The Spectrum of Behaviors Influenced by Serotonin

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The diverse array of behavioral effects of serotonin form the basis for understanding its potential role as an etiological marker in psychiatric disorders and for the successful pharmacologic intervention of drugs regulating serotonin neurotransmission in behavior. General theories of the behavioral functions of serotonin have implicated serotonin as a general inhibitor of behavioral responding and in modulating motor behavior. The ability of serotonin to regulate behavioral satiety and macronutrient selection provides the basis for pharmacologic treatment of obesity and eating disorders. The role of serotonin in behavioral suppression may be important in social behavior involving aggression and anxiety. The role of serotonin in neuroendocrine regulation provides a basis for understanding serotonin dysregulation in depression. Animal behavior tests are being used to better understand the neural substrates underlying the behavioral effects of antidepressant drugs and to address important issues in clinical treatment. The integration of information between basic and clinical studies provides the basis for future development of more sophisticated pharmacologic treatments of psychiatric disorders. Biol Psychiatry 1998;44:151–162
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Introduction

Serotonin (5-hydroxytryptamine, 5-HT) was identified initially as the active substance from brain extracts that produced peripheral vasoconstriction (Rapport et al 1948). This substance was later shown to be identical to a contractile substance isolated earlier from the enterochromaffin cells of the gastrointestinal mucosa called enteramine (Erspamer and Asero 1952). Subsequent studies demonstrated the localized distribution of 5-HT neurons throughout the brain (and gut) using fluorescence histochemistry and, later, immunocytochemical methods (Dahlstrom and Fuxe 1964; Jacobs and Azmitia 1992). Most 5-HT-containing neurons are localized along the midline of the brain stem and send long axons to innervate a wide distribution of receiving areas throughout the nervous system from the spinal cord to the cortex. Forebrain serotonin is derived nearly entirely from neurons located in the dorsal and median raphe nuclei of the midbrain. Prominent forebrain terminal regions include the hypothalamus, cortex, hippocampus, amygdala, and striatum. Furthermore, 5-HT neurons are highly bifurcated, indicating that they are structured ideally for influencing the function of several regions of the central nervous system (CNS) simultaneously. These innervation patterns are relatively conserved throughout mammalian species including man.

Serotonin has been shown to influence a broad range of physiological systems, such as cardiovascular regulation, respiration, and thermoregulation, and a variety of behavioral functions, including circadian rhythm entrainment, sleep–wake cycle, appetite, aggression, sexual behavior, sensorimotor reactivity, pain sensitivity, and learning. It is not surprising that the pharmacologic regulation of 5-HT function has been found to influence a range of traditional psychiatric disorders. These disorders include depression, a spectrum of anxiety disorders (generalized anxiety disorder, panic disorder, obsessive–compulsive disorder, and social phobia), schizophrenia, and anorexia nervosa. In addition, a less-structured range of impulse-related disorders or personality features has been associated with alterations of 5-HT function, including aggression, substance abuse, gambling, obsessive control, and attention-deficit disorder. Finally, recent findings suggested that 5-HT receptors may also be targeted to treat neurodegenerative disorders and Alzheimer's disease (Bowen et al 1994; McLoughlin et al 1994).

This paper will review some of the diverse behavioral effects for 5-HT that form the basis for understanding its role in psychiatric disorders and neuropharmacology. General theories relating 5-HT to animal behavior form the framework for understanding how 5-HT produces a general modulation of behavior across species and will be reviewed. Some examples of systems where the role of 5-HT in basic neurobiology has impacted psychiatric investigations will be highlighted. These areas include the role of 5-HT in feeding behavior, neuroendocrinology and stress, and behavioral suppression and aggression. Finally,

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research is described, some from my laboratory, that associates animal behavior tests for antidepressants with a developing neurobiology associated with important issues of clinical treatment and a developing neurobiological model for the effects of antidepressant drugs.

General Theories Relating 5-HT to Behavior

The involvement of 5-HT in many behavioral functions has caused speculation that 5-HT may function in a higher-order capacity to integrate a variety of behavioral functions. Despite 5-HT being involved in temperature regulation, feeding, sexual behavior, responding to painful stimuli, escape, and stress, most of these response systems continue to function without 5-HT. A general theory of 5-HT function in behavior can help to account for why 5-HT appears to influence so many behaviors, but also is an unlikely neurotransmitter to be the principal or sole mediator of any of these behaviors.

One of the traditional general theories suggests that increased 5-HT function acts to constrain behavioral activation, whereas reduced 5-HT function facilitates behavioral activation across diverse environmental situations. Brodie and Shore (1957) originally described a general role for 5-HT in behavioral inhibition, in contrast with the presumed excitatory role of norepinephrine (NE) systems on arousal. A number of subsequent reviews of 5-HT in behavior have focused on the general principle that 5-HT functions to constrain the response of organisms to external arousing stimuli and that the response to a variety of external stimuli is potentiated in its absence (for review, see Soubrie 1986; Depue and Spoont 1986; Spoont 1992). This argument is supported by a substantial body of literature showing consistent behavioral changes produced by the depletion of 5-HT. For example, reduced 5-HT function generally is reported to increase pain sensitivity, increase exploration or locomotor activity, increase startle behavior, increase the output of operant behavior suppressed by punishment, and increase aggressive and sexual behavior. Increasing serotonergic function can also produce the opposite behavioral effect in many of these environmental situations. Most consistent are numerous reports that decreased serotonergic function is associated with increasing the effects of psychomotor stimulants, such as amphetamine. These effects are thought to be mediated by the interaction of serotonergic neurons with mesolimbic dopamine systems that function to regulate behavior in complementary directions.

A second formulation emerged from the search for behavioral correlates of neuronal discharge patterns of serotonin neurons. The principal role for serotonin was to facilitate motor output and suppress ongoing processing of sensory input during motor behavior (Jacobs and Fornal 1995). Serotonin neurons appear to be autoactive, continuously firing at a rate ranging between 0.5 and 2.5 spikes/sec, as an intrinsic pacemaker. The activity of 5-HT neurons varies most dramatically between various states of arousal, ranging between waking (most active), slow-wave sleep (slow), and REM sleep (completely inhibited). 5-HT neurons facilitate central motor tone and can promote the elicitation of tonic and repetitive behavioral patterns, known as central pattern generators. For example, oral–buccal behavior patterns (chewing, licking, biting, grooming) in the cat are associated with activity of dorsal raphe nucleus, whereas other motoric behaviors (walking or running) are correlated with activity of more caudal raphe neurons. Also, administration of high doses of 5-HT precursors or 5-HT receptor agonists can produce a series of distinctive spinal-mediated motor patterns in various species including man, known as the 5-HT motor behavioral syndrome (Jacobs 1976). Otherwise, 5-HT neuronal discharge rate in the cat dorsal raphe nucleus appears to be impervious to change by many environmentally perturbing stimuli, such as noise, temperature, fear, restraint, etc. Sensory information processing is simultaneously suppressed by 5-HT to inhibit irrelevant input that might disrupt motor output. During abrupt orientation to sensory stimuli, however, serotonin neurons can be suppressed, thereby sharpening sensory function while disfacilitating motor output. Autonomic and neuroendocrine functions are coordinated with changing motor activity functions. This view of the modulatory effects of 5-HT on motor patterns and sensory stimuli may be related to some general classes of symptoms in psychiatric disorders. For example, enhancing 5-HT function may inhibit responding to inhibitory extraneous stimuli that promotes a loss of impulse control (Baumgarten and Grozdanovic 1995).

In contrast to electrophysiological studies in cats, a variety of microdialysis studies conducted in rats examining regional patterns of extracellular 5-HT and behavior have shown that 5-HT release can be altered by a variety of external stimuli. Consistent differences in extracellular 5-HT values are obtained by comparing rats during different behavioral states, such as sleep and wakefulness, and extracellular 5-HT can be increased due to nonspecific behavioral activation (Rueter et al 1997); however, environmental stressors can produce dramatic changes in 5-HT release that are quite specific according to the precise nature of the stimulus or the relatively discrete regional localization of effects (Kirby et al 1995, 1997; Wilkinson et al 1996; Adell et al 1997; van Erp and Miczek 1997). For example, extracellular 5-HT increases in the anterior lateral hypothalamic area, but not in the medial preoptic area, of male rats only during the immediate postejaculation period of a sexual encounter (Lorrain et al 1997). Extracellular 5-HT in the hippocampus increases in re-

sponse to the presentation of contextual, but not discrete, stimulus elements after contextual fear conditioning (Wilkinson et al 1996). Forced swimming produced increases, reductions, or no change in extracellular 5-HT measured in different brain regions (Kirby et al 1995). A series of environmental challenges produced changes in extracellular 5-HT in the striatum and hippocampus without association with their ability to increase plasma levels of corticosterone (Kirby et al 1997). In contrast to increases in extracellular 5-HT that are produced by wakefulness, feeding, or anxiety (Rueter et al 1997; Schwartz et al 1990; Wright et al 1992), reductions in extracellular 5-HT may be produced by forced swimming, aggression, insulin, or drug withdrawal states (Kirby et al 1995; Orosco and Nicolaidis 1994; van Erp and Miczek 1997; Parsons et al 1995; Weiss et al 1996). Thus, it is unlikely that simple, uniform interactions with behavioral state are capable of explaining the complex patterns of 5-HT release produced by various stimuli.

Future directions for identifying the role of 5-HT in behavior with microdialysis studies will involve understanding the nature of these relatively specific stimulus effects on neural mechanisms involved in organizing the functional activity of 5-HT neurons. The activation of diverse, but functionally selective, 5-HT-containing cells in the raphe by diverse afferent pathways could organize topographically selective patterns of 5-HT release (Peyron et al 1998). Although most midbrain raphe neurons thus far seem unresponsive to most phasic physiological stimuli in the cat (Jacobs and Fornal 1995), this may not be surprising given the diverse functional organization and topographical heterogeneity of cells in this region. Such limitations, and potential differences between cats and other species, may make it difficult to settle this issue definitively. In addition, control of 5-HT release is also likely to be exercised by interactions at 5-HT terminals with afferent input from other neural systems to specific regions. This type of interaction is also likely to contribute to regionally selective alterations of 5-HT release.

Although the general theories of 5-HT and behavior are not being specifically criticized here, limitations and inconsistencies exist for both theories. The effects of 5-HT on many specific behaviors and in specific regions must be understood before a general theory of 5-HT can explain which functions and regions should be organized into a systems framework. Generalized functional theories may not account for many specialized roles that 5-HT may exert in different regions of the brain that are not encompassed by the framework. Finally, general theories of 5-HT and behavior do not account for the potential distinctive roles of various 5-HT receptor subtypes (Hoyer et al 1994). Drugs with selective affinities of various 5-HT receptor subtypes produce selective effects on behavior (Glennon and Lucki 1988), and may often appear to influence similar 5-HT-mediated responses in very different ways, such as the role of 5-HT_{1A} and 5-HT_{2C} receptors in anxiety. Although general theories relating 5-HT to behavior can provide a heuristic framework for interpreting the results of a wide range of data concerning neurochemistry and behavior that is applicable to psychiatric disorders, greater detail concerning the physiological basis for the behavioral effects of 5-HT, including behavioral, anatomical, and pharmacologic specificity, must be understood before explanations referring to global functions for 5-HT can serve as more than a heuristic exercise.

Serotonin and Feeding Behavior

Studies of the involvement of serotonin in feeding behavior provide a good model for how multiple pharmacologic, physiological, and anatomical components are integrated in the functional regulation of complex behavior. In animal models and in humans, 5-HT releasers, such as fenfluramine, and selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and sertraline, have implicated 5-HT in the inhibitory control of feeding (for review, see Simansky 1996a). Behavioral studies have shown that these drugs reduce the rate of eating and size of meals in a manner suggesting that increased serotonergic transmission terminated feeding by specifically enhancing satiation (McGuirk et al 1992). Analysis of the 5-HT receptor subtypes, using selective agonists and antagonists, has implicated 5-HT_{1B}, 5-HT_{2C}, or 5-HT_{2A} receptors in regulating food intake. Interestingly, the behavioral patterns produced by activating these receptors implicate different behavioral mechanisms. 5-HT_{1B} and 5-HT_{2C} receptors appear to be involved in regulating meal size, whereas 5-HT_{2A} receptors disrupt the continuity of feeding (Simansky and Vaidya 1990). In addition, activation of 5-HT receptors leads to selective reduction of carbohydrate intake (Leibowitz 1993). Activation of each of these receptor subtypes may be required for complete expression of behavioral satiety.

The hypothalamic paraventricular nucleus has been proposed as an important terminal field that is involved in 5-HT's role in satiety (Leibowitz 1993); however, recent studies have implicated additional brain regions in this function (Fletcher et al 1993). In addition, peripherally administered 5-HT also decreases food intake in rats in a behaviorally selective manner, suggesting that peripheral sites may contribute to serotonergic functions in ingestion (Simansky 1996b).

Serotonin and Neuroendocrine Function

In animal models and in humans, drugs that enhance brain 5-HT function (direct agonists, SSRIs, and 5-HT releasers)

increase serum concentrations of corticosterone in rats, or cortisol in humans, and adrenocorticotropic hormone (ACTH) (for review, see Fuller 1996). These effects are mediated by serotonergic innervation of corticotropin-releasing factor (CRF)-containing neurons in the paraventricular nucleus that project to the median eminence and release CRF into the venous portal circulation (Liposits et al 1987; Bagdy and Makara 1994). Analysis of the 5-HT receptor subtypes associated with regulating corticosterone release in rats, using selective agonists and antagonists, has implicated 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors. In addition, 5-HT receptors in the hypothalamic paraventricular nucleus have also been implicated in the secretion of the hormones prolactin and renin (Bagdy and Makara 1994; Van de Kar et al 1996). Activation of both 5-HT_{1A} and 5-HT_{2A} or 5-HT_{2C} receptors is associated with prolactin release, but activation of only 5-HT_{1A} receptors increases the secretion of renin.

Serotonin neurons and receptors in the hypothalamus may be involved in mediating hormonal responses to stress elicited under certain conditions (see Chaouloff 1993). For example, lesions of serotonin neurons in young rats prior to the appearance of the serum corticosterone rhythm prevented the development of that rhythm during adulthood (Banky et al 1986). The corticosterone responses to photic and acoustic stimuli are prevented following neurotoxic destruction of hypothalamic serotonin neurons (Feldman et al 1991). The increase of serum corticosterone by 2-deoxyglucose, which inhibits intracellular glucose utilization, was blocked by the 5-HT_2 receptor antagonist ketanserin (Weidenfeld et al 1994). Since the release of corticosterone, prolactin, and renin is increased in rats after exposure to environmental stress, drugs that alter 5-HT receptor function may interfere with both the behavioral and endocrine effects of some stressors (Van de Kar et al 1991).

There is also compelling evidence implicating hippocampal neurons in the interaction between the hypothalamic pituitary adrenal axis and the serotonin system in response to stress. Elevation of corticosterone levels by stress or direct stimulation of glucocorticoid receptors (GR) by dexamethasone reduces levels of 5-HT_{1A} receptor binding in discrete subfields of the hippocampus (Mendelson and McEwen 1992; Chalmers et al 1994), whereas adrenalectomy increases hippocampal 5-HT_{1A} receptor density (Tejani-Butt and Labow 1994). Selective neurotoxic lesion of 5-HT neurons decreases GR and GR messenger RNA (mRNA) levels in the hippocampus (Seckl et al 1990). Conversely treatment with antidepressants that inhibit serotonin reuptake increase GR and GR mRNA levels in this structure (Seckl and Fink 1992). GR mediate feedback inhibition mechanisms of corticosterone release, and lesion of hippocampal neurons impairs feedback inhibition of corticosterone release following stress (Sapolsky et al 1984). A disturbance in the ability to terminate the release of cortisol, the human analog of corticosterone, is involved in clinical depression, and antidepressants restore feedback inhibition of cortisol (Barden et al 1995); however, the role of hippocampal 5-HT_{1A} receptors in this process needs further clarification.

Because 5-HT is an important modulator of pituitary hormone production, drugs that alter brain 5-HT function (precursors, direct agonists, SSRIs, 5-HT releasers and antagonists) have been used in pharmacologic challenge studies in which changes in the plasma levels of pituitary or adrenal hormones are used as putative indices of the functional status of serotonin neurotransmission in humans (Murphy et al 1996; Yatham and Steiner 1993). These physiological effects also provide the basis for comparison of these responses between subject populations to assess alterations of serotonergic activity associated with various psychiatric conditions.

Serotonin and Aggression

Serotonin is one of the neurotransmitters most specifically related to the neurobiologic mechanisms of social and aggressive behaviors. A great deal of evidence has been presented that links 5-HT transmission to aggressive behavior in animals (Miczek et al 1994). The strongest evidence for an inhibitory role of 5-HT in animal aggression has accumulated from neuropharmacologic studies of 5-HT and predatory aggression by laboratory rats, usually directed toward a mouse (Miczek and Donat 1989). These studies have shown that rats develop the ability to kill mice after depletion of 5-HT and that drugs that enhance 5-HT transmission suppress predatory behavior; however, the role of 5-HT as an inhibitor of predatory aggression is less clear in other species (Miczek et al 1994).

The role of 5-HT in aggressive behavior involving conflict between members of the same species, often referred to as agonistic behavior, has also been studied because these models may be closer to human aggression. Drugs that enhance 5-HT transmission nonselectively, such as the SSRI fluvoxamine, can reduce offensive aggression but not without simultaneously affecting other categories of behavior. In contrast, drugs that selectively activate 5-HT_{1A} or 5-HT_{1B} receptors appear to reduce social aggression in rats in a more behaviorally specific manner, without decreasing social interaction or novelty exploration in both the resident-intruder and maternal aggression models (Miczek et al 1994; Olivier et al 1995). Drugs that produce a behaviorally selective decrease in aggression are referred to as “serenics,” and selective 5-HT receptor agonists may be candidates for this special

category of pharmacologic agents. Recently, mice with genetic deletion of 5-HT_{1B} receptors were shown to demonstrate increased fighting behavior and increased resident-intruder aggression (Saudou et al 1994), an effect consistent with the general inhibitory role of 5-HT in rodent aggression.

Primate social colonies have been a prime target for studies of the relationship between 5-HT and social dominance and aggression. Male vervet monkeys with high rank within a group's social dominance hierarchy demonstrate elevated levels of 5-HT in whole blood or in blood platelets and higher levels of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) (Raleigh et al 1980, 1983). The administration of drugs that increase 5-HT transmission to individuals results in their acquiring higher dominance status in the colony (Raleigh et al 1991). Conversely, low CSF 5-HIAA levels were associated with increased ratings of aggression and risk-taking behavior in adolescent male rhesus macaques (Mehlman et al 1994). It is unclear, however, how measurements of whole blood 5-HT or CSF levels of 5-HIAA relate to the actual functional turnover of 5-HT in discrete regions of the brain associated with social behavior.

Studies with human subjects have investigated the association of CSF 5-HIAA levels with depression and other behavioral characteristics. An identifiable subset of depressed psychiatric patients was shown to demonstrate reduced concentrations of CSF 5-HIAA levels (for review, see Brown and Goodwin 1986; Asberg 1994; Tuinier et al 1995). Subsequent studies suggested that low CSF 5-HIAA levels occurred preferentially in depressed patients who had attempted suicide before hospital admission. In addition, low CSF 5-HIAA levels appeared to persist after treatment for depression, suggesting the identification of a neurochemical vulnerability marker rather than a neurochemical response to an altered state. Subsequently, the association of low CSF 5-HIAA levels with suicide were extended to other populations of psychiatric patients, such as alcoholism, adjustment disorder, and schizophrenia (Brown and Goodwin 1986). A common behavioral characteristic or trait distinguishing patients with low CSF 5-HIAA levels was impulsive and destructive behaviors, particularly where aggression and violence were involved, irrespective of the psychiatric diagnostic category (Brown and Linnoila 1990). Subjects with personality disorders involving aggression also demonstrate reduced prolactin response to acute challenge with the 5-HT releaser d-fenfluramine, an index of reduced central 5-HT function (Coccaro et al 1996).

The key element asserted for 5-HT in the biology of aggression is its role in controlling the impulse to engage in aggressive, antisocial, or punished behaviors. This is similar to the proposed role of 5-HT in mediating the effects of punishment, although punishment is usually defined in more operational terms than impulse control. Stimuli associated with punishment produce suppression of ongoing behavior in a wide variety of circumstances. A common behavioral effect of antianxiety drugs is their ability to reverse the effects of behavioral suppression or punishment. Antianxiety drugs, either benzodiazepines or buspirone, may inhibit the effects of punishment because of their reduction of 5-HT release, albeit through different physiological mechanisms. Benzodiazepines reduce 5-HT release by augmenting inhibition of raphe neurons by gamma-aminobutyric acid (GABA), but buspirone reduces 5-HT release by activating presynaptic 5-HT_{1A} autoreceptors. In addition, a number of 5-HT receptor antagonists have been suggested to cause antianxiety effects. Thus, inhibition of 5-HT function, either by reducing neuronal discharge or by blocking postsynaptic 5-HT receptors, has also emerged as a key substrate associated with the effects of antianxiety drugs (Eison and Eison 1994; Handley and McBlane 1993; Barrett and Vanover 1993; Lucki 1996).

Despite the difficulty in defining the necessary and sufficient conditions for measuring impulse control, a proposed role for brain serotonin in mediating impulse control has emerged as a major theme in biological psychiatry. The foundation idea, that a dysfunction of impulse control is associated with impaired serotonin function in the biology of aggression and social violence, has been extended in clinical investigations for individuals with tendencies toward suicide, alcoholism, criminal behavior, substance abuse, gambling, antisocial behaviors, and obsessive–compulsive disorder. If low 5-HT function mediates some of these disorders, it is reasoned that SSRIs may be effective at controlling them. Accordingly, SSRIs are being examined for efficacy in a variety of disorders that extend far beyond their initial indication for depression.

Serotonin and Depression

Dysfunctions of serotonin neurotransmission have been associated with the occurrence of major depressive disorder (for review, see Maes and Meltzer 1995). Disorders of serotonergic activity could contribute to many of the symptoms of major depression, for example, mood, appetite, sleep, activity, suicide, and sexual and cognitive dysfunction. Abnormalities in serotonergic activity in depressed patients have been reported to occur at several critical points in serotonin transmission, such as diminished availability of 1-tryptophan, impaired 5-HT synthesis, release, reuptake, or metabolism, or malfunction of postsynaptic 5-HT receptors. Interference with 5-HT synthesis or function by environmental or genetic factors may

induce depression in some vulnerable individuals. Of potential precipitating factors, increased functional activity of postsynaptic 5-HT_2 receptors, reduced functional activity of 5-HT_{1A} receptors, and the relationship between these systems and the hypothalamic–pituitary–adrenal (HPA) axis may be of special importance in depression.

SSRIs have been demonstrated to be effective in treating major depression and are the most popularly prescribed class of antidepressant drugs. Depletion of 5-HT with the tryptophan hydroxylase inhibitor para-chlorophenylalanine (PCPA) prevented the therapeutic effects of tranylcypromine and imipramine (Shopsin et al 1975, 1976). In addition, dietary depletion of 5-HT precursors leads to clinical relapse in depressed patients who were successfully treated with SSRIs (Heninger et al 1996; Delgado et al 1991). These studies are consistent with the view that enhanced 5-HT transmission is necessary to maintain the therapeutic effectiveness of antidepressants.

Efforts to model human affective disorders in animals involve both animal models of depression, based on environmental or genetic manipulations, and animal behavioral tests sensitive and selective for detecting antidepressant drugs (see Willner 1990; Weiss and Kilts 1995). When the SSRI fluoxetine was initially developed as an antidepressant, most animal tests for antidepressant activity in use at that time were based on the detection of behaviors mediated by NE (Wong et al 1995). Thus, the effects of fluoxetine could not be detected with the animal tests in use at that time because of its relatively novel mechanism of action. Since the time of fluoxetine's development, however, newer animal behavior tests for antidepressant effects have been developed and shown to be associated with antidepressant drugs from multiple pharmacologic classes, including the SSRIs (see Willner 1990). Thus, the clinical development of SSRIs has also had an important reciprocal impact on the development and evaluation of animal tests that are sensitive to antidepressant drugs.

Most of the animal tests for antidepressant activity that are currently in use have been validated by their sensitivity to antidepressants with pharmacologically diverse effects, including the NE reuptake inhibitor desipramine and the SSRI fluoxetine. Some behavioral tests involved delayed reinforcement or withholding of responses, behavioral effects potentially associated with impulse control. For example, operant performance under a differential reinforcement of low rate schedule (DRL 72-sec) requires that food-deprived rats withhold their responses for at least 72 sec to obtain food reward. Acute administration of most antidepressants produces an increase in the number of reinforcer presentations in food-deprived rats responding for reward under this reinforcement schedule (Seiden and O'Donnell 1985; Marek et al 1989). Food-deprived rats also exhibit preference for smaller immediate rewards over larger-but-delayed rewards, a model of reinforcement delay that involves impulse control and is sometimes called waiting behavior. Antidepressant drugs selective for either 5-HT or NE systems shift the preference from smaller-immediate rewards to larger-delayed rewards (Bizot et al 1988).

Other behavioral tests for antidepressant drugs involve interactions with stressful conditions. The olfactory bulbectomy model measures the ability of chronic administration of antidepressants to reverse behavioral deficits, e.g., locomotor activity or passive avoidance learning, induced by lesions of the olfactory bulb (Cairncross et al 1978; Joly and Sanger 1986). This test is also sensitive toward drugs selective for enhancing either NE or 5-HT transmission. The chronic mild stress procedure measures deficits in sucrose consumption produced by the continuous and repeated exposure of rats to various types of stressors (Willner et al 1992). Muscat et al (1992) showed that sucrose consumption deficits are reversed by chronic treatment with antidepressant drugs that selectively enhance either NE or 5-HT transmission. Learned helplessness procedures directly measure deficits in escape behavior induced when an animal is exposed to prolonged presentations of an inescapable stressor (Seligman et al 1975). Many types of antidepressants counteract escape behavior deficits in animals after learned helplessness training (Leshner et al 1979; Sherman et al 1982; Martin et al 1990), including antidepressants that selectively enhance either NE or 5-HT transmission.

The forced swimming test (FST), or "behavioral despair" test (Porsolt et al 1977, 1978), is one of the most frequent behavioral tests used to measure potential antidepressant activity. Rodents are placed in an inescapable cylinder of water and, after a period of active behavior, display placid immobility, or only those movements necessary for the animal to keep its head above water. The development of immobility is facilitated by administering a pretest session. The immobility is thought to represent a failure to persist in escape-directed behavior or the development of behavioral passivity in response to prolonged stress. Treatment with antidepressant drugs decreases the duration of immobility in the FST. Although the FST is sensitive to most antidepressants that increase NE transmission (Borsini and Meli 1988), the effects of SSRIs were reported either to be active in the FST, inactive in the FST, or active only at high doses (for review, see Borsini 1995).

Recently, we reevaluated the effects of different types of antidepressant drugs in the FST (Detke et al 1995b). We developed a new scoring procedure that measured active behaviors [swimming and climbing (a.k.a. thrashing)] as well as the development of passive immobility in the FST

using a water depth greater than typically employed in the cylinder (Detke and Lucki 1995). These conditions for the FST provided a more sensitive behavioral test for the effects of serotonergic antidepressants and a test that distinguished antidepressant drugs working through different pharmacologic mechanisms. Antidepressants that selectively inhibit NE reuptake, such as desipramine and maprotiline, were shown to reduce immobility and selectively increase climbing without affecting swimming. In contrast, the SSRIs fluoxetine, sertraline, and paroxetine also reduced immobility but increased swimming without affecting climbing. The behavioral distinction between fluoxetine and desipramine in the FST was maintained even after chronic administration for 14 days (Detke et al 1997), indicating no crossover of their respective behavioral patterns. None of the drugs produced increases in locomotor activity, indicating the active behaviors were not due to nonspecific changes in activity. This behavioral scoring system for the FST has also been used by other investigators (Hansen et al 1997), and the results with SSRIs have been replicated (Hemby et al 1997; A. Eison, personal communication).

The study of active behaviors in the FST demonstrates the value of a behavioral test for antidepressants that could detect drugs with a common effect on a core behavior (immobility) produced by all antidepressants, but also distinguish behavioral components (climbing and swimming) that act through distinct neurotransmitter systems (Lucki 1997). The neurochemically distinctive behavioral effects are similar to the distinctive contributions of NE and 5-HT systems to the clinical efficacy of antidepressant drugs that have been described recently (Heninger et al 1996). Dietary depletion of 5-HT precursors led to clinical relapse in depressed patients treated with SSRIs, but not with NE-selective reuptake inhibitors (Delgado et al 1991). Conversely, blockade of NE synthesis led to clinical relapse in depressed patients successfully treated with NE-selective reuptake inhibitors, but not with SSRIs (Delgado et al 1993). Although the function of the different component behaviors is not known, the different behaviors shown by rats in the FST could be a potential model for corresponding multiple behavioral effects in depressed patients that may be produced by antidepressant drugs acting on different neurotransmitters (Katz et al 1994).

We have used this pattern of antidepressant drug effects in the FST to address several questions related to clinical treatment. One question we addressed is whether the pattern of behavioral effects produced by the combined administration of a SSRI (fluoxetine) with a selective NE reuptake inhibitor (desipramine) could provide indications of a more effective antidepressant treatment than either treatment when given alone (Reneric and Lucki 1998). Combining fluoxetine and desipramine at certain dose combinations increased both component behaviors climbing and swimming, although the core measure of immobility did not show additive effects. Other drugs with mixed neurochemical effects, such as the antidepressant venlafaxine or the tropane derivative 8-methyl-2β-propanoyl-3β-(4-(l-methylphenyl)-8-azabicyclo[3.2.1] octane (PTT), both mixed 5-HT and NE and weak dopamine reuptake inhibitors, also produced the pattern of simultaneously increasing both climbing and swimming behavior at certain doses (Hemby et al 1997; Reneric and Lucki 1998). Thus, although most antidepressant drugs seem to reduce immobility in the FST through a single component mechanism according to their pharmacologic effects, it is possible to identify certain drugs that alter multiple components of the FST (Lucki 1997). Active behaviors would appear to be more informative measures of effects in the FST, then, because for a given reduction of immobility, drug effects on multiple components may potentially predict different therapeutic values. By detecting novel behavioral effects of antidepressant drugs according to their neuropharmacologic effects, the new FST scoring system may enhance the clinical significance of the FST for testing newer antidepressant drugs. Combining distinct neurobiological components of the antidepressant response, such as combining effects on 5-HT and NE systems, may provide a rationale for the development of more effective drug treatments or for the treatment of nonresponders (Artigas 1995). If the therapeutic efficacy of antidepressants is increased by merging effects of multiple behavioral components, then examining different behavioral components in the FST in animals may predict conditions that achieve this (Lucki 1997).

Another value of a behavioral test that is sensitive and selective toward SSRIs is that it can be used to determine important information concerning the neural substrates underlying the antidepressant effects. For example, prior depletion of 5-HT, induced by pretreatment with the tryptophan hydoxylase inhibitor PCPA, prevented the behavioral effect of fluoxetine in the FST (Detke et al 1995a), indicating that the behavioral effects of fluoxetine are dependent on the availability of 5-HT. Drugs with different effects on subtypes of 5-HT receptors have been tested in the FST to determine more specific mechanisms that may be associated with serotonergic antidepressant effects. Drugs that were selective 5-HT receptor agonists, either the 5-HT_{1A} receptor agonists 8-OH-DPAT or gepirone or the 5-HT_{1B} receptor agonist CGS 12066, produced antidepressant effects by increasing swimming behavior, whereas several 5-HT receptor agonists were ineffective (Detke et al 1995a, 1995b). In addition, antagonists at different 5-HT receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_2, or 5-HT_3 receptors) were ineffective at producing antidepres-

sant effects. The pattern of these results indicates that postsynaptic 5-HT_{1A} receptors mediate swimming behavior in the FST, as suggested previously (Lucki et al 1994; De Vry 1995), but also that 5-HT_{1B} receptors may also be involved. In addition, a role for 5-HT_{2A} receptor antagonists as antidepressants has also been described (Sibille et al 1997). The list of tested compounds with selective effects on 5-HT receptors is incomplete; however, as selective pharmacologic tools become available, results with this behavioral test will present important leads toward identifying specific 5-HT receptor mechanisms associated with antidepressant effects.

In addition, we have attempted to develop a neurobiological model of the FST by using in vivo microdialysis to measure the neurochemical changes in extracellular 5-HT produced by the FST and SSRIs. Our initial studies showed that the effects of forced swimming on extracellular 5-HT concentrations in forebrain regions differed from those of other stressors (Kirby et al 1997). Forced swimming produced large changes in extracellular 5-HT that began temporally with the onset of swimming and ended several hours later. The phasic effects of swimming on extracellular 5-HT varied in different brain regions; increases occurred in the striatum, decreases were produced in the lateral septum and amygdala, and no changes were found in cortex or hippocampus (Kirby et al 1995).

Subsequent studies showed that the phasic reduction in extracellular 5-HT in the lateral septum was correlated with changes in behavior and the effects of antidepressant treatments during the FST. The specific accumulated evidence from our laboratory is: 1) forced swimming for 15–30 min, which produces climbing and swimming behaviors that precede the development of immobility, produces an acute phasic reduction of 5-HT release in the lateral septum; 2) a second forced swimming session 24 hours later, which produces predominately behavioral immobility, was associated with the loss of the acute phasic reduction of 5-HT release in the lateral septum; 3) fluoxetine treatment during the FST procedure increased tonic levels of extracellular 5-HT; and 4) fluoxetine treatment, which increases swimming and reduces behavioral immobility, restores the acute phasic reduction of 5-HT in the lateral septum (Kirby et al 1995; Kirby and Lucki 1997, in press). Changes in extracellular 5-HT in the striatum were not correlated with behavioral changes in the FST.

These observations agree with other evidence that also points to the likely involvement of 5-HT in the lateral septum in the behavioral effects of antidepressants. For example, cellular or metabolic markers of neuronal activity in the lateral septum are altered by the FST or learned helplessness (Cullinan et al 1995; Duncan et al 1993). The lateral septum has been linked to aversion or behavioral suppression, because electrical stimulation of the septal region has the ability to inhibit aversive states, activity of cells in the lateral septum is increased in the presence of stimuli that inhibit aversion, and lesions of the septal region reduce or abolish the ability of environmental stimuli to inhibit aversion (Thomas 1988). The role of 5-HT in the lateral septum appears predominantly to inhibit neuronal activity of the septum (Van den Hoof and Galvan 1992). Thus, a neurobiological model for the role of 5-HT in the lateral septum in the forced swimming test would assume that a phasic reduction of 5-HT release in the lateral septum during the FST initial pretest would be associated with behavioral facilitation due to the disinhibition of lateral septal neurons. The predicted behavioral consequences of this effect would be the emission or persistence of escape-oriented behavioral responses, such as in the pretest session of the FST. The behavioral immobility or increased behavioral suppression shown during the test session of the FST would be associated with a loss of the phasic reduction of 5-HT in the lateral septum. The restoration of the acute phasic reduction of 5-HT in the lateral septum, such as that produced by fluoxetine treatment (Kirby and Lucki 1997), would predict a return of escape-directed behaviors, such as increased swimming and reduction of immobility. Additional studies are needed to test this role for the lateral septum in the behavioral effects of antidepressants.

Finally, the neuropeptide CRF may be a critical mediator in regulating decreases of extracellular concentrations of 5-HT during stress (Price et al 1998). CRF immunoreactive fibers innervate the dorsal raphe nucleus, and this peptide has frequently been associated with coordinating the autonomic and behavioral effects of stress (Valentino et al 1993). The administration of low doses of CRF (0.1 and 0.3 μg, ICV) to rats significantly decreased striatal 5-HT concentrations by 58% and 60% at peak, respectively. CRF, administered ICV or directly into the dorsal raphe nucleus, also predominantly decreased the discharge rates of 5-HT neurons, so that CRF should presumably be capable of reducing extracellular concentrations of 5-HT in other dorsal raphe projection areas. As CRF plays a critical role in orchestrating the effects of stressors in the CNS, interest leads to speculation on the role of CRF in mediating the effects of a variety of stressful stimuli that have already been shown to reduce extracellular levels of 5-HT in terminal regions. For example, since CRF and forced swimming both reduce the release of 5-HT in the lateral septum (Price and Lucki, unpublished), it is conceivable that CRF–5-HT interactions may participate in the neural effects of forced swimming and in mediating the behavioral effects associated with antidepressant drugs in the FST (Price et al 1998). This hypothesis is currently under investigation.

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