Chapter 14

Neurobiology of Startle Response Abnormalities in PTSD

Jeffrey L. Rausch, M.D.
Mark A. Geyer, Ph.D.
Melissa A. Jenkins, B.A.
Curtis Breslin, M.S.
David L. Braff, M.D.

An exaggerated startle response has been consistently described as a central feature of the heightened physiological reactivity found in patients diagnosed with DSM-III-R posttraumatic stress disorder (PTSD; American Psychiatric Association 1987). These observations date back to the descriptions of combat soldiers sensitized to stress during World War I. Campbell (1918, p. 1622) indicated that once a World War I soldier had been "un-nerved" by his experience of high explosives, he would later succumb to otherwise *trivial* stimuli. Numerous observations have since then strengthened the association of exaggerated startle responses to the syndrome of PTSD. New developments now present an opportunity to understand better whether specific aminergic influences may underlay the exaggerated startle responses in PTSD patients.

This work was supported by the Veterans Affairs and grants from the State of California Department of Mental Health (DMH 89-7000) and the National Institute of Mental Health (MH42228). M. A. Geyer was supported by a Research Scientist Development Award from the National Institute of Mental Health (MH00188).

DEFINITION

The *startle response* is defined by a constellation of *motor movements* that occur immediately after a sudden, strong sensory stimulus. This immediate reaction is distinguished from the more slowly evolving autonomic responses that may present after a sudden stimulus (Graham 1979; Wilkins et al. 1986). Indeed, a cardinal feature of the startle response is its very short latency. In the jaw muscles the response occurs in as few as 14 milliseconds (msec) after a loud noise (Davis 1984). Although the earliest detectable change in movement may occur in the jaw muscles, a rapid contraction of the eyelid may be the only evidence noted at the mildest levels of measurable startle response (Jacobson 1926). Accordingly, the human startle response can be measured reliably by the amplitude of eyeblink in response to a sudden abrupt auditory stimulus (Hoffman and Ison 1980; Landis and Hunt 1939). As such, the eyeblink movements of the orbicularis oculi muscle are considered to be a useful motor component of startle response measurement in human studies.

DESCRIPTION

Although the eyeblink has been designated as a convenient site for startle measurement, the components of the human startle response also include forward head movement; widening of the mouth; flexion of the shoulders, elbows, fingers, knees, and trunk; and pronation of the lower arms and abduction of the upper arms, as catalogued by Straus (cited in Davis 1984). These movements are largely flexor in nature. Startle responses emerge at no earlier than 6 weeks of age in humans, although the brain mechanisms that modulate the responses undergo change during early childhood and do not mature until about 8 years of age (Ornitz et al. 1986).

ANATOMY

Although the motor expression of the startle response comprises a number of reflexes, its basic neuroanatomy is relatively simple, as found from a variety of lesion studies and electrical stimulation paradigms. These studies have investigated the locus of the basic "startle circuit" in laboratory rats. The neuroanatomic foundation of the startle circuit has been well delineated in the pioneering work of Davis (1984) and others. Davis and colleagues (1984) have painstakingly delineated the brain-stem startle circuit as involving the posteroventral cochlear nucleus (VCN), the lateral lemniscus, the reticulospinal tract, and the lower motor neurons of the spinal cord. Although the fundamental brain-stem startle circuitry seems straightforward, it is the more complex physiological modulation of startle, often involving inputs from higher brain centers, that is of great interest to psychopathology researchers. For example, it has been noted that lesions of the amygdala impair fear-potentiated startle, and these observations provide preliminary evidence that the amygdala may be involved in processing information related to conditioned fear or may be part of an output pathway for the expression of conditioned fear (Hitchcock and Davis 1986). As discussed later in this chapter, evidence now exists that cortical elements may influence the tone of the startle response, insofar as cognitive or perceptual influences may affect startle in humans (Vrana et al. 1988).

PHYSIOLOGY

Startle responses have, in fact, been shown to be modulated by a variety of factors, as evidenced by various paradigmatic manipulations. This apparent plasticity of the response has proved useful to psychopathology researchers. Two examples can be considered:

1. Startle magnitude shows prepulse inhibition (PPI) or gating, as reflected by decreased startle magnitude when the startle-eliciting stimulus is preceded by a weak prestimulus or warning stimulus at an interval of 60 to 100 msec in humans (Graham 1975) and at shorter intervals in rodents (Hoffman and Ison 1980). Schizophrenic patients show a loss of this normal preattentive and theoretically "protective" gating activity (Braff et al. 1978). This same loss is seen in rats with

nucleus accumbens dopamine overactivity (Swerdlow et al. 1986).

2. Startle responses show habituation or a decrement of responding upon repeated presentation of the same, initially novel stimulus. The observed habituation is theoretically the result of the two opposite underlying processes of habituation and sensitization (Groves and Thompson 1970), and is complexly determined. Schizophrenic patients, for example, exhibit impairments of startle habituation that may be linked to abnormalities of serotonergic systems (Geyer and Tapson 1988).

BASIC STUDIES

A particularly useful model for the study of PTSD is the behavioral paradigm of *conditioned fear*, a phenomenon that can be conceptualized as a sensitization emergent from an enduring anxiety state. Anderson and Parmenter (1941), for example, described sheep and dogs that had been followed for over 12 years after the induction of "experimental neuroses." In this paradigm, an electric shock was used as an *unconditioned* stimulus, and the sound of a metronome was used as a *conditioned* stimulus. The investigators noted a chronic physiological state in these animals characterized by a startle reaction that would generalize in response to extraneous low-level stimuli, such as touch or merely scratching on the wall of the experimental chamber. The animals' responses to such stimuli included crouching, trembling, running, and even defecation. The authors characterized these behavioral states well in noting that from all appearances the animal seemed already set to react before it had cause for reacting (Anderson and Parmenter 1941).

Such exaggerated startle responses have since defined conditioned fear in the laboratory. Davis (1986) described a paradigm measuring increases in whole-body startle in laboratory rats in the presence of a light that had previously been paired with electric footshock. Davis's group demonstrated that the increased startle amplitude in the fear-conditioned rats could be pharmacologically attenuated by diazepam, morphine, or buspirone, but not imipramine (Cassella and Davis 1985).

Contributing to clinical paradigms aimed at understanding PTSD treatment, the neuropsychopharmacology and pathophysiology of human startle have been informed by observations from animal studies investigating the basis for the startle reaction. Clinical researchers have now just begun to look at startle modulation in humans to understand whether changes in gating, habituation, or sensitization occur in patients previously exposed to traumatic stimuli. Ultimately the treatment and prevention of sensitization to stress will involve not only considerations in the already stress-sensitized organism, but also knowledge pertaining to what factors may best prevent, prior to or during trauma, the acquisition of subsequent pathological responses.

CLINICAL STUDIES

It has been only recently that human startle has been measured in clinical studies of patients diagnosed with PTSD. Previously, several clinical studies (Blanchard et al. 1986; Malloy et al. 1983; Ornitz and Pynoos 1989; Pitman et al. 1987; see also McFall and Murburg, Chapter 7, this volume, for review) had demonstrated increases in heart rate, respiration, and electromyographic activity in war veterans exposed to gunfire or other abrupt auditory stimuli. A less consistent finding was a higher basal heart rate in PTSD subjects (Blanchard et al. 1982, 1986; see also McFall and Murburg, Chapter 7; Murburg et al., Chapter 8, this volume, for review). Changes in heart rate in response to traumatic stimuli had previously been shown to provide a degree of diagnostic discrimination of PTSD subjects (Blanchard et al. 1986).

More recently, startle response measures per se have been assessed in clinical PTSD populations, once the validity (Braff and Geyer 1990; Graham 1975) and the methodological advantages (Vrana et al. 1988) of eyeblink startle measures had been verified. Startle reactions of PTSD subjects have since been specifically studied by measuring the subjects' response to sudden abrupt stimuli, differentiating direct measures of startle motor reactions from other more slowly evolving autonomic responses.

In an early study of startle response physiology in human subjects, Ornitz and Pynoos (1989) recorded startle responses in six children (ages 8 to 13) meeting DSM-III (American Psychiatric Association 1980) criteria for PTSD. The children were exposed to 104-decibel bursts of white noise. During some trials, warning stimuli were administered at time intervals that normally would either facilitate (i.e., 800 and 2,000 msec) or inhibit (i.e., 120 and 250 msec) a startle response. Results of the "warned" trials indicated that children with PTSD showed a loss of startle inhibition from the prepulse warning. The PTSD children also demonstrated an exaggerated startle facilitation compared with the control children, although the startle response of the PTSD children on "unwarned" trials was significantly smaller than that of the control children.

Our own group recently studied eyeblink responses to startling acoustic or tactile stimuli in 13 Vietnam combat veterans with chronic PTSD, compared with 12 combat veterans without PTSD (Butler et al. 1990). The study was designed to examine whether the veterans with chronic PTSD would exhibit measurable startle responses at lower sound intensities than the intensities required to elicit startle in the non-PTSD patients. Subjects in either group who failed to show an eyeblink response to the startle stimulus were excluded. Thirteen of 20 identified PTSD-positive subjects (65%), and 12 of 18 control subjects (67%) were included as having measurable eyeblink reactions to the acoustic stimulus. Of these, the PTSD group had measurably greater startle responses than did the control group at the intermediate sound intensities (i.e., 95 and 100 decibels). The PTSD patients were not significantly different on measures of prepulse inhibition and were equivalent to control subjects in their responses to tactile startle stimuli. Our results suggested that there was a lower threshold for acoustic startle responses in the PTSD subjects (Figure 14–1). The identical startle responses to tactile stimuli could reflect differences between weak and strong stimuli. Alternatively, it may be that increased startle responses are specific to stimuli that resemble the traumatic event.

There is evidence that the cognitive or perceptual set may influence the startle response. Vrana et al. (1988) tested the eyeblink responses to unsignaled white noise bursts while subjects viewed photographic slides depicting either pleasant, neutral, or unpleasant scenes or objects. Independent of interest levels or arousal, eyeblink startle magnitudes evoked by the noise bursts were largest while subjects were viewing unpleasant material, and smallest while they were viewing pleasant material.

It is debatable whether white noise bursts may be cognitively associated with perceptions of gunshots (Ornitz and Pynoos 1989). It had previously been asserted that activation of conditioned responses in PTSD patients requires stimuli that resemble the traumatic event (Kolb 1984). The present data suggest that age, the cognitive/perceptual context of the stimulus, its character and modality, and the interval between preceding stimuli all may influence the startle response.

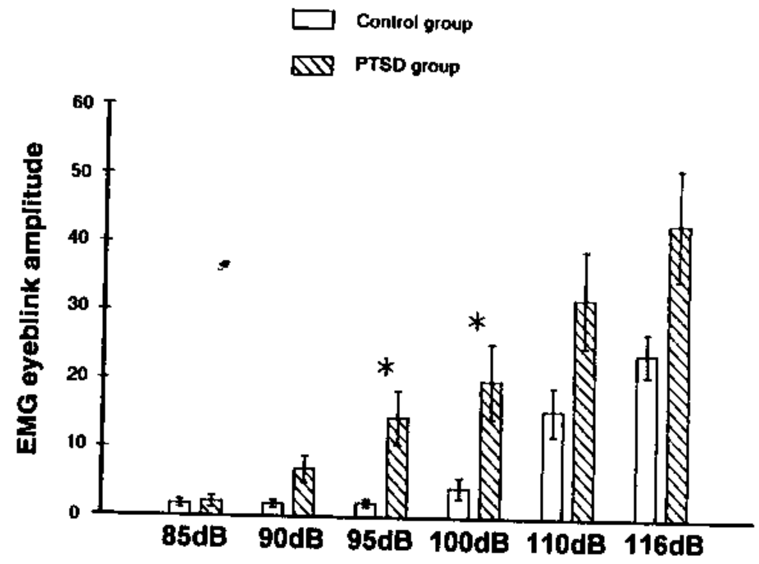

Figure 14–1. Startle response reactivity in subjects with combat-related PTSD and in control subjects. Reprinted from Butler RW, Braff DL, Rausch JL, et al: "Physiological Evidence of Exaggerated Startle Response in a Subgroup of Vietnam Veterans With Combat-Related PTSD." *American Journal of Psychiatry* 147:1308–1312, 1990. Copyright 1990, American Psychiatric Association. Used with permission.

NEUROCHEMISTRY OF STARTLE

It is not yet known whether startle response differences between PTSD patients and control subjects are correlated with specific neurochemical abnormalities. These issues are potentially important in understanding the physiological basis for PTSD and may well be important in advancing effective treatment of the condition. For example, we now know that startle responses can be increased or decreased by disparate lesions and drug manipulations, although these neurochemical influences are still being investigated in basic studies.

Generally, it appears that dopamine and possibly norepinephrine agonists increase acoustic startle (Davis 1980), whereas serotonin exerts a largely inhibitory influence (Davis et al. 1980). In the case of serotonin, for example, decreases in startle activity have been linked to increased activity in forebrain serotonergic pathways in studies using pharmacological probes (Davis 1980; Davis et al. 1984), electrolytic or neurotoxic lesions (Geyer et al. 1976, 1980), synthesis inhibitors (Conner et al. 1970), precursor manipulations, and direct intracerebral injections of serotonin (Davis et al. 1980; Geyer et al. 1975). Various serotonergic pathways (Geyer et al. 1976) and different serotonin receptors (Davis et al. 1986; Geyer and Tapson 1988) contribute differentially to these effects. Indeed, descending serotonergic pathways appear to be excitatory rather than inhibitory to startle (Davis et al. 1980).

Among the anatomically defined subdivisions of the central noradrenergic system, only the influence of the locus coeruleus (LC) itself has been studied systematically. Neurotoxic lesions of the LC or its projections decrease startle reactivity (Adams and Geyer 1981; Kehne and Davis 1985), as do several drugs that inhibit the activity of LC neurons (Davis 1980). Conversely, drugs that increase activity in the LC have the opposite effect (Davis et al. 1977). The demonstrated increases in startle induced by anxiogenic stimuli and decreases by anxiolytic drugs have been linked tentatively to noradrenergic influences (Davis et al. 1979), though the involvement of serotonin$_{1A}$ receptors has also been a recent focus of investigation (Mansbach and Geyer 1988).

Dopamine agonists such as amphetamine and apomorphine increase startle, whereas dopamine antagonists such as haloperidol have the opposite effect (Davis 1980; Davis et al. 1975). The effects of amphetamine on startle reactivity, in contrast to its effects on locomotor activity, appear to be independent of the dopaminergic projections to the nucleus accumbens (Swerdlow et al. 1990). Instead, these effects may reflect the activation of the nigrostriatal dopaminergic system and/or some complex interactions between dopaminergic and noradrenergic systems (Davis 1984). Recent results have added some complexity to what originally appeared to be a simple, direct relationship between dopamine activity and startle reactivity, because different subtypes of dopamine receptors appear to have opposite influences on startle reactivity (Melia and Davis 1988). Nevertheless, the converging evidence from a variety of studies indicates that all three monoamine neurotransmitters have important influences that combine to modulate the level of startle reactivity in mammals.

Miserendino and colleagues (1990) have demonstrated that N-methyl-D-aspartate (NMDA) receptors may be linked to the acquisition, but not the expression, of fear-potentiated startle. These receptors seem to play a critical role in synaptic plasticity, and NMDA antagonists prevent long-term facilitation as a potential mechanism underlying memory and learning. The ability of NMDA antagonists, infused into the amygdala, to block the acquisition of fear-conditioned startle suggests that NMDA-dependent processes in the amygdala may subserve associative fear conditioning (Miserendino et al. 1990).

MORPHOLOGY

Evidence also exists to suggest that fundamental morphological changes may occur in response to conditioned behavioral dishabituation and sensitization. Organisms as simple as Aplysia can be shown to overrespond to a light touch with a defensive gill withdrawal if the light touch is previously paired with an electric shock. The network of neurons responsible for the gill withdrawal has been identified by Kandel and co-workers, who found that shock-conditioning strengthens neuronal connections within this network, augmenting the signal transmission in the sensorimotor synapse (Glanzman et al. 1990). This synapse can be strengthened by applying serotonin, a transmitter known to strengthen connections between neurons associated with conditioning in the intact animal (Glanzman et al. 1989; Mackey et al. 1989). It is not known whether such an increase in transmitter release (Dale et al. 1988), or growth of new points of synaptic contact between sensory and motor neurons (Korn et al. 1981), or an activity-dependent enhancement of synaptic activity (Miserendino et al. 1990) might represent a specific aspect of the fundamental mechanisms underlying perturbations of the startle threshold in PTSD patients.

CONCLUSIONS

Animal models of fear-conditioned startle consistently suggest that enduring changes in startle response may occur with sensory cues paired to traumatic stimuli. Experimental paradigms of stress dishabituation or sensitization, and fear-conditioning are contributing important information that may allow us to make inferences about the startle response abnormalities found in PTSD patients. A vital test for future investigations will be to ascertain which neurotransmitters known to affect the startle response are implicated in both the acquisition and the retention of such heightened physiological states in patients. The identification of such specific neurotransmitter systems may support the development of receptor-specific psychopharmacological preventions of, and treatment interventions for, PTSD. The ability to quantify specific neurobiological parameters of the startle response in clinical populations can now contribute to a delineation of the appropriate subject population for studies of the pathophysiology, treatment, and prevention of acquisition of exaggerated startle reactions in persons with PTSD.

REFERENCES

Adams LM, Geyer MA: Effects of 6-hydroxydopamine lesions of locus coeruleus on startle in rats. Psychopharmacology (Berlin) 73:394–398, 1981

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition. Washington, DC, American Psychiatric Association, 1980

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised. Washington, DC, American Psychiatric Association, 1987

Anderson OD, Parmenter R: Long-term study of the experimental neurosis in the sheep and dog: with nine case histories. Psychosom Med Monograph, Vol 2, Nos 3–4, 1941

Blanchard E, Kolb L, Pallmeyer T, et al: A psychophysiological study of post traumatic stress disorder in Vietnam veterans. Psychiatr Q 54:220–229, 1982

Blanchard E, Kolb L, Gerardi R, et al: Cardiac response to relevant stimuli as an adjunctive tool for diagnosing post-traumatic stress disorder in Vietnam veterans. Behavior Therapy 17:592–606, 1986

Braff DL, Geyer MA: Sensorimotor gating and schizophrenia: human and animal model studies. Arch Gen Psychiatry 47:181–188, 1990

Braff DL, Stone C, Callaway E, et al: Prestimulus effects of human startle reflex in normals and schizophrenics. Psychophysiology 15:339–343, 1978

Butler RW, Braff DL, Rausch JL, et al: Physiological evidence of exaggerated startle response in a subgroup of Vietnam veterans with combat-related PTSD. Am J Psychiatry 147:1308–1312, 1990

Campbell CM: The role of instinct, emotion and personality in disorders of the heart. JAMA 71:1621–1626, 1918

Cassella JV, Davis M: Fear-enhanced acoustic startle is not attenuated by acute or chronic imipramine treatment in rats. Psychopharmacology (Berlin) 87:278–282, 1985

Conner RJ, Stolk JM, Barchas SD, et al: Parachlorophenylalanine and habituation to repetitive auditory startle stimuli in rats. Physiol Behav 5:1215–1219, 1970

Dale N, Schacher S, Kandel ER: Long-term facilitation in aplysia involves increase in transmitter release. Science 239:282–285, 1988

Davis M: Neurochemical modulation of sensory-motor reactivity: acoustic and tactile startle reflexes. Neurosci Biobehav Rev 4:241–263, 1980

Davis M: The mammalian startle response, in Neural Mechanisms of Startle Behavior. Edited by Eaton RC. New York, Plenum, 1984, pp 287–352

Davis M: Pharmacological and anatomical analysis of fear conditioning using the fear-potentiated startle paradigm. Behav Neurosci 100:814–824, 1986

Davis M, Svensson TH, Aghajanian GK: Effects of D- and L-amphetamine on habituation and sensitization of the acoustic startle response in rats. Psychopharmacologia 43:1–11, 1975

Davis M, Cedarbaum JM, Aghajanian GK, et al: Effects of clonidine on habituation and sensitization of acoustic startle in normal, decerebrate, and locus coeruleus lesioned rats. Psychopharmacology (Berlin) 51:243–253, 1977

Davis M, Redmond DE Jr, Baraban JM: Noradrenergic agonists and antagonists: effects on conditioned fear as measured by the potentiated startle paradigm. Psychopharmacology (Berlin) 65:111–118, 1979

Davis M, Astrachan DI, Kass E: Excitatory and inhibitory effects of serotonin on sensorimotor reactivity measured with acoustic startle. Science 209:521–523, 1980

Davis M, Kehne JH, Commissaris RL, et al: Effects of hallucinogens on unconditioned behaviors, in Hallucinogens: Neurochemical, Behavioral and Clinical Perspectives. Edited by Jacobs BL. New York, Raven, 1984, pp 35–75

Davis M, Cassella JV, Wrean WH, et al: Serotonin receptor subtype agonists: differential effects on sensorimotor reactivity measured with acoustic startle. Psychopharmacol Bull 22:837–843, 1986

Geyer MA, Tapson GS: Habituation of tactile startle is altered by drugs acting on serotonin-2 receptors. Neuropsychopharmacology 1:135–147, 1988

Geyer MA, Warbritton JD, Menkes DB, et al: Opposite effects of intraventricular serotonin and bufotenin on rat startle responses. Pharmacol Biochem Behav 3:687–691, 1975

Geyer MA, Puerto A, Menkes DB, et al: Behavioral studies following lesions of the mesolimbic and mesostriatal serotonergic pathways. Brain Res 106:256–270, 1976

Geyer MA, Petersen LR, Rose GJ: Effects of serotonergic lesions on investigatory responding by rats in a holeboard. Behav Neural Biol 30:160–177, 1980

Glanzman DL, Mackey SL, Hawkins RD, et al: Depletion of serotonin in the nervous system of aplysia reduces the behavioral enhancement of gill withdrawal as well as the heterosynaptic facilitation produced by tail shock. J Neurosci 9:4200–4213, 1989

Glanzman DL, Kandel ER, Schacher S: Target-dependent structural changes accompanying long-term synaptic facilitation in aplysia neurons. Science 249:799–802, 1990

Graham FK: The more or less startling effects of weak prestimuli. Psychophysiology 12:238–248, 1975

Graham F: Distinguishing among orienting, defense, and startle reflexes, in The Orienting Reflex in Humans: An International Conference Sponsored by the Scientific Affairs Division of the North Atlantic Treaty Organization. Edited by Kimmel H, van Olst E, Orlebeke J. Hillsdale, NJ, Lawrence Erlbaum, 1979, pp 137–167

Groves PM, Thompson RF: A dual process theory. Psychol Rev 77:419–450, 1970

Hitchcock J, Davis M: Lesions of the amygdala, but not of the cerebellum or red nucleus, block conditioned fear as measured with the potentiated startle paradigm. Behav Neurosci 100:11–22, 1986

Hoffman HS, Ison JR: Reflex modification in the domain of startle, I: some empirical findings and the implications for how the nervous system processes sensory input. Psychol Rev 87:175–189, 1980

Jacobson E: Response to a sudden unexpected stimulus. J Exp Psychol 9:19–25, 1926

Kehne JH, Davis M: Central noradrenergic involvement in yohimbine excitation of acoustic startle: effects of DSP4 and 6-OHDA. Brain Res 330:31–41, 1985

Kolb L: The post-traumatic stress disorders of combat: a subgroup with a conditioned emotional response. Milit Med 149:237–243, 1984

Korn H, Triller A, Mallet A, et al: Fluctuating responses at a central synapse: N of binomial fit predicts number of stained presynaptic boutons. Science 213:898–901, 1981

Landis C, Hunt WA (eds): The Startle Pattern. New York, Farrar and Rinehart, 1939

Mackey SL, Kandel ER, Hawkins RD: Identified serotonergic neurons LCB1 and RCB1 in the cerebral ganglia of aplysia produce presynaptic facilitation of siphon sensory neurons. J Neurosci 9:4227–4235, 1989

Malloy P, Fairbank J, Keane T: Validation of a multimethod assessment of posttraumatic stress disorders in Vietnam veterans. J Consult Clin Psychol 51:488–494, 1983

Mansbach RS, Geyer MA: Blockade of potentiated startle responding in rats by 5-hydroxytryptamine$_{1A}$ receptor ligands. Eur J Pharmacol 156:375–383, 1988

Melia KR, Davis M: Differential effects of selective dopamine agonists and antagonists on startle elicited electrically from the brainstem. Society for Neuroscience Abstracts 14:849, 1988

Miserendino MJ, Sananes CB, Melia KR, et al: Blocking of acquisition but not expression of conditioned fear-potentiated startle by NMDA antagonists in the amygdala. Nature 345:716–718, 1990

Ornitz EM, Pynoos RS: Startle modulation in children with posttraumatic stress disorder. Am J Psychiatry 146:866–871, 1989

Ornitz EM, Guthrie D, Kaplan A, et al: Maturation of startle modulation. Psychophysiology 23:624–634, 1986

Pitman R, Orr S, Forgue D, et al: Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. Arch Gen Psychiatry 44:970–975, 1987

Swerdlow NR, Braff DL, Geyer MA, et al: Central dopamine hyperactivity in rats mimics abnormal sensory gating of the acoustic startle response in schizophrenics. Biol Psychiatry 21:23–33, 1986

Swerdlow NR, Mansbach RS, Geyer MA, et al: Amphetamine disruption of prepulse inhibition of acoustic startle is reversed by nucleus accumbens denervation. Psychopharmacology (Berlin) 100:413–416, 1990

Vrana SR, Spence EL, Lang PJ: The startle probe response: a new measure of emotion? J Abnorm Psychol 97:487–491, 1988

Wilkins DE, Hallett M, Wess MM: Audiogenic startle reflex of man and its relationship to startle syndromes. Brain 109:561–573, 1986

Chapter 15

Use of Tricyclics and Monoamine Oxidase Inhibitors in the Treatment PTSD: A Quantitative Revie

Steven M. Southwick, M.D.
Rachel Yehuda, Ph.D.
Earl L. Giller, Jr., M.D., Ph.D.
Dennis S. Charney, M.D.

Posttraumatic stress disorder (PTSD) has a lifetime
lence of 1% in the general population (Helzer et a
and a 15% prevalence among Vietnam combat veterans (
al. 1990). Yet, study of the rational use of psychotropic ag
the treatment of PTSD is in its infancy. Although many d
pharmacological agents have been tried, no one drug of c
pharmacological treatment strategy has yet emerged. T
commonly used medications for the treatment of PTSD a
depressants. However, results of treatment outcome ha
varied across published reports. Clearly, antidepressants
"curative" in PTSD, and they do not appear to treat all as
the disorder.

Nonetheless, by nearly all reports, antidepressants do
to have some beneficial effects in the treatment of patien
PTSD. However, the extent to which these drugs affe

Support of this work was provided in part by Veterans Administrati
Award to SMS and National Institute of Mental Health Postdoctoral-
Grant 5-T32-MH17122 to RY.