with behavioral pharmacology experiments. Mice lacking the 5-HT_{1B} receptor show reduced anxiety in certain tests, including novel object exploration and isolation-induced ultrasonic vocalization – but not in the elevated plus maze (Brunner *et al.*, 1999; Malleret *et al.*, 1999).

Another dimension of the relationship between serotonin and anxiety is the role of gonadal hormones such as estrogen and progesterone, which influence anxiety behavior in a variety of tests (Hiroi and Neumaier, 2006; Morgan *et al.*, 2004). Since there are numerous suggestions that fluctuating levels of these hormones regulate serotonergic function (Bethea *et al.*, 1998) and gonadal hormone receptors are expressed throughout raphe (Alves *et al.*, 1998; Vanderhorst *et al.*, 2005), the effects may be mediated in part by altered expression of 5-HT autoreceptors in the DRN. Estrogen, progesterone, and testosterone all reduce 5-HT_{1A} mRNA in the DRN of rodents and primates (Pecins-Thompson and Bethea, 1999; Zhang *et al.*, 1999) – but see (Hiroi and Neumaier, 2009; Sumner and Fink, 1993). These hormones reduce 5-HT_{1A} binding in the DRN without affecting affinity or G-protein coupling efficiency (Le Saux and Di Paolo, 2005; Lu and Bethea, 2002). Additionally, estrogen decreases 5-HT_{1B} mRNA in the DRN (Hiroi and Neumaier, 2009).

Taken together, the above data suggest that acute decreases in 5-HT function via 5-HT_{1A} or 5-HT_{1B} autoreceptors are anxiolytic. While this conclusion is not consistent with results from all mouse genetics experiments, it is supported by experiments demonstrating anxiogenic effects of acute serotonin-specific reuptake inhibitor (SSRI) administration in humans (Mir and Taylor, 1997; Spigset, 1999) and rodents (Burghardt *et al.*, 2007; Dekeyne *et al.*, 2000; Griebel *et al.*, 1994; Matto *et al.*, 1996; Sanchez and Meier, 1997).

5.3 Helplessness

The influence of serotonin on helplessness is less straightforward than its role in mediating anxiety or aversion. Because stress alters 5-HT autoreceptor function, and behavioral testing of helplessness and despair can induce stress, we must approach a discussion of this topic with caution. In this section we provide an overview of research focusing on the immediate expression of helplessness/despair behaviors. Later we will devote a section to discussing the role of stress in altering 5-HT autoreceptor function – which may play a mechanistic role in the development of depressive behavior. The behavioral models presented in this section all employ measurements of reactivity to a behavioral challenge, and may be considered at the most simple level to be models of stress reactivity. Additionally, the behavioral measures in these tests – particularly the forced swim test – are influenced by antidepressant drug treatment, which causes an increase in swimming in the forced swim test (Cryan *et al.*, 2005), increased active escape in the two-way shuttlebox (Martin *et al.*, 1990), and reduced measures of social avoidance/submission in conditioned social defeat (Marrow *et al.*, 1999; Razzoli *et al.*, 2011). Thus, these tests may be considered to have predictive validity in modeling “antidepressant-like” behavior. For a more in-depth discussion of validity in animal models of depression, we refer the reader elsewhere (Holmes, 2003).

The influence of 5-HT autoreceptors on behavior in the forced swim test is less straightforward than their role in anxiety and aversion. There is consistency in studies that employ acute or subchronic enhancement of autoreceptor function, showing that inhibiting 5-HT function has antidepressant-like behavioral effects. Intra-DRN infusion of a 5-HT_{1A} agonist or overexpression of 5-HT_{1B} receptors in the caudal DRN both result in increased swimming (McDevitt *et al.*, 2011; Schreiber and De Vry, 1993). Findings in other behavioral models of helplessness are similar: systemic injection at low doses or intra-DRN infusion of a 5-HT_{1A} agonist at the time of behavioral testing reverses the induction of stress-induced shuttlebox escape deficits in rats (Maier *et al.*, 1995) and conditioned social defeat in Syrian hamsters (Cooper *et al.*, 2008). Rats bred for congenital susceptibility to learned helplessness have reduced 5-HT_{1B} mRNA in the DRN, suggestive of reduced inhibitory control of serotonergic neurons (Neumaier *et al.*, 2002). From the above observations one might conclude that 5-HT exacerbates the expression of helplessness and depression. This would contradict the popular “monoamine hypothesis” of depression (Schildkraut, 1965) as well as several important findings in animal models. First, given in acute, subchronic, or chronic schedules, serotonin reuptake inhibitors increase swimming in the forced swim test (Cryan *et al.*, 2005). Second, knockout of 5-HT_{1A} receptors has antidepressant-like effects in the forced swim and tail suspension tests (Heisler *et al.*, 1998; Parks *et al.*, 1998; Ramboz *et al.*, 1998). Similar effects are seen in mice with inducible suppression of 5-HT_{1A} autoreceptor expression, confirming that they are not a product of heteroreceptors or developmental abnormality (Richardson-Jones *et al.*, 2010). Curiously, however, measurements of extracellular 5-HT concentrations in several brain regions of these mice are identical to controls. This would suggest that behavior in the forced swim test is mediated by some factor(s) other than absolute concentration of 5-HT.

One such factor that may influence swimming behavior in the forced swim test is the relative change in extracellular 5-HT from pre-swim baseline. Extracellular 5-HT concentrations in the lateral septum are decreased during a swim session, and when individual differences are examined there is a positive correlation between extracellular 5-HT concentration during swim (as percent of baseline) and immobility behavior (Kirby and Lucki, 1997). Furthermore, pretreatment with fluoxetine – which increases baseline levels – actually magnifies the drop in 5-HT seen during the swim test. Interestingly, the lateral septum receives serotonergic input preferentially from the caudal DRN (Waselus *et al.*, 2006), the region that we targeted in 5-HT_{1B} overexpression (McDevitt *et al.*, 2011). Acute

5-HT_{1A} stimulation or 5-HT_{1B} overexpression may serve to directly reproduce the decrease in lateral septum 5-HT seen with fluoxetine treatment.

The equivocal data on serotonin autoreceptors and rodent models of helplessness are also seen in human research. The fact that SSRI treatment alleviates symptoms of depression might lead one to predict that reduced autoreceptor function should exert antidepressant effects. However, depressed human subjects are reported to have decreased expression of 5-HT_{1A} autoreceptors – an effect that, on its own, would be expected to enhance serotonergic function. Several PET scan studies have demonstrated reduced 5-HT_{1A} binding in the raphe of humans with depression (Drevets *et al.*, 1999; Meltzer *et al.*, 2004; Sargent *et al.*, 2000), panic disorder (Neumeister *et al.*, 2004), and social anxiety disorder (Lanzenberger *et al.*, 2007) - however, see (Bhagwagar *et al.*, 2004; Parsey *et al.*, 2006). Similar evidence of reduced 5-HT_{1A} autoreceptor expression has been documented in post-mortem studies of suicidally depressed humans (Arango *et al.*, 2001; Boldrini *et al.*, 2008) – but see (Stockmeier *et al.*, 1998). These observations and the animal model literature suggest that the relationship between 5-HT and depression is highly complex, likely to be influenced by many variables including which DRN subregion and terminal region are studied, acute versus chronic treatment, baseline extracellular 5-HT versus challenge-evoked changes, and context of stress. A great deal more research is necessary to understand how these dimensions influence the relationship between serotonin and helplessness.

5.4 Comment on DRN subregional heterogeneity

In studies employing 5-HT_{1B} overexpression, the pattern of behavioral results is dependent on the rostrocaudal location of injection within the DRN. Because virus generally has less spread than small molecule drugs, and the exact location of infected cells can be determined *ex vivo* with GFP fluorescence, this method is ideal for distinguishing small subregions. While conditioned fear is influenced by 5-HT_{1B} overexpression throughout the DRN, anxiety – or behavior in conflict tests involving innate fear - is affected only by rostral DRN injections (Clark *et al.*, 2002; Clark *et al.*, 2004; McDevitt *et al.*, 2011). A selective role for the rostral DRN in anxiety is consistent with correlational data in the literature. Exposure to the open field test induces greatest Fos expression in the rostral DRN (Bouwknecht *et al.*, 2007), and anxiety behavior in the open field test and elevated plus maze correlates inversely with endogenous expression of 5-HT_{1B} in middle, but not caudal, DRN (Hiroi and Neumaier, 2009; Kaiyala *et al.*, 2003). The subregions of the DRN that influence anxiety may be distinct from those regulating helplessness. We found that 5-HT_{1B} overexpression in the caudal DRN reduced immobility in the first 5 minutes of a forced swim test (McDevitt *et al.*, 2011). Though we did not detect effects of 5-HT_{1B} overexression in the mid-rostral DRN (Clark *et al.*, 2002), only the second day swim session was investigated, and it is conceivable that there were effects that went undetected. Similarly, behavior in the forced swim test correlates with measures of 5-HT release in target regions of the caudal, but not rostral, DRN (Kirby and Lucki, 1997). Furthermore, intra-DRN infusions of the stress-related peptide corticotropin-releasing factor induces helplessness behavior in an active escape task when infused in the caudal, but not rostral, DRN (Hammack *et al.*, 2002). These studies suggest that conditioned fear is regulated by the full rostrocaudal axis of the DRN, whereas anxiety and helplessness are specifically regulated by rostral and caudal subregions, respectively.

6. Role of 5-HT autoreceptors in stress

6.1 Effects of stress on extracellular 5-HT levels

Acute stress exposure has heterogeneous effects on 5-HT release, with reports of increases, decreases, and no change in extracellular 5-HT depending on terminal region examined and

stressor used (Amat *et al.*, 1998a, b; Bland *et al.*, 2003a; Bland *et al.*, 2003b; Kirby *et al.*, 1995; Rueter *et al.*, 1997). Interestingly, some brain regions that show elevated acute 5-HT release during inescapable tailshock show persisting changes in 5-HT function. Inescapable tailshock 24 hours prior to a behavioral challenge causes enhanced 5-HT release in the basolateral amygdala, ventral hippocampus, and medial prefrontal cortex (Amat *et al.*, 1998a, b; Bland *et al.*, 2003a; Christianson *et al.*, 2010; Petty *et al.*, 1994). It has been proposed that 5-HT_{1A} autoreceptor desensitization may account for the enhancements in 5-HT function seen 24 h post-stress (Maier and Watkins, 2005). Here we present a modified form of that theory, suggesting that both 5-HT_{1A} and 5-HT_{1B} autoreceptors are desensitized during uncontrollable stress. The desensitization of these receptors results in increased 5-HT activity and, consequently, greater expression of fear and anxiety behavior.

6.2 Stress and 5-HT_{1A} autoreceptors

Studies employing various stressors have demonstrated stress-induced reduction in 5-HT_{1A} autoreceptor function, as assessed by electrophysiological recordings (Bambico *et al.*, 2009; Laaris *et al.*, 1997; Lanfumey *et al.*, 1999), receptor affinity (Flugge, 1995), 5-HT synthesis (Haleem, 1999), and hormonal responsiveness (Korte *et al.*, 1995) - however, see (Cornelisse *et al.*, 2007; Kirby *et al.*, 2007). Preliminary electrophysiological evidence for stress-induced 5-HT_{1A} autoreceptor desensitization has been recently presented by two other research groups (Lemos *et al.*, 2010; Rozeske *et al.*, 2010). In addition to the above effects, there is a downregulation of 5-HT_{1A} autoreceptor expression after uncontrollable stress which has been shown via reduced DRN 5-HT_{1A} binding (Briones-Aranda *et al.*, 2005; Leventopoulos *et al.*, 2009) and mRNA (Cooper *et al.*, 2009) – however, these effects may depend on specific stress procedures or measurements, as there are several publications finding no effect on 5-HT_{1A} autoreceptor expression (Abumaria *et al.*, 2006; Flugge, 1995; Pare and Tejani-Butt, 1996). Interestingly, 6 weeks of exercise – which is protective against the behavioral consequences of inescapable tailshock (Greenwood *et al.*, 2005a) has an opposite effect on DRN 5-HT_{1A} expression, increasing 5-HT_{1A} mRNA in the middle dorsal and dorsolateral DRN (Greenwood *et al.*, 2005b). This may protect against the behavioral effects of stress in part by suppressing DRN activity during stressor exposure and/or providing a buffer of spare receptors to reduce the extent of autoreceptor desensitization. Puzzlingly, an increase in 5-HT_{1A} mRNA is also seen – albeit in a different subregion, the middle ventromedial DRN – after chronic infusion of corticotropin-releasing factor, a treatment which was anxiogenic (Clark *et al.*, 2007).

Strong activation of the DRN appears to be a critical component in the stress-induced desensitization of 5-HT_{1A} autoreceptors. Manipulations of stressor controllability that restrict DRN activation also limit the sensitization of 5-HT release 24 h post-stress (Amat *et al.*, 1998a, b). Furthermore, directly inhibiting the DRN during uncontrollable stress exposure via infusion of a 5-HT_{1A} agonist (or electrolytic lesion) prevents behavioral consequences of stress in a variety of tasks including shuttlebox escape, fear conditioning, social exploration, and drug reward (Christianson *et al.*, 2008; Maier *et al.*, 1995; Will *et al.*, 2004). Similarly, intra-DRN infusions of the 5-HT_{1A} agonist flesinoxan in Syrian hamsters at the time of social defeat reduces behavioral consequences in tests carried out 24 h later (Cooper *et al.*, 2008). Uncontrollable stress exposure results in large increases in extracellular 5-HT within the DRN (Maswood *et al.*, 1998), and 5-HT_{1A} autoreceptors are susceptible to internalization (Riad *et al.*, 2001) and functional desensitization (Kennett *et al.*, 1987) after acute activation by agonist. Stress hormones appear to be a permissive factor in this process: glucocorticoids are necessary for stress-induced desensitization (Laaris *et al.*, 1997) but unlikely to be sufficient to explain the phenomenon, as manipulations of stressor controllability that prevent the sensitization in 5-HT function (Amat *et al.*, 1998a, b) do not reduce plasma levels of stress hormones (Maier *et al.*, 1986). Another possible mechanistic

component is the neuropeptide galanin – the DRN contains galanin-positive fibers and cell bodies (Gundlach *et al.*, 1990; Melander *et al.*, 1986) and expresses galanin receptors (Melander *et al.*, 1988) - but note important species differences in mouse (Fu *et al.*, 2010). Galanin is capable of modulating 5-HT_{1A} function and may play a role in stress-induced autoreceptor desensitization (Ogren *et al.*, 2007) and psychiatric disease states (Holmes and Picciotto, 2006).

6.3 Stress and 5-HT_{1B} autoreceptors

Like 5-HT_{1A} autoreceptors, 5-HT_{1B} autoreceptors also desensitize after stress. Using K^+-stimulated release of 5-HT from synaptosomes to isolate autoreceptor-specific effects, Bolanos-Jimenez et al (Bolanos-Jimenez *et al.*, 1995) showed that stress reduced the efficacy of 5-HT_{1B} autoreceptors in inhibiting this effect, without altering total number of binding sites. Our laboratory has observed behavioral evidence for stress-induced 5-HT_{1B} desensitization. First, we found that overexpression of 5-HT_{1B} autoreceptors increased swimming in the first 5 minutes of a 15 minute forced swim session in naïve rats; however, when the same rats were tested 24 hours later in a 5 minute swim, 5-HT_{1B} overexpression had no effect on behavior (McDevitt *et al.*, 2011). Though interpretation of this experiment is limited by its within-subject experimental design, we have seen similar results in other studies in which either stressed or unstressed rats were tested once for a particular behavior. 5-HT_{1B} overexpression reduced fear-potentiated startle in naïve rats, but not in rats that had been exposed to water-restraint stress 24 hours prior to testing (Clark *et al.*, 2004). The same pattern of results emerged in experiments using inescapable tailshock as a stressor and contextual fear conditioning as a behavioral measure. In unstressed rats, 5-HT_{1B} overexpression reduced measures of conditioned fear (McDevitt *et al.*, 2011). When identical procedures were carried out using rats that were first exposed to inescapable tailshock, however, there was no effect of overexpression (Figure 1). We interpreted these results to reflect a lack of 5-HT_{1B} efficacy; however, it is conceivable that stress might upregulate 5-HT_{1B} autoreceptor expression to some maximal amount, where some other biological factor limits 5-HT_{1B} function. Under this scenario, however, the 5-HT_{1B} agonist CP-94,253 would be expected to have equal or greater efficacy in reducing fear in stressed, versus unstressed, rats – which it did not. In unstressed rats, systemic injections of CP-94,253 at low doses paired with exposure to a fear-conditioned context reduced the expression of fear (McDevitt *et al.*, 2011). However, CP-94,253 had no effect in rats that had prior exposure to inescapable tailshock stress (Figure 2). Collectively, these results demonstrate that 5-HT_{1B} autoreceptors lose their ability to regulate emotional behavior after uncontrollable stress exposure.

Accordingly, the correlations between anxiety and endogenous expression of 5-HT_{1B} mRNA that are seen in unstressed animals vanish in rats with a history of uncontrollable stress exposure (Kaiyala *et al.*, 2003) – as would be expected if these receptors are desensitized and no longer contributing to behavior. Uncontrollable stress does increase expression of 5-HT_{1B} autoreceptor mRNA (Neumaier *et al.*, 1997) (Figure 3). Because of the technical challenges of measuring total protein levels of autoreceptors versus heteroreceptors, it has not been possible to test whether stress increases the number of 5-HT_{1B} autoreceptors. However, the fact that 5-HT_{1B} autoreceptors are functionally desensitized by stress would suggest that increased mRNA expression levels may not be relevant. The increase in expression may be a direct homeostatic response to the loss of 5-HT_{1B} function; alternatively, it could simply be a consequence of greater activity of DRN neurons. Because desensitization of 5-HT_{1B} receptors would render their expression levels physiologically irrelevant, studying 5-HT_{1B} autoreceptor function is critical in understanding the relationship between stress and behavior.

The apparent loss of 5-HT_{1B} autoreceptor function in stressed animals may be due to direct desensitization of 5-HT_{1B} autoreceptors, desensitization of postsynaptic receptors in terminal regions, or increases in DRN function – via desensitization of somatodendritic 5-HT_{1A} receptors or sensitization of afferent inputs - that result in synaptic 5-HT levels so high that 5-HT_{1B}-mediated inhibition is unable to reduce 5-HT enough to alter behavior. While direct stress-induced desensitization of 5-HT_{1B} receptors has been demonstrated (Bolanos-Jimenez *et al.*, 1995), it is unknown to what degree the other proposed factors might contribute to 5-HT_{1B}-mediated behavior. A closer look at the behavioral evidence for desensitization reveals ideas that could be explored in future experiments utilizing more direct measures of 5-HT_{1B} autoreceptor function. In several of our experiments utilizing 5-HT_{1B} overexpression in stressed rats, the animals were exposed to inescapable tailshock stress several days before stereotaxic surgery was performed (Figure 1). Thus, it appears that stress disrupted the function of 5-HT_{1B} autoreceptors that did not exist until several days after termination of the stressor. It seems unlikely that stress produces a simple desensitization or internalization of existing receptors, since newly synthesized receptors should be deployed to the terminals in the several days following stress exposure. The observation that these newly-synthesized 5-HT_{1B} autoreceptors appeared functionally impaired suggests the possibility that uncontrollable stress causes some disruption in serotonergic terminal function that is independent of 5-HT_{1B} autoreceptors *per se*. Possible mechanisms could include allosteric modulators of 5-HT_{1B} function such as the tetrapeptide Leu-Ser-Ala-Leu (LSAL; “5-HT moduline”) (Ischia *et al.*, 1997; Massot *et al.*, 1998), intermediary signal transduction molecules (Bolanos-Jimenez *et al.*, 1995), downstream effectors of 5-HT_{1B} autoreceptors, or other proteins known to interact with 5-HT_{1B} receptors such as glycogen synthase kinase-3 (Chen *et al.*, 2009) or p11/S100A10 (Svenningsson *et al.*, 2006).

6.4 Differences in 5-HT_{1A} and 5-HT_{1B} reactivity to stress

5-HT_{1B} autoreceptors may be more susceptible to stress-induced desensitization than 5-HT_{1A} autoreceptors. While caution must be employed in comparing across studies, there are two separate lines of evidence supporting this idea. First, there is a disparity in the severity of stressor required to desensitize 5-HT_{1A} and 5-HT_{1B} autoreceptors. A single session of restraint stress is sufficient to reduce physiological measurements of 5-HT_{1B} (Bolanos-Jimenez *et al.*, 1995) but not 5-HT_{1A} function, which requires more severe or prolonged stressors for functional desensitization (Bambico *et al.*, 2009; Laaris *et al.*, 1997). Similarly, while a single 15-minute forced swim session completely disrupts the behavioral effects of 5-HT_{1B} autoreceptor overexpression in a subsequent 5-minute test (McDevitt *et al.*, 2011), it has no effect on electrophysiological measures of 5-HT_{1A} autoreceptor function (Kirby *et al.*, 2007). A preliminary electrophysiological study in mice suggests that chronic, but not acute, exposure to forced swim is required for desensitization of 5-HT_{1A} autoreceptors (Lemos *et al.*, 2010). A second line of evidence for differences in stress susceptibility of 5-HT_{1A} and 5-HT_{1B} autoreceptors is suggested in behavioral pharmacology experiments. In rats with a history of inescapable tailshock exposure, overexpression of 5-HT_{1B} autoreceptors or systemic low doses of 5-HT_{1B} agonist – treatments that reduce fear in unstressed rats - fail to affect conditioned fear, even when tested several days post-stress (Figure 1, Figure 2). In contrast, 5-HT_{1A} agonists administered intra-DRN or systemically at low doses do alter helplessness behavior (Maier *et al.*, 1995) and social exploration (Christianson *et al.*, 2010) in rats exposed to inescapable tailshock 24 h prior to testing. Thus, 5-HT_{1A} and 5-HT_{1B} autoreceptors may have different thresholds for desensitization, may desensitize to stress in varying degrees.

The differences in 5-HT_{1A} and 5-HT_{1B} autoreceptor desensitization may have behavioral relevance. Inescapable tailshock stress has been shown to induce a variety of behavioral

consequences – interestingly, however, these effects appear to segregate neatly into two groups on the basis of their duration. While some effects last about 1–2 days post-stress, such as anxiety and shuttlebox deficits (Christianson *et al.*, 2008; Maier, 1990), sensitization of subsequent fear conditioning lasts at least a week post-stress (Baratta *et al.*, 2007; Maier, 1990). In a similar stress model, enhanced fear conditioning effects were seen even at three months post-stress (Rau and Fanselow, 2009). One possible explanation for the short- and long-lasting behavioral effects of stress is that they are mediated by desensitization of autoreceptors with different rates of recovery. Our laboratory has seen behavioral evidence for stress-induced desensitization of overexpressed 5-HT_{1B} autoreceptors as early as 24 hours post-stress (Clark *et al.*, 2004; McDevitt *et al.*, 2011) and as late as 6–8 days post-stress (Figures 1B, 1C). Additionally, experiments using the 5-HT_{1B} agonist CP-94,253 yielded similar results, suggesting desensitization at 4–7 days post-stress (Figure 2). These experiments show a relatively long-lasting time course of 5-HT_{1B} desensitization that appears to mirror the behavioral effects of stress on conditioned fear. There is a paucity of published data on the duration of desensitization of 5-HT_{1A} autoreceptors induced by acute stress. More detailed information on the duration of 5-HT_{1A} and 5-HT_{1B} desensitization would be valuable in further supporting or denying the theory that these effects mediate different behavioral consequences of stress.

7. Role of 5-HT autoreceptors in antidepressant treatment

A mystery in 5-HT research is the delayed onset of antidepressant drug efficacy. One theory invokes autoreceptor desensitization (Hjorth *et al.*, 2000; Pineyro and Blier, 1999). Because autoreceptors provide negative feedback that serves to drive 5-HT function towards equilibrium, they may initially provide homeostatic opposition to the effects of antidepressant drugs. However, as the autoreceptors are chronically exposed to high levels of 5-HT, they gradually desensitize and allow 5-HT levels to reach an asymptotic maximum. This theory posits that therapeutic effects of antidepressant drugs do not occur until these maximal levels of extracellular 5-HT are achieved.

There is extensive evidence that antidepressants drugs desensitize 5-HT_{1A} autoreceptors - reviewed in greater detail in (Pineyro and Blier, 1999). Functional desensitization following chronic antidepressant treatment has been demonstrated via electrophysiology (Blier and De Montigny, 1983; Blier *et al.*, 1984; Chaput *et al.*, 1986; Jolas *et al.*, 1994; Le Poul *et al.*, 1995; Rueter *et al.*, 1997), adenylate cyclase activity (Newman *et al.*, 1993) and microdialysis (Cremers *et al.*, 2000; Dawson *et al.*, 2002; Invernizzi *et al.*, 1994; Kreiss and Lucki, 1995). Acute antidepressant treatment results in internalization of 5-HT_{1A} autoreceptors, however this effect is abolished in rats treated chronically with antidepressant drugs (Riad *et al.*, 2008; Riad *et al.*, 2001). Thus antidepressant drugs may cause repeated activation and internalization of 5-HT_{1A} autoreceptors, which are gradually replaced on the plasma membrane by receptors in an inactivated state. This idea is supported by observations that chronic antidepressant treatment decreases agonist-stimulated binding of GTPγS to 5-HT_{1A} autoreceptors, despite unchanged total receptor binding (Castro *et al.*, 2003; Hensler, 2002; Pejchal *et al.*, 2002; Shen *et al.*, 2002). The above evidence would predict that pharmacological blockade of 5-HT_{1A} receptors would accelerate antidepressant onset. Indeed, in eight out of ten published placebo-controlled clinical trials, the 5-HT_{1A}/β-adrenergic antagonist pindolol was found to accelerate SSRI onset - reviewed in (Blier, 2003). While the human 5-HT_{1B} (formerly 5-$HT_{1Dβ}$) is pindolol-insensitive like 5-HT_{1D} receptors, a single amino acid substitution in the rat 5-HT_{1B} sequence confers high affinity binding of pindolol (Metcalf *et al.*, 1992; Oksenberg *et al.*, 1992; Parker *et al.*, 1993). A recent animal study showed that mice with genetically reduced expression of 5-HT_{1A} autoreceptors responded more quickly to antidepressants in terms of extracellular 5-HT concentrations (Richardson-Jones *et al.*, 2010). However, behavioral responding to the drug

treatment did not correspond with neurochemical changes: although four weeks of antidepressant treatment resulted in similar 5-HT concentrations in multiple terminal brain regions of control and transgenic mice, it produced an anxiolytic behavioral response in the novelty-suppressed feeding test in transgenic mice only.

Independently of electrophysiological activity at cell bodies, chronic antidepressants also result in greater evoked terminal release of 5-HT (Blier *et al.*, 1988; Chaput *et al.*, 1986; Maura and Raiteri, 1984; Moret and Briley, 1990). Studies attempting to identify the receptor(s) mediating this effect have yielded equivocal results. For example, studies testing sensitivity of 5-HT release to nonselective 5-$HT_{1B/1D}$ drugs have reported both functional desensitization (Pineyro and Blier, 1996) and a lack of desensitization (Cremers *et al.*, 2000; Jongsma *et al.*, 2005; Moret and Briley, 1996). Studies employing selective drugs suggest that there is desensitization of 5-HT_{1B}, not 5-HT_{1D} autoreceptors (Davidson and Stamford, 2000; el Mansari *et al.*, 1995; O'Connor and Kruk, 1994; Sayer *et al.*, 1999) – but see (Bosker *et al.*, 1995). Detection of 5-HT_{1B} autoreceptor desensitization by antidepressant is dependent upon circadian phase (Sayer *et al.*, 1999), specific terminal region examined (el Mansari *et al.*, 1995), and blockade of masking effects of 5-HT_{1A} autoreceptors (Davidson and Stamford, 2000). Conservatively, we might conclude that chronic antidepressants do reduce the sensitivity of 5-HT_{1B} autoreceptors, but this effect does not appear to be as robust as the effect on 5-HT_{1A} autoreceptors. In addition, chronic antidepressants also reduce expression of 5-HT_{1B} autoreceptor mRNA in the DRN, but this effect is rapidly reversed by discontinuation of drug (Anthony *et al.*, 2000; Neumaier *et al.*, 1996a). This result also raises the methodological concern that many of these studies have investigated 5-HT autoreceptors after acute withdrawal from the antidepressant, which may be a serious confound limiting their interpretability. Nevertheless, the preponderance of the data indicates that antidepressants desensitize both somatodendritic and terminal 5-HT autoreceptors, thereby increasing overall activity of the 5-HT system and resulting extracellular concentrations of 5-HT.

8. Conclusions

Serotonin function is regulated primarily by 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} autoreceptors. Although investigating these autoreceptors is technically challenging because they are also expressed widely in CNS as heteroreceptors, their central role as key regulators of the pattern of serotonin neuron firing and transmitter release makes them an important focus of attention. Manipulations of these autoreceptors reveal roles in regulating aversion, anxiety, and helplessness behaviors. Acute stimulation of 5-HT_{1A} and 5-HT_{1B} autoreceptors generally exert anxiolytic and antidepressant-like effects on behavior. There are discrepancies in the conclusions of literature using behavioral pharmacology versus genetic approaches, perhaps due in part to limitations of traditional “knockout” approaches. New genetic approaches allowing cell type and temporal specificity are critical in exploring the role of 5-HT autoreceptors. Numerous studies show that exposure to stress, sex hormones, and both therapeutic and illicit drugs modulate the expression and function of these 5-HT autoreceptors, thereby conferring changes in 5-HT functioning and behavior that can last from days to weeks. The contradiction that 5-HT autoreceptor desensitization has been demonstrated following both uncontrollable stress exposure and chronic SSRI administration, stimuli that have seemingly opposing effects on behavior, remains perplexing. Greater understanding of autoreceptor desensitization is needed to reconcile these disparate findings. Further study will help reveal the utility and limitations of 5-HT autoreceptors as a class of therapeutic target in the treatment of anxiety disorders and depression.

Highlight

In this review of serotonin autoreceptors, we primarily cover the role of 5-HT1A and 5-HT1B receptors in regulating behavior.

Overall, activation of these autoreceptors is rewarding and anxiolytic, but has more complex effects in models of helplessness.

Both stress and antidepressant treatment appear to desensitize these autoreceptors.

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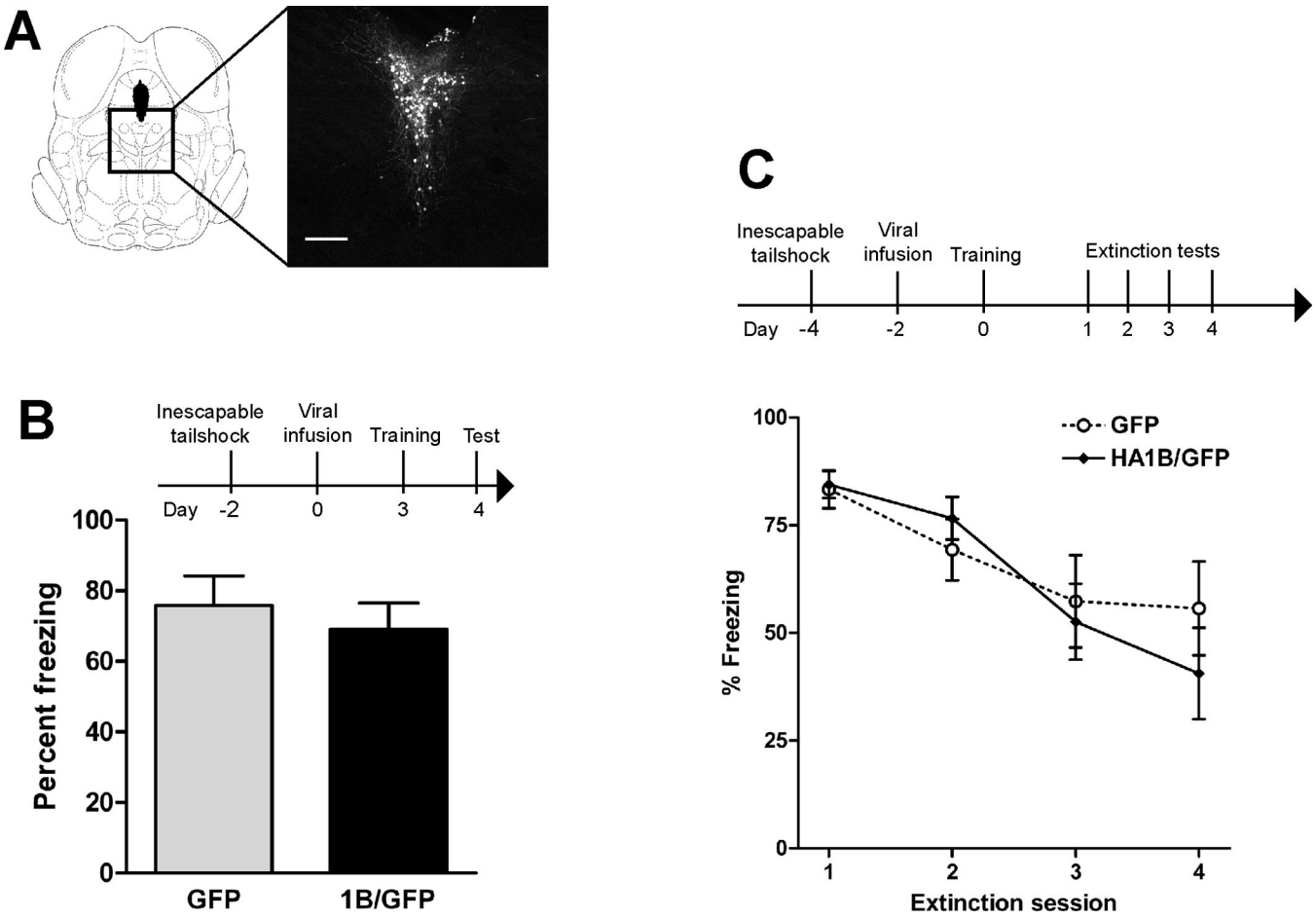

Figure 1.

Overexpression of 5-HT_{1B} receptors in the caudal DRN does not reduce conditioned fear in rats with a history of inescapable tailshock stress. In contrast, unstressed rats receiving 5-HT_{1B} overexpression demonstrate reduced expression of conditioned fear (McDevitt *et al.*, 2011). Surgeries and behavioral testing were carried out as previously described (McDevitt *et al.*, 2011). A, demonstration of viral-mediated gene transfer in the caudal DRN. Left, depiction of tissue targeted in stereotaxic surgery (reprinted from (Paxinos and Watson, 1986), with permission from Elsevier, copyright 1997). Right, viral-mediated expression of GFP seen in a 40 µl slice of tissue. Scale bar = 400 µm. B, Rats were exposed to inescapable tailshock, infused with GFP (n=9) or 1B/GFP (n=11) viral vector, and underwent contextual fear conditioning. Graph depicts mean (+SEM) percent of observations spent freezing during a test session. C, to ensure that negative results in the above experiment were not due to a "ceiling" of percent freezing, an extinction experiment was performed in a separate cohort of animals. Rats were exposed to inescapable tailshock, infused with GFP (n=8) or 1B/GFP (n=8) viral vector, trained in contextual fear conditioning, and then tested on four consecutive days. Data points depict mean (± SEM) percent of observations spent freezing during test sessions.

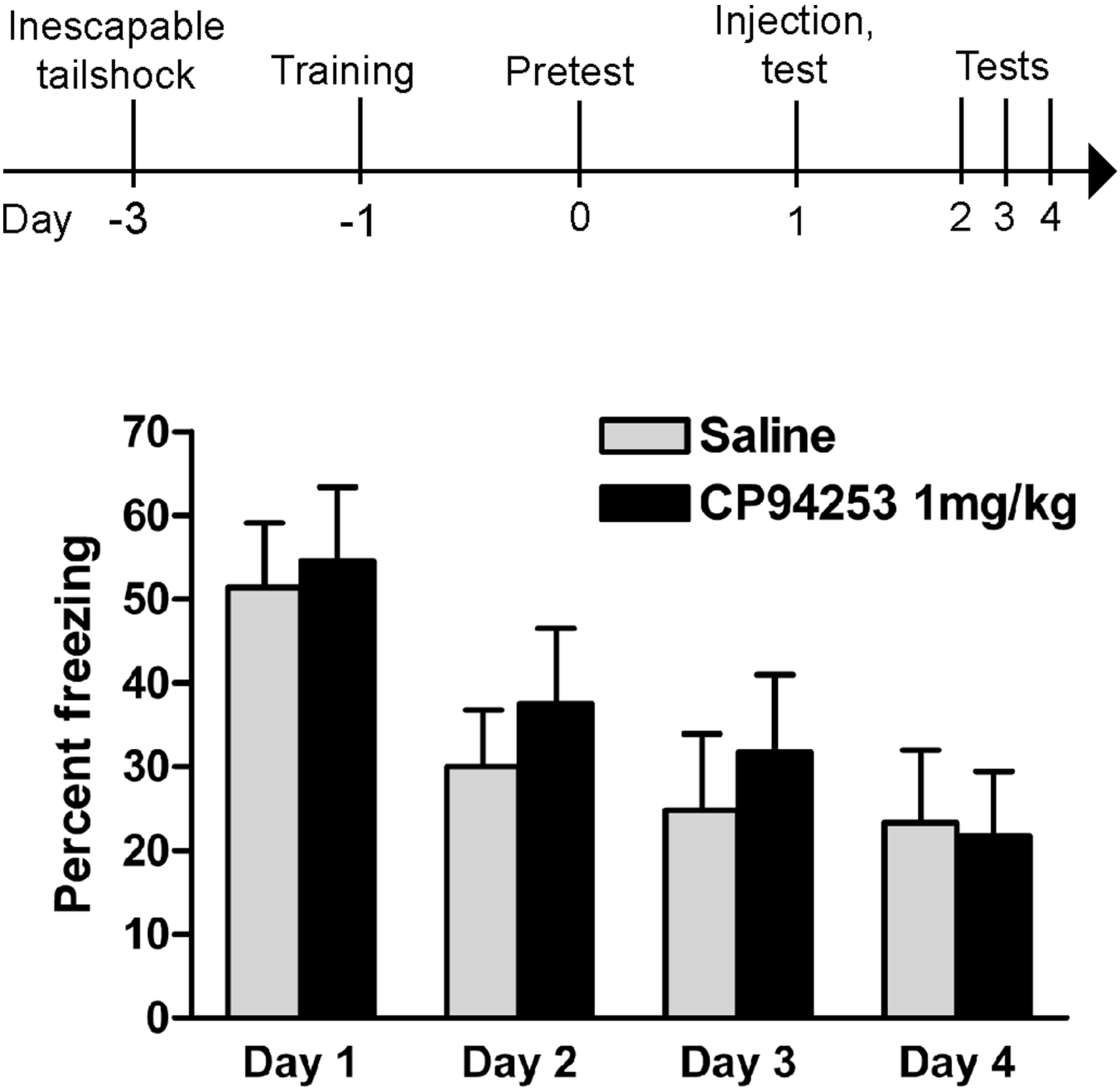

Figure 2.

Systemic injection of the 5-HT_{1B} agonist CP-94,253 does not reduce conditioned fear in rats with a history of inescapable tailshock stress. These results are in contrast to the fear-reducing effects of this drug in unstressed rats (McDevitt *et al.*, 2011). Drug injections and behavioral testing were carried out as previously described (McDevitt *et al.*, 2011). Rats were exposed to inescapable tailshock stress, trained in fear conditioning, and then exposed to the context for a brief pretest session to assess conditioned fear and balance groups (no difference in pretest freezing; $p = 0.85$). The following day (Day 1), rats were then injected intraperitoneally with saline (n=7) or CP-94,253 (1 mg/kg, n=8) 30 min prior to a test session. For 3 subsequent days (Days 2–4), rats were retested without injections.

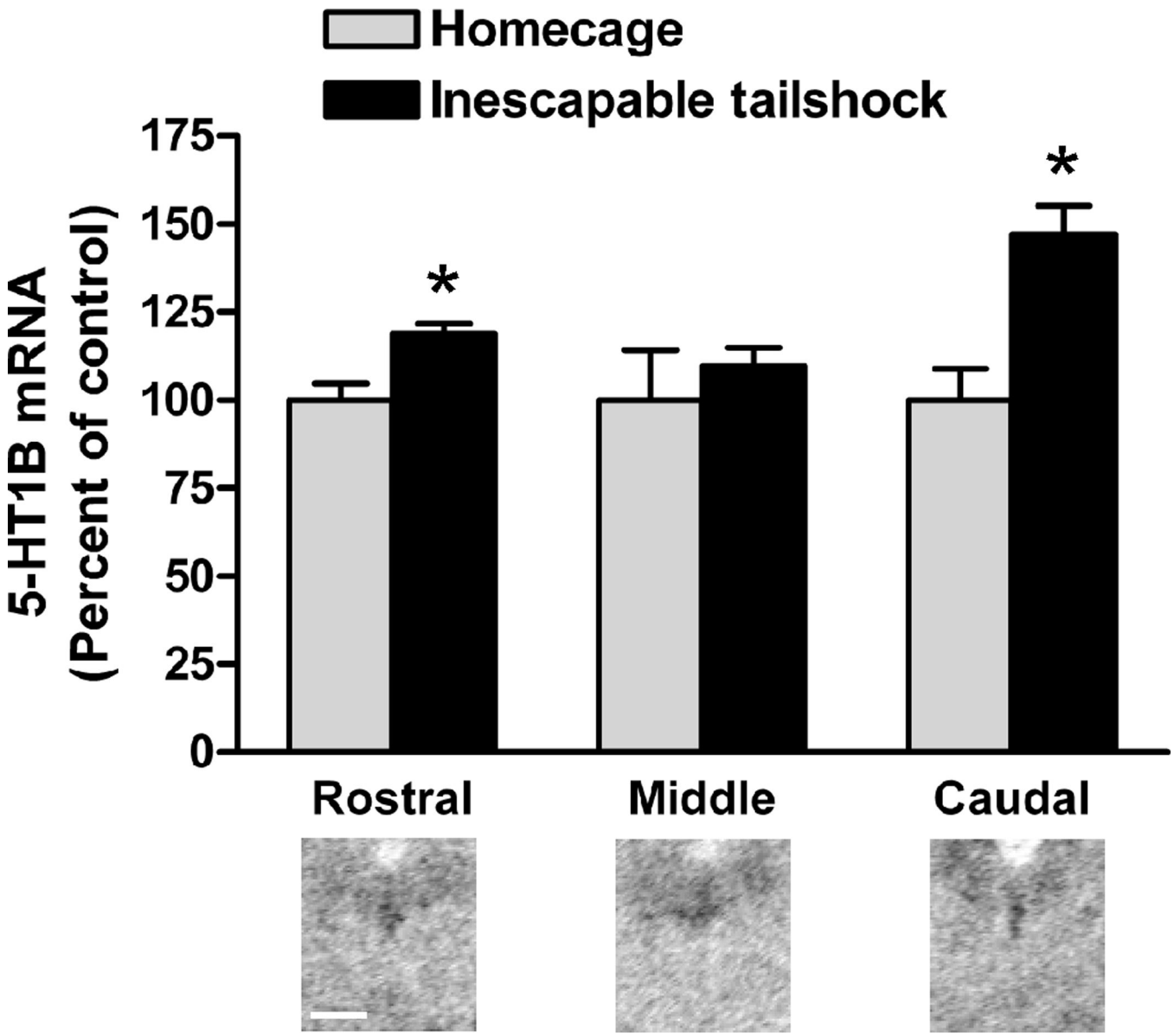

Figure 3.

Inescapable tailshock stress increases 5-HT_{1B} mRNA in rat DRN. 5-HT_{1B} expression in DRN was examined in brains previously used for a study of stress and locus coeruleus gene expression (McDevitt *et al.*, 2009). *In situ* hybridization histochemistry was carried out as previously described (Clark *et al.*, 2006). Briefly, rats were exposed to inescapable tailshock and sacrificed at 1, 2, 4, or 24 hours after the termination of stress session. Unstressed rats remained in homecage until time of sacrifice. Within each DRN subregion, measures of 5-HT_{1B} mRNA signal were normalized to unstressed homecage control. Comparison of stress groups by two-way ANOVA with factors stress time point and DRN subregion (not shown) did not reveal significant differences between stress time points [$F(3,39)$=0.805, p=0.50], therefore all stress time points were combined into a single group (n=17) and compared to homecage controls (n=6). Graph represents mean (+SEM) optical density of in situ hybridization autoradiograms, grouped by DRN subregion. Below graph is sample autoradiogram of tissue at respective rostrocaudal level. Scale bar = 1 mm. * $p < 0.01$ vs. homecage control.