# 5

# Animal Models of Anxiety Vulnerability - The Wistar Kyoto Rat

X. Jiao[1], K.D. Beck[1,2,3], K.C.H. Pang[1,2,3] and R.J. Servatius[1,2,3]
[1]*Stress and Motivated Behavior Institute*
[2]*GSBS, NJMS-UMDNJ, Newark, NJ;*
[3]*Neurobehavioral Research Laboratory (129),*
*VANJHCS, East Orange, NJ,*
*U.S.A.*

## 1. Introduction

### 1.1 Anxiety

Anxiety disorders are the most common psychiatric disorders with a worldwide lifetime prevalence of 16-29% (Kessler *et al.*, 2005; Somers *et al.*, 2006). People with anxiety disorders are likely to suffer from depression and drug (or alcohol) abuse in an effort to gain relief from their symptoms, therefore, eliciting secondary disorders (Kessler *et al.*, 2005). Although each subtype (i.e. generalized anxiety disorder, obsessive-compulsive disorder (OCD), panic disorder, post traumatic stress disorder (PTSD) and social phobia) has unique features, the core symptom of all anxiety disorders is excessive avoidance. The etiology of anxiety disorders remains elusive (the presumed role of trauma in PTSD notwithstanding). What is abundantly clear is anxiety disorders arise as a complex interaction of genetic, epigenetic, sociocultural factors with life experiences; that is, anxiety disorders are best explained with diathesis models (Kendler *et al.*, 2002; Mineka and Zinbarg, 2006; Zinbarg and Barlow, 1996).

Among a variety of neurobiological and neurobehavioral factors representing a source of risk for anxiety disorders, inhibited temperament is consistently linked to anxiety disorders (Biederman *et al.*, 1993; Fox *et al.*, 2005a; Hirshfeld *et al.*, 1992; Hirshfeld-Becker *et al.*, 2007; Kagan *et al.*, 1987; Rosenbaum *et al.*, 1993; Smoller *et al.*, 2003). Behavioral inhibition is characterized as extreme withdrawal in the face of social and nonsocial challenges (Fox *et al.*, 2005b; Kagan *et al.*, 1989; Rosenbaum *et al.*, 1991). Those with inhibited temperament exhibit excessive physiological reactivity to environmental challenges (Kalin *et al.*, 2000; Kalin and Shelton, 2003; Keltikangas-Jarvinen *et al.*, 1999; Perez-Edgar *et al.*, 2007; Schwartz *et al.*, 2003; Smoller *et al.*, 2005; Tyrka *et al.*, 2006; Tyrka *et al.*, 2008).

Although there is support for temperament as a risk factor, the translation of risk to actualized disorder is unclear. Acquisition, expression and retention of avoidance may be the final common pathway to anxiety disorders. The particularly debilitating feature of avoidance is that, left untreated, avoidance increases over time and leads to a worsening of symptoms. Avoidance acquisition is more apparent in PTSD; the growth of avoidance traces the full expression of PTSD (Karamustafalioglu *et al.*, 2006; Kashdan *et al.*, 2006; North *et al.*, 2004; O'donnell *et al.*, 2006a). Given this prominent position, avoidance learning may represent an endophenotype for anxiety disorders (Gould and Gottesman, 2006).

Here, we present the case for inbred WKY rats to serve as a model for risk of anxiety disorders. Evidence is presented for the concordance of neurobehavioral, neuroendocrine, and neurochemical features to that observed in humans at risk for expressing an anxiety disorder. Particular emphasis is placed on enhanced avoidance acquisition and resistance to extinction as an endophenotype for vulnerability to anxiety disorders. Implications for treatment and efficacy are discussed.

## 2. Putative animal model for vulnerability to anxiety disorders - The WKY rat

The Wistar Kyoto (WKY) rat strain was first developed as a normotensive control strain for the spontaneously hypertensive rat (SHR) strain derived from the Wistar (WIS) rat (Okamoto and Aoki, 1963). Unlike its parent strain WIS rat, the WKY rat exhibits many unique behavioral characteristics differing from an out-bred rat strain. The most significant features are behavioral withdrawal, propensity to avoid, hyper-responsiveness to stress and hypervigilance (Drolet *et al.*, 2002; Lemos *et al.*, 2011; McAuley *et al.*, 2009; Pare, 1992a; Pare, 1989b; Pare, 1992b; Pare, 1993; Solberg *et al.*, 2001).

### 2.1 Temperament: Behavioral inhibition

The WKY rat displays features of inhibited temperament in a variety of situations (Braw *et al.*, 2008; Ferguson and Cada, 2004; Malkesman *et al.*, 2005; Pare, 1992b; Pare, 1994; Pare, 1996; Pare *et al.*, 2001; Servatius *et al.*, 1998; Tejani-Butt *et al.*, 2003). For example, Figure 1 depicts activity in the open field test comparing WKY rats to outbred SD rats. Upon placement into the center of the open field (which is brightly lit), the WKY rat remains immobile for a period of time; the latency to leave the center segment is often 2-3 times as long as exhibited by outbred strains (Drolet *et al.*, 2002; Ferguson and Cada, 2003; Nosek *et al.*, 2008). This reluctance to leave the center segment is followed by slow deliberate exploration. However, activity will generally increase over several minutes. Hypolocomotion is not

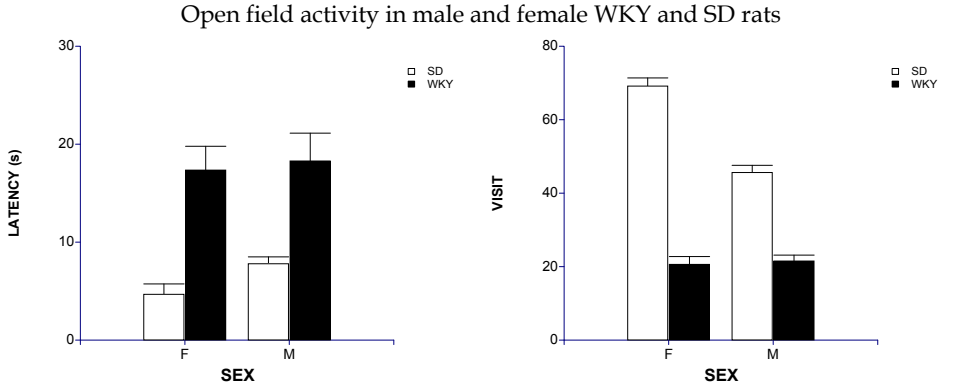



Fig. 1. Both female and male WKY rats display longer latencies to leave the center segment and overall lower numbers of segments crossed in a 2-min open field test. These data represent several studies (male: N = 60/strain; female: N=25/strain) and are obtained as the initial assessment of phenotype two weeks after delivery from breeders.

secondary to a motoric disturbance, in that WKY rats exhibit normal motor activity in a running wheel (Ferguson and Cada, 2003), a rotarod (Ferguson *et al.*, 2003b) and a turning wheel avoidance task (Pare, 1992a). Together, these data suggest that the lack of movement is not physical, but psychological. Moreover, inhibited temperament is displayed by both female and male WKY rats compared to their outbred counterparts.

Inhibited temperament extends to more explicit nonsocial and social threats. In terms of social interactions, WKY rats generally exhibit normal play behaviors with conspecifics (Braw *et al.*, 2006; Malkesman *et al.*, 2006b), but reductions in play and more subordinate-type behaviors when faced with outbred rats (Ferguson and Cada, 2004). In response to an electrified probe, normal rats bury the probe; WKY rats simply freeze (Ahmadiyeh *et al.*, 2005; Carr and Lucki, 2010; Gutiérrez-Mariscal *et al.*, 2008; Pare, 1994). Thus, WKY rats represent an animal model of behavioral withdrawal in the face of social and non-social challenges.

### 2.2 Anxiety signs and symptoms

As stated earlier, the core feature of anxiety disorders is avoidance. There are a variety of expressions of avoidance; however, all will have a common process of acquisition and resistance to extinction. In addition to avoidance as a learned response, common features of anxiety disorders are altered arousal, social interaction, communication, attention, learning and memory. Still, each anxiety disorder has distinct features. Thus, endophenotypes may relate to the core features of avoidance learning, common characteristics (e.g., heighten arousal), or disorder-specific features (e.g., compulsions). Accordingly, behavioral assessments may be sensitive to a particular aspect or a general process concordant with anxiety.

#### 2.2.1 Arousal

Arousal has two general aspects, the basal or undisturbed state and the relative magnitude of response to challenges. Moreover, arousal may be indexed through neuroendocrine or neurobehavioral measures. For each, the WKY has documented abnormalities.

Neuroendocrine and neurochemical. Within the hypothalamic-pituitary-adrenal axis (HPAA), levels of corticosterone (CORT) and adrenocorticotropic hormone (ACTH) are measured to evaluate arousal levels as affected by circadian rhythms and stress (Ottenweller *et al.*, 1994). WKY rats has been proposed as a model of stress vulnerability, exhibiting exaggerated HPAA responses to stress regimens compared to common rat strains (Pare *et al.*, 1999b; Pare and Kluczynski, 1997; Pare and Redei, 1993b; Redei *et al.*, 1994). Basal peripheral ACTH and CORT levels are generally higher in WKY rats and remained significantly higher after the diurnal peak as compared to WIS rats (Solberg *et al.*, 2001). Moreover, WKY rats exhibit a sustained CORT response to acute stress and an enhanced plasma ACTH response to various stressors (De La Garza II and Mahoney III, 2004; Malkesman *et al.*, 2006a; Pare and Redei, 1993a; Rittenhouse *et al.*, 2002). Others reported that CRH content and mRNA binding are not different in WKY rats relative to other strains suggesting that a defective negative feedback system may contribute to hyperresponsive HPAA in WKY rats (Gomez *et al.*, 1996; Redei *et al.*, 1994). Together, neuroendocrine evidence suggests that WKY rats are inherently hyperresponsive to stress. Exaggerated HPAA activity is reminiscent of inhibited temperament (Smoller *et al.*, 2003; Smoller *et al.*, 2005).

In general the neurochemical profile of the WKY rat is aberrant compared to outbred rats. WKY rats have inherently low butyrylcholinesterase level (Figure 2) and activity (Servatius *et al*., 1998), leading to greater sensitivity to cholinomimetics (Beck *et al*., 2001). Among the neurotransmitters, WKY rats have altered levels of monoamines, namely norepinephrine (NE), dopamine (DA) and serotonin (5-HT), and their metabolites as compared to out-bred strains with a high degree of specificity in various regions (De La Garza II and Mahoney III, 2004; Ferguson *et al*., 2003a; Pardon *et al*., 2003; Scholl *et al*., 2010). Moreover, these monoamine systems show greater responsiveness in the face of acute stress (Pardon *et al*., 2002; Pardon *et al*., 2000) and chronic stress (Pardon *et al*., 2003). We will discuss this point in a later section (section 5).

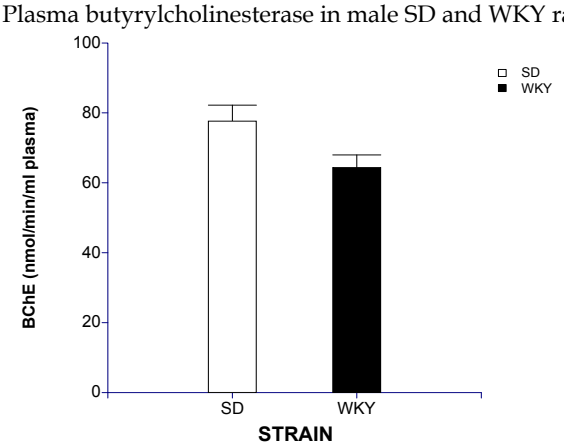
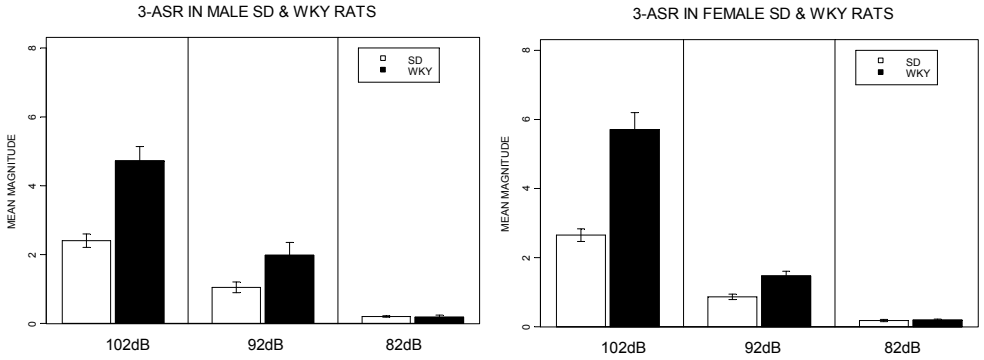



Fig. 2. WKY rats exhibit significant lower level of butyrylcholinesterase compared to SD rats. (n=19-20/strain, $p<.05$)

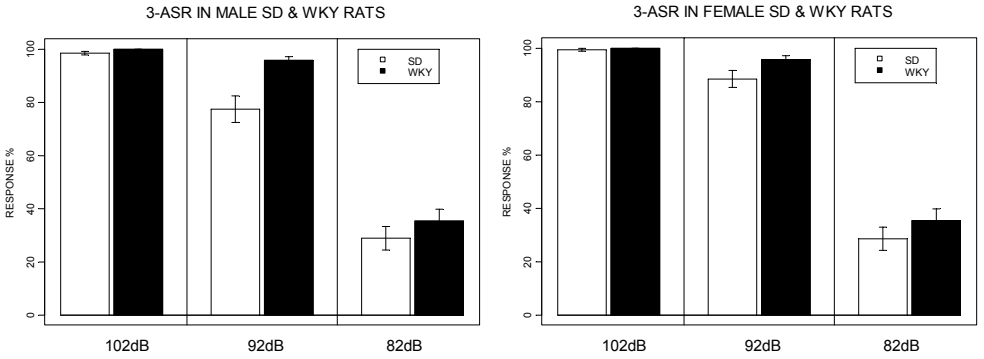
Neurobehavioral. The acoustic startle response (ASR) is a simple reflex used to index arousal and vigilance in mammals (Ardekani *et al*., 1989). The ASR can be used to reveal differences in sensitivity (threshold to elicit a reflex response), responsivity (the magnitude of response), latency, as well as nonassociative processes of habituation, dishabituation and sensitization.

We and others demonstrated that WKY rats made larger startle responses to a white noise within a wide range (92dB to 120dB) as compared to other inbred and outbred rat strains (Glowa and Hansen, 1994; McAuley *et al*., 2009; Servatius *et al*., 1998). Of 45 inbred and outbred rat strains including SD rats, male WKY rats exhibited the highest ASR magnitude when exposed to 8 trials of 110dB white noise (Glowa and Hansen, 1994). We found that WKY rats exhibited significantly higher startle responsivity at 92 and 102dB white noise after correction for each subject's body weight (Figure 3a). In addition to greater startle responsivity, male WKY showed higher sensitivity compared to male SD rats, measured by a multi-intensity startle test (3-ASR) (Figure 3b). Although both male and female WKY exhibit substantially higher ASRs compared to SD rats, only male rats demonstrate habituation when single intensity startle test (1-ASR) was used (Figure 4). Yet others reported that WKY show similar or lower ASR magnitude compared to SD rats (Buuse,

2004; Palmer *et al.*, 2000). We reasoned the inconsistency may be due to variant procedures used and whether subjects' body weight was factored into the startle response.




(3a) Startle responsivity in male and female SD and WKY rats.




(3b) Startle sensitivity in male and female SD and WKY rats

Fig. 3. WKY rats display higher startle magnitude compared to the same sex outbred SD rats regardless of sex (n=12-17/strain/sex) (a). WKY rats of both sexes also exhibited greater sensitivity to respond, responding more to acoustic stimuli of moderate intensity (b).

WKY rats exhibited exaggerated stress response and elevated arousal following stress stimulation. Stress has been described as one of the key risk factors of anxiety disorders (Chantarujikapong *et al.*, 2001; Grillon *et al.*, 2007b; Mineka and Zinbarg, 1996). As described in previous literatures, WKY rats are behaviorally hyperresponsive to stress with the stress-induced exaggerated HPAA response (Redei *et al.*, 1994; Solberg *et al.*, 2001). Inasmuch as the basal behavioral state of WKY is abnormal, assessing the impact of stress on behavioral reactivity has been problematic. For example, assessing freezing to context or to cues is difficult given the propensity to freeze in novel situations. However, prior acute stress have been noted to increase freezing behavior and reduce activity in the OFT and elevated plus maze in WKYs (Nosek *et al.*, 2008). When challenged in the forced swim test (FST), the WKY rat predominantly exhibits floating behavior and fewer struggling responses compared to other strains. The lack of struggling has been interpreted as 'behavioral despair', a sign of depression-like behavior in rodents (Malkesman and Weller, 2009; Pare, 1992a; Pare and

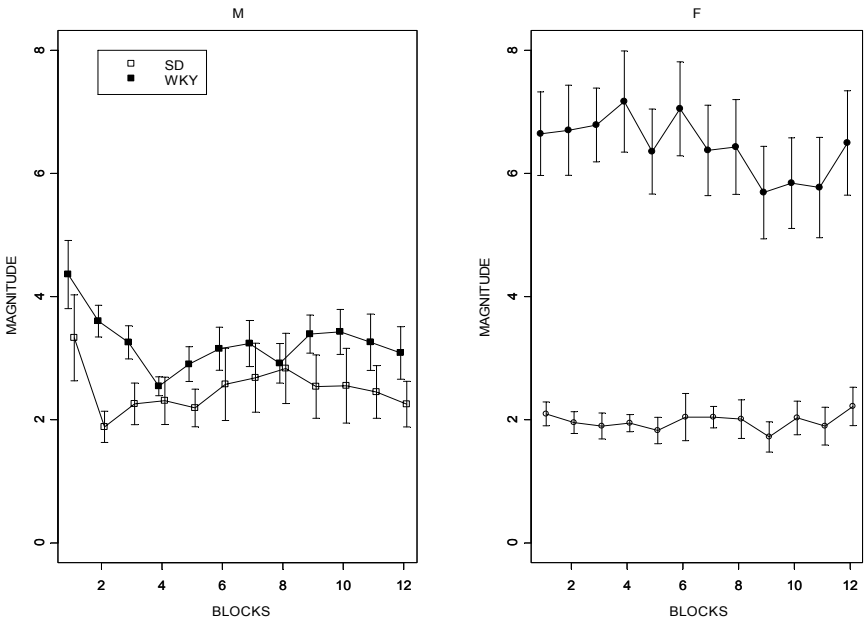



Fig. 4. Habituation of acoustic startle responses in WKY and SD rats: nonassociative processes. Although WKY rats generally display larger ASRs than SD rats, habituation appears normal (n=8/strain/sex).

Redei, 1993a). The heightened stress reactivity is most clearly evident in the enhanced susceptibility to develop stress-induced ulcers in WKY rats compared to outbred strains (Pare, 1989a; Pare, 1989c; Pare and Schimmel, 1986). Pretreatment with drugs that elevate central monoamines reduce the severity of ulceration (Pare *et al.*, 1999a; Tejani-Butt *et al.*, 2003). Evidence from elevated arousal or exaggerated stress response in WKY rats may provide insight to the alterations in the CNS neurochemistry that may be responsible for anxiety. The effects of stress are discussed in the following sections in more detail.

### 2.2.2 Sleep disturbances

Sleeping disruption is one of the major symptoms of anxiety disorder and a hallmark of PTSD (Ross et al., 1989). WKY rats exhibit altered sleep-wake cycle and longer rapid eye movement sleep (REMS) episodes compared to other strains (Dugovic et al., 2000). REMS fragmentation was significantly altered following stress in WKY rats compared to control strain (DaSilva *et al.*, 2011; Dugovic *et al.*, 2000; Laitman *et al.*). Altered sleep patterns may also preexist as a vulnerability to anxiety, that are further disturbed after exposure to psychological distress.

### 2.2.3 Avoidance

As the core symptom of all anxiety disorders, avoidance behavior differs between patients with anxiety disorder and normal population (Foa *et al.*, 2006; O'Donnell *et al.*, 2006b). In

humans avoidance is characterized in the form of emotions, ideations, and behaviors. In animal models, avoidance is characterized as passive (withholding a likely response to avoid aversive stimulation) and active (performing a target response to prevent aversive stimulation). Early work showed WKY rats exhibit superior acquisition in passive avoidance tasks compared to SD or WIS rats (Pare 1993; Pare 1996). Given that being immobile/freezing is the dominant coping strategy for WKY rats, superior acquisition of passive avoidance is not a surprise. However, when tested with a wheel-turning avoidance task, WKY performed equally well compared to WIS rat (Pare, 1992a). In contrast, Berger and Starzec found that WKY rats performed poorly in lever-press avoidance task compared to SHR rats (Berger and Starzec, 1988). As an arbitrary target response, a leverpress is not among the species specific defense reactions (Bolles, 1970). We reasoned that the inconsistency between studies and laboratories may due to the procedure applied, the nature of the test and the reference strain to which WKYs were compared.

In our institute, we utilized a signalled lever-press avoidance paradigm to study anxiety and its vulnerability in rats. It is known that anxiety is a disorder that develops over a period of time, so is the avoidance. Thus, a lever-press avoidance learning model allows the acquisition of avoidance to develop over an extended period of time, mimicking the developmental process of anxiety in humans. Our data indicated that the learning of WKY rats is superior in the lever-press avoidance task compared to a noninhibited reference strain, the SD rat (Beck et al., 2010; Jiao et al., 2011; Servatius et al., 2008). The superior active avoidance performance of WKY rats is in stark contrast to other rat strains with features of trait behavioral inhibition such as the Maudsley High Reactive (Blizard and Adams, 2002), which are generally poor in active avoidance. Moreover, rats bred for superior active avoidance are typically the least behaviorally inhibited (Syracuse high avoiders, Roman high avoiders and Australian high avoiders) (Aguilar *et al.*, 2004; Brush, 2003; Driscoll, 1986; Overstreet *et al.*, 1990; Overstreet *et al.*, 1992).

Over the past several years we have amassed a substantial database concerning the avoidance performance of WKY rats. For one, the avoidance performance of WKY rats reaches asymptotic levels that approach unity; that is, once acquired WKY rats typically exhibit near perfect avoidance (Figure 5.). That perfect avoidance begins with the first trial of a session. Outbred rats display a typical pattern of avoidance performance in which each session begins with escape responses, although avoidance was expressed at the end of the previous session (i.e., warm up) (Hineline, 1978a; Hineline, 1978b). WKY rats generally do not exhibit warm up as acquisition progresses. This near perfect expression of avoidance resembles human avoidance. Facilitated avoidance acquisition is apparent in both female and male rats compared to their respective outbred counterparts. The near perfect avoidance behavior also insulates the rat from experiencing changes in shock contingencies. Accordingly, WKYs display perseveration of avoidance responding in the absence of shock, but continued presence of the explicit safety signal (Servatius *et al.*, 2008). Perseveration/resistance to extinction has been implicated in neuropathology of anxiety (Barad, 2005; Myers and Davis, 2002).

WKY rats also display another interesting and potentially clinically-relevant feature. Each training session begins with a 60-s stimulus free period prior to the first warning signal. As WKY rats acquire avoidance they emit bar presses, which are not reinforced, during this period (Figure 6.). This pattern of response is only exhibited prior to the first trial; nonreinforced responses are rarely displayed on subsequent trials. These nonreinforced

responses may be akin to worry (Mineka, 2004), accompanying avoidance acquisition only in those at risk.

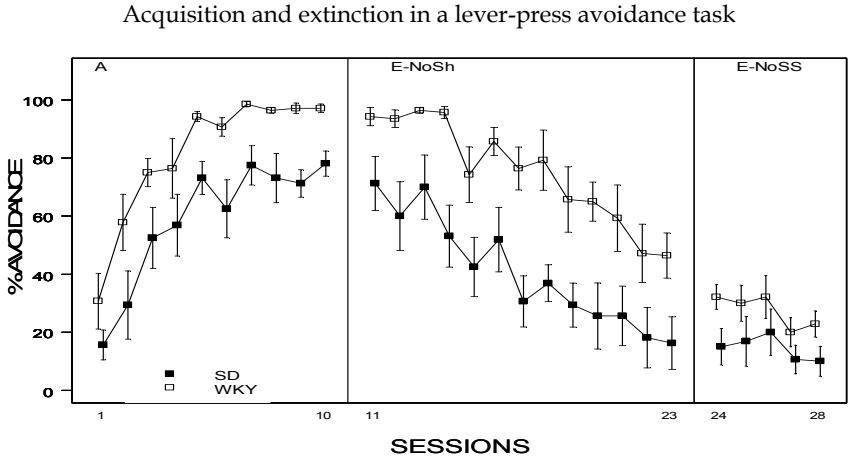



Fig. 5. Avoidance responses made during acquisition and extinction in WKY and SD rats. WKY rats acquired lever-press avoidance faster and to a higher degree (sessions 1-10). However, WKY rats extinguished slower during early extinction phase while the transition between acquisition and extinction was more significant in SD rats (sessions 11-23, shock-off, safety signal on; sessions 24-28, shock-off, safety signal off). (N=8/strain)

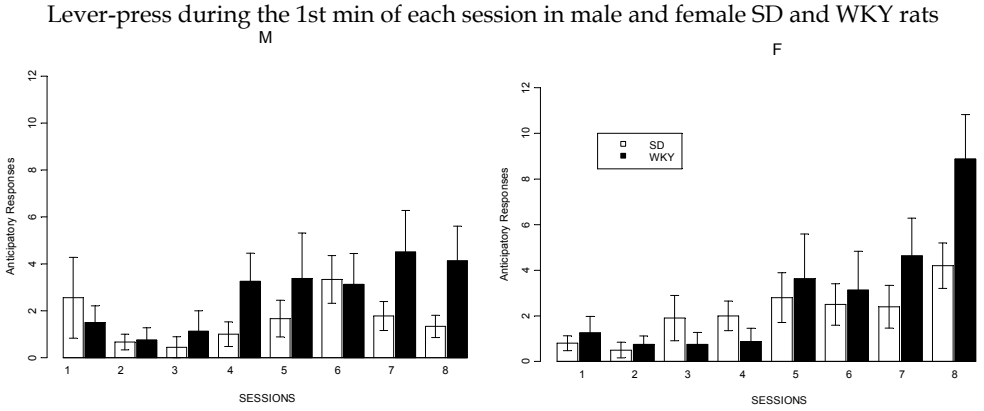



Fig. 6. WKY rats emitted more anticipatory lever-presses during the initial minute of each session during acquisition. (N=8-10/strain/sex)

On the other hand, stress intensity is often cited as a contributing factor in the development of anxiety disorders (Braunstein-Bercovitz *et al.*, 2001; Foa *et al.*, 2006; Grillon *et al.*, 2007b; Grillon *et al.*, 2007a; Mineka and Zinbarg, 1996; Silver *et al.*, 2002). Given the relationship between anxiety disorders and avoidance, one expects stress to accelerate avoidance acquisition, raise the asymptotic levels, or affect extinction. The results from a recent study

suggest that stressor intensity only affects extinction. Training with a greater shock intensity than our standard, did not affect the acquisition curves of either SD or WKY rats (Figure 7.) (Jiao *et al.*, 2011). Of course, there is little room to enhance asymptotic performance of WKY rats, but the rate to reach this level could differ. However, WKY rats trained with higher intensity shock exhibited perseveration of avoidance response during extinction compared to WKY rats trained with the lower intensity shock; extinction curves of SD rats resembled WKY rats trained with a lower intensity.

A long standing discrepancy between the basic science literature and clinical descriptions concerns the relationship between avoidance acquisition and arousal. In rats, arousal decreases as avoidance is acquired (Coover *et al.*, 1973). However, arousal is sustained in humans with anxiety disorders and who are employing avoidance. Therefore, we assessed ASRs prior to avoidance acquisition and toward the end of acquisition training. Whereas the ASRs of SD rats are virtually unchanged between the measures, the ASRs of WKY rats *increase* (Figure 8.). The increase is evident at a period of training in which WKY rarely, if at all, experience shock. This increase is beyond the basal exaggerations normally noted between strains. There is emerging data that exaggerated ASRs in PTSD may be increases beyond preexisting ASR differences; that is, exaggerated ASRs are an amplification of a preexisting condition (Guthrie and Bryant, 2005). These data suggest that exaggerated ASRs are an interaction of subject vulnerabilities and avoidance acquisition.

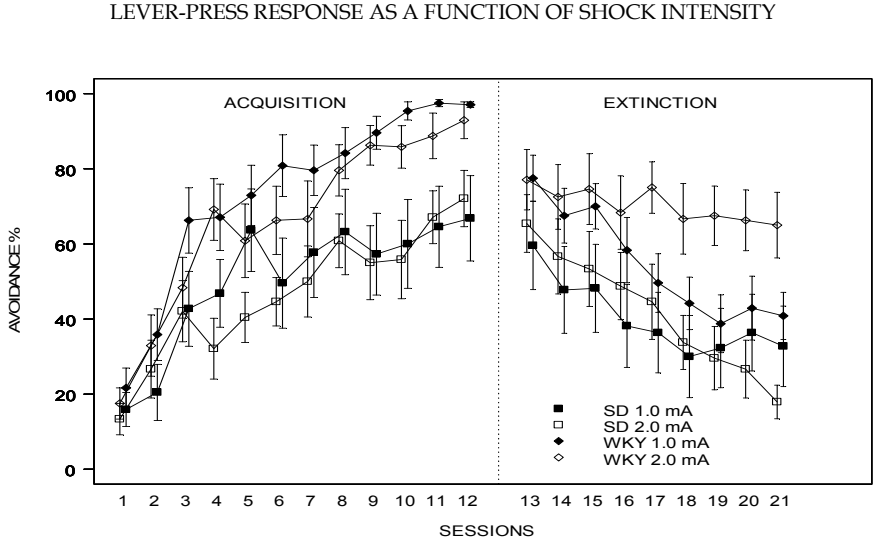



Fig. 7. WKY rats acquired lever-press avoidance faster and to a higher degree regardless of shock intensity. However, WKY rats trained with 2.0-mA foot-shock resisted extinction while the transition between acquisition and extinction was more significant in all SD rats and WKY rats trained with 1.0-mA foot-shock (Jiao *et al.*, 2011).

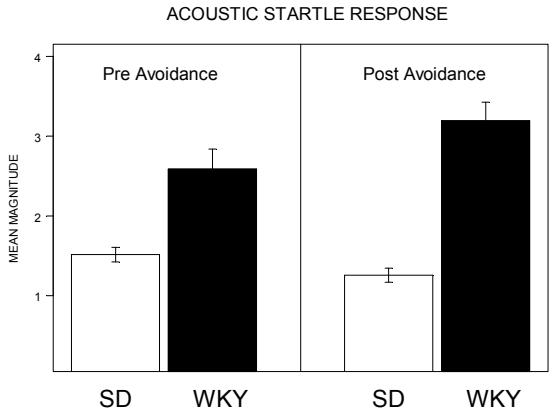



Fig. 8. WKY and SD rats were tested for 1-ASR before and after 10 sessions of avoidance acquisition. In both tests, WKY startled with a higher magnitude than SD rats. WKY rats exhibited elevated startle response following acquisition training while SD showed similar startle magnitude in both tests. (N=24/strain; strain difference, $p<.05$; test difference, $p<.05$)

## 3. Genetic components

Genetic components (trait vulnerability) play an important role in various psychiatric disorders, including anxiety disorders. Quantitative trait loci (QTL) analysis indicated that common loci, which influence certain behavioral characteristics tested by OFT and defensive bury test in rats, may represent genetic factors contributing to anxiety and depression (Ahmadiyeh *et al.*, 2005; Boyle and Gill, 2001; Cloninger *et al.*, 1998; Henderson *et al.*, 2000; Solberg *et al.*, 2004). Several QTL (*Imm 1* D2Rat188, *Imm3* D5Rat40, *Imm6* D16Arb5, *Climb2* D1Rat147, *FST1* D16Rat75) were identified for climbing, immobility and swimming in WKY rats, sharing common target regions with susceptibility loci mapped by genome scan analyses for emotionality QTL in rodents and human genetic linkage to emotional disorder (Solberg *et al.*, 2004). Significance of microarray analysis (SAM) revealed that expression of 66 genes was increased in the locus coeruleus (LC) of WKY compared to SD rats (Pearson *et al.*, 2006), including genes that encoded for enzymes involved in NE turnover. Moreover, the mRNA of catechol-O-methyltransferase *(COMT)*, a key enzyme in the catabolism of catecholamines, was found at levels four- to sevenfold higher in the cerebral cortex in WKYs than SDs (Walker *et al.*, 2004). Thus, this rat strain may be genetically predisposed to psychiatric disorders that are linked to altered monoaminergic system.

## 4. Brain anatomy and neuronal activity

Converging data from structural and functional magnetic resonance imaging (MRI) studies suggest that differential patterns of anatomical brain abnormalities appear to be involved in mood and anxiety disorders (Brambilla *et al.*, 2002; Lind *et al.*, 2006; Milad *et al.*; Ohara *et al.*, 2004). Abnormalities were found in orbital frontal lobe, basal ganglia, temporal lobe and hippocampus in patients with various subtypes of anxiety (Brambilla *et al.*, 2002; Bystritsky *et al.*, 2001; McEwen, 2005). Moreover, imaging data from humans suggest that medial prefrontal cortex, amygdala, thalamus and periaquaductal gray are involved in avoidance

acquisition (Mobbs *et al*., 2007; Samanez-Larkin *et al*., 2008; Simmons *et al*., 2006; Straube *et al*., 2009; Suslow *et al*., 2009). However, the neurocircuitry underlying avoidance extinction and its perseveration in anxiety states is largely a matter of speculation. Mainly supported by fear extinction studies, mPFC plays a key role in both humans and experimental animals (rodents). Anxiety patients exhibit reduced activity of the anterior cingulate cortex and thalamus during episodes of re-experiencing (Hopper *et al*., 2007; Lanius *et al*., 2003), leading to a suggestion that reduced cortical influence on structures such as the amygdala may explain the resistance to extinction. Reduced cortical influence on the amygdala is also presumed to underlie the persistent expression of heightened arousal (e.g., increased acoustic startle) observed in PTSD patients (Nutt and Malizia, 2004).

The knowledge of anatomical difference between WKY and other rats is quite limited. A recent volumetric study evaluated hippocampus in female rats in which the hippocampal volume of WKY rats is 20% less than that of WIS rats (Lemos *et al*., 2011). On the other hand, alterations in neuronal activation are demonstrated in the expression of c-Fos or brain derived neurotrophic factor (BDNF) in various brain regions in WKY rats compared to out-bred rat strains (Ma and Morilak, 2004; O'Mahony *et al*., 2011). We recently reported that the c-Fos immunoreactivity is lower in the medial prefrontal cortex in the WKY rat than the SD rat at the end of extinction of a lever-press avoidance task, whereas a reduced GABAergic activation was found in basal amygdala in the WKY rat trained with higher shock intensity (Jiao *et al*., 2011).

However, the structures that are critical for acquisition and extinction of lever press avoidance are relatively unknown. In our initial work, we assessed c-Fos immunoreactivity in various regions in the SD rat at multiple time points within the phases of acquisition and extinction. Our results indicated that there is a trend of increased c-Fos expression in the prefrontal regions as extinction starts and proceeds. Interestingly, a similar pattern was observed in the lateral and basolateral amygdala where a reduced activity was expected during extinction. A further analysis targeting GABAergic neuron revealed that GABAergic activation arises during the extinction phase. An elevated GABAergic activation (detected by the double staining for c-Fos and parvalbumin (PV, a calcium binding protein that is expressed in 50-60% amygdalar GABAergic neurons (Kemppainen and Pitkanen, 2000)) in the basolateral and lateral amygdala would reduce the excitatory output from the amygdala as GABA neurons in the basolateral amygdala are mainly interneurons that make synaptic contact on projection neurons (Rosenkranz and Grace, 2001). Thus an elevated GABAergic activity may be responsible for the increased neuronal activation during extinction phase in the basolateral amygdala. However, this assumption needs further investigation since parvalbumin positive neurons represent 50-60% of GABAergic neurons in the basolateral amygdala (Kemppainen and Pitkanen, 2000). We do not as yet know whether these neuronal alterations are present or different in WKY rats.

From a different perspective, enhanced avoidance learning may be secondary to deficits in neurotrophins. Converging data supports the role of neurotrophins in mood disorders; one of the latest theories of the neuropathology of anxiety and depression disorders (Chen *et al*., 2006; Martinowich *et al*., 2007). For example, low levels of the brain derived neurotrophic factor (BDNF) are found in stress-related disorders in humans (Duman and Monteggia, 2006). In general, lower BDNF is related to anxiety and depression disorders that are not responsive to serotonergic antidepressant treatment (Duman, 2004; Kalueff *et al*., 2006). Consistent with this perspective, a recent study illustrated that BDNF levels are significantly lower in the CA3 of hippocampus in WKY rats compared to SD rats (Malkesman *et al*., 2009).

## 5. Potential mechanisms in psychopharmacology

Alterations in neurochemistry in the CNS are implicated in various psychiatric disorders (i.e. depression, addiction and anxiety). Recent investigations targeting central neurochemical pathways have enhanced our understanding of anxiety disorders.

### 5.1 Serotonin (5-HT)

Evidence for the association of altered serotonergic activity in anxiety, that decreasing serotonergic function is anxiogenic and increasing it anxiolytic, is mostly supported by the use of selective serotonin reuptake inhibitors (SSRIs) in various sub-types of anxiety disorders (Bremner, 2006; Vaswani *et al.*, 2003). WKY rats showed significant lower basal 5-HT tissue level in limbic regions and cell body area compared to WIS or SD rats (De La Garza II and Mahoney III, 2004; Scholl *et al.*, 2010). Acute stress elicits an increased tissue level of 5-HT in the amygdala in WIS but not in WKY rats, it increased 5-HT turnover rate in the mPFC only in WKY rats (De La Garza II and Mahoney III, 2004). When exposed to chronic stress, WKY rats failed to show stress-induced reduction of 5-HT tissue level as SD rats did, whereas the turnover rate was increased in both WKY and SD rats (O'Mahony *et al.*, 2011). Previous studies showed increased binding of 5-$HT_{1a}$ receptors in hippocampus and hypothalamus, but decreased binding of 5-HT transporters in the cell body area in WKY rats following chronic stress, compared to SD rats (Pare and Tejani-Butt, 1996). However WKY rats are insensitive to serotonergic drugs (e.g. SSRIs and receptor agonists) in terms of activity in the EPM and OFT, immobility in the FST, or severity of gastric ulceration after stress (Chaouloff *et al.*, 1998; Griebel *et al.*, 1999; Lahmame and Armario, 1996; Lopez-Rubalcava and Lucki, 2000; Pare *et al.*, 2001; Tejani-Butt *et al.*, 2003), suggesting serotonergic manipulation may not affect the temperamental behaviors of these rats.

### 5.2 Dopamine (DA)

Converging literatures demonstrate that an aberrant DA circuitry is associated with anxiety disorders (Gendreau *et al.*, 1998; Hamner and Diamond, 1996; Mathew *et al.*, 1981; Taylor *et al.*, 1982).WKY rats exhibit altered dopaminergic function in various brain regions. DA levels in WKY rats do not differ between WIS or SD rats in most brain areas; DA turnover is higher in the nucleus accumbens shell in the WKY rat compared to the WIS rat (De La Garza II and Mahoney III, 2004; Ferguson *et al.*, 2003a; Scholl *et al.*, 2010). Receptor and transporter binding studies show that WKY rats have altered dopaminergic pathways compared to control strains. The results from those studies reveal a significant strain difference, with WKY rats exhibiting lower levels of D1 receptor binding in the caudate putamen and nucleus accumbens core, but higher binding levels in the substantia nigra pars reticulata compared to WIS rats (Novick *et al.*, 2008). D1 receptors in the substantia nigra are involved in mediating the startle response (Meloni and Davis, 1999), thus a higher D1 receptor level in this region may lead to heightened ASR magnitude in WKY rats. Results from a recent study demonstrated that WKY rats exhibited higher D2 receptor binding levels in the nucleus accumbens shell and ventral tegmental area, but lower D2 receptor binding in the caudate putamen, nucleus accumbens core and hypothalamus compared to WIS rats (Yaroslavsky *et al.*, 2006). It is known that the D1 and D2 receptors represent critical sites where DA acts to modify behavior related to anxiety and reward; the altered expression of this receptor in the WKY rat may be reflective of the anxiety susceptibility noted in this rat strain. Moreover, DA transporter binding levels were lower in the nucleus accumbens core,

amygdala and cell body regions (ventral tegmental area and substantia nigra), but higher in the hippocampus and hypothalamus compared to SD and WIS rats (Jiao *et al.*, 2003). The observed differences in the density and distribution of DAT sites in WKY rats may lead to altered modulation of synaptic DA levels in the cell body and mesolimbic regions, thereby contributing to the noted anxiety- and depression-like behaviors reported in this rat strain. This speculation was supported by a further study in which some of the alterations in DAT binding was reversed by chronic nomifensine (i.e. a dopamine transporter blocker) treatment (Jiao *et al.*, 2006). Moreover, after 8-12 days of nomifensine administration, WKY rats showed significantly increased head poke responses in the emergence test, reduced latency to leave the center in an open field and increased activity in the FST (Tejani-Butt *et al.*, 2003). Therefore, the WKY rat may represent a good model for a sub-type of anxiety disorder exhibiting imbalanced DA distribution in the CNS.

### 5.3 Norepinephrine (NE)

Defective noradrenergic function is one of the major mechanisms in the neuropathology of anxiety in human (Bremner *et al.*, 1996; Charney and Redmond, Jr., 1983; Hamner and Diamond, 1996; Neumeister *et al.*, 2005; Sullivan *et al.*, 1999). The WKY appears to have normal tissue levels of NE (De La Garza II and Mahoney III, 2004; O'Mahony *et al.*, 2011; Scholl *et al.*, 2010) and tyrosine hydroxylase (TH, the rate-limiting enzyme in NE synthesis) (Mann and Bell, 1991; Vachette *et al.*, 1993). In response to acute stress, noradrenergic reactivity appears to be blunted. For example, acute stress-induced increases of NE tissue levels in the lateral bed nucleus of the stria terminalis (BSTL) were significantly lower in WKY compared to SD rats (Pardon *et al.*, 2002; Pardon *et al.*, 2003). Moreover, the acute stress-induced increases in neuronal activity (cFos expression) in medial amygdala and locus ceruleus (LC) was lower in WKY rats compared to SD rats (Ma and Morilak, 2004). Alternatively, NE reactivity may be delayed. Acute stress-induced increases of TH mRNA level in WKY rats were apparent, but delayed by 2-hr in WKY rats compared to control strains (Pardon *et al.*, 2002; Sands *et al.*, 2000). Although reactivity to acute stress is blunted, chronic stress appears to sensitize NE in WKY rats. After chronic exposure to cold stress, increased BSTL NE release was induced by acute stress challenge only in WKY rats, but not in SD rats (Pardon *et al.*, 2003). Chronic stress decreases NE transporter binding in the cell body area and decreases $\alpha 2$ and $\beta$ receptor binding in terminal regions, suggesting aberrant NE modulatory responses towards stress in WKY rats (Tejani-Butt *et al.*, 1994; Zafar *et al.*, 1997). Although the NE response to acute stress is blunted, , WKY rats may exhibit less habituation to stress appearing as larger levels of reactivity as the reactivity of SD rats declines. A sustained NE response may underlie hypervigilance and elevated arousal in response to specific or generalized stress (Cameron *et al.*, 2004; Lahdesmaki *et al.*, 2002; Maes *et al.*, 2002; Schramm *et al.*, 2001). The efficacy of NE-targeted drugs in altering behaviors relevant to anxiety is limited. Much of the past research has focused on altering behaviors in the FST. Drugs which act by blocking NE transporters reduced immobility in FST and increase activity in the OFT in WKY rats (Lahmame and Armario, 1996; Lucki and Nobler, 1985; Pare, 1992b; Pare *et al.*, 2001; Will *et al.*, 2003). Thus, increasing NE availability affects inhibited temperament of WKY rats.

### 5.4 Others

There is a dearth of knowledge about strain difference between the WKY rat and comparison strains in the glutamatergic and the GABAergic pathways. A recent

autoradiographic study demonstrated that WKY rats exhibited lower N-methyl-d-aspartate (NMDA) receptor binding in anterior cingulate cortex, caudate putamen, nucleus accumbens, CA1 of hippocampus and substantia nigra compared to WIS rats (Lei *et al.*, 2009). Interestingly, chronic stress increased NMDA receptor binding in the prefrontal cortex, caudate putamen and nucleus accumbens only in the WKY rat (Lei and Tejani-Butt, 2010). Thus the authors speculated that NMDA receptors in these regions may be more sensitive to stress in WKY rats. Consistent with the previous report (Jiao *et al.*, 2011), our recent preliminary data suggest that naïve WKY rats exhibited altered density of PV immunoreactive cells in the amygdala and prefrontal cortex compared to SD rats (Table 1.). Although basal tissue level of GABA does not differ between WKY and WIS rats, stress increased it only in WKY rats (O'Mahony *et al.*, 2011). Moreover, the levels of GABA-A receptor binding are higher in amygdala, caudate putamen, CA2 and CA3 of hippocampus, periaqueductal gray and substantia nigra in WKY compared to WIS rats (Lei *et al.*, 2009). Given the role of GABA and GABA-A receptor in the pathophysiology of stress and anxiety, future investigation should emphasize GABAergic system in order to understand the unique behavioral aspects in WKY rats, a field that has not been studied sufficiently in this strain. So far only one report demonstrated the effect of diazepam on WKY rats measured by emergence test (Pare *et al.*, 2001). Single dose of diazepam reduced WKY rats' activity in an OFT. Thus the effects of pharmacological manipulation on GABAergic system need further investigation in WKY rats.

| REGIONS | STRAIN | MEAN PV (ir) CELL DENSITY ± S.E.M. (CELL COUNTS/mm3) |
|---|---|---|
| Anterior Cingulate | SD | 2208.08 ± 716.27 |
| | WKY | 3503.53 ± 111.97 |
| Prelimbic Cortex | SD | 2364.65 ± 281.96 |
| | WKY | 3181.51 ± 241.74 |
| Infralimbic Cortex | SD | 2891.72 ± 408.16 |
| | WKY | 2989.72 ± 442.44 |
| Basal Amygdala | SD | 2939.07 ± 211.16 |
| | WKY | 1786.03 ± 445.31 |
| Lateral Amygdala | SD | 2294.93 ± 251.59 |
| | WKY | 1427.58 ± 265.70 |

Table 1. PV (ir) positive cell densities in the prefrontal cortex and amygdala in WKY and SD rats. (N=4/strain)

### 5.5 Summary

The WKY rat exhibits a neurochemical profile reminiscent of anxiety disorders. The profile is also reminiscent of behavioral inhibition in nonhuman primates (Kalin, 2004; Kalin and Shelton, 2003; Kalin *et al.*, 2007). Past research has focused on the WKY as animal model of depression owing to the stress reactivity, susceptibility to ulcers, and reduced FST. Faster avoidance acquisition, avoidance perseveration and sustained arousal induced by avoidance learning are strong signs of anxiety vulnerability. Thus, investigation of psychotropic drugs

in their ability to affect avoidance may have relevance for treatment of human anxiety. Recent findings of GABAergic activity selective to avoidance acquisition and extinction in WKY rats suggest a novel target for this class of anxiolytics.

## 6. Overall summary

Anxiety disorders develop as an interaction of trait vulnerabilities (e.g., behavioral inhibition), early life experiences and environmental exposures. The interplay of these influences determines success or failures to effectively cope, especially under stress. WKY rats model trait inhibited temperament, a risk factor for anxiety disorders. Accordingly, WKY rats have neurobehavioral, neuroanatomical, neurochemical and neuropharmacological features consistent with inhibited temperament. In particular, WKY rats acquire active avoidance faster; avoidance that is resistant to extinction. Moreover, WKY rats display two behavioral features which are hallmarks of anxiety as avoidance develops: worry and increased arousal. In the respect of neurochemistry and neuroendocrine, WKY rats demonstrated over stimulated NE circuitry and exaggerated HPAA activity in response to stress stimulation, and innate 5-HT deficit together with altered receptors function in monoamine systems and GABAergic system, which all contribute to hyper-reactivity towards stress and the phenotypes that related to anxiety behavior in this rat strain. Together, these significant findings suggest that the WKY rats should be studied as an animal model of vulnerability to develop anxiety disorders.

## 7. Acknowledgement

This research was supported by NIH grants and a Department of Veterans Affairs Merit Review research program and the Stress & Motivated Behavior Institute of the New Jersey Medical School. The described experimentations were conducted with approval by the VANJHCS Institutional Animal Care and Use and Research and Development Committees. The authors would like to thank the technical expertise of Toni Marie Dispenziere, Tracey Longo and Amanda Agley in the behavioral testing of the animals in these experiments.

## 8. References

Aguilar, R., Gil, L., Fernandez-Teruel, A., and Tobena, A. (2004) Genetically-based behavioral traits influence the effects of Shuttle Box avoidance overtraining and extinction upon intertrial responding: a study with the Roman rat strains. *Behav. Processes* 66, 63-72.

Ahmadiyeh, N., Churchill, G. A., Solberg, L. C., Baum, A. E., Shimomura, K., Takahashi, J. S., and Redei, E. E. (2005) Lineage is an epigenetic modifier of QTL influencing behavioral coping with stress. *Behav. Genet.* 35, 189-198.

Ardekani, A. M., Walker, S. J., Donohue, S. J., Stitzel, R. E., Connors, J. M., and Vrana, K. E. (1989) Adrenocorticotropin and corticosterone levels in pre-weanling spontaneously hypertensive rats. *Life Sciences* 44, 919-925.

Barad, M. (2005) Fear extinction in rodents: basic insight to clinical promise. *Current Opinion in Neurobiology* 15, 710-715.

Beck, K. D., Zhu, G., Beldowicz, D., Brennan, F. X., Ottenweller, J. E., Moldow, R. L., and Servatius, R. J. (2001) Central nervous system effects from a peripherally acting

cholinesterase inhibiting agent: interaction with stress or genetics. *Ann. N. Y. Acad. Sci.* 933, 310-314.

Berger, D. F. and Starzec, J. J. (1988) Contrasting Lever-Press Avoidance Behaviors of Spontaneously Hypertensive and Normotensive Rats (Rattus norvegicus). *Journal of Comparative Psychology* 102, 279-286.

Biederman, J., Rosenbaum, J. F., Bolduc-Murphy, E. A., Faraone, S. V., Chaloff, J., Hirshfeld, D. R., and Kagan, J. (1993) A 3-year follow-up of children with and without behavioral inhibition. *J. Am. Acad. Child Adolesc. Psychiatry.* 32, 814-821.

Blizard, D. A. and Adams, N. (2002) The Maudsley Reactive and Nonreactive strains: a new perspective. *Behav. Genet.* 32, 277-299.

Bolles, R. C. (1970) Species-specific defense reactions and avoidance learning. *Psychological Review* 77, 32-48.

Boyle, A. E. and Gill, K. (2001) Sensitivity of AXB/BXA recombinant inbred lines of mice to the locomotor activating effects of cocaine: a quantitative trait loci analysis. *Pharmacogenetics* 11, 255-264.

Brambilla, P., Barale, F., Caverzasi, E., and Soares, J. C. (2002) Anatomical MRI findings in mood and anxiety disorders. *Epidemiol. Psichiatr. Soc.* 11, 88-99.

Braunstein-Bercovitz, H., mentman-Ashkenazi, I., and Lubow, R. E. (2001) Stress affects the selection of relevant from irrelevant stimuli. *Emotion.* 1, 182-192.

Braw, Y., Malkesman, O., Dagan, M., Bercovich, A., Lavi-Avnon, Y., Schroeder, M., Overstreet, D. H., and Weller, A. (2006) Anxiety-like behaviors in pre-pubertal rats of the Flinders Sensitive Line (FSL) and Wistar-Kyoto (WKY) animal models of depression. *Behavioural Brain Research* 167, 261-269.

Braw, Y., Malkesman, O., Merenlender, A., Bercovich, A., Dagan, M., Overstreet, D. H., and Weller, A. (2008) Withdrawal emotional-regulation in infant rats from genetic animal models of depression. *Behavioural Brain Research* 193, 94-100.

Bremner, J. D. (2006) The relationship between cognitive and brain changes in posttraumatic stress disorder. *Ann. N. Y. Acad. Sci.* 1071, 80-86.

Bremner, J. D., Krystal, J. H., Southwick, S. M., and Charney, D. S. (1996) Noradrenergic mechanisms in stress and anxiety: II. Clinical studies. *Synapse* 23, 39-51.

Brush, F. R. (2003) The Syracuse strains, selectively bred for differences in active avoidance learning, may be models of genetic differences in trait and state anxiety. *Stress.* 6, 77-85.

Buuse, M. v. d. (2004) Prepulse inhibition of acoustic startle in spontaneously hypertensive rats. *Behavioural Brain Research* 154, 331-337.

Bystritsky, A., Pontillo, D., Powers, M., Sabb, F. W., Craske, M. G., and Bookheimer, S. Y. (2001) Functional MRI changes during panic anticipation and imagery exposure. *Neuroreport* 12, 3953-3957.

Cameron, O. G., Abelson, J. L., and Young, E. A. (2004) Anxious and depressive disorders and their comorbidity: Effect on central nervous system noradrenergic function. *Biological Psychiatry* 56, 875-883.

Carr, G. V. and Lucki, I. (2010) Comparison of the kappa-opioid receptor antagonist DIPPA in tests of anxiety-like behavior between Wistar Kyoto and Sprague Dawley rats. *Psychopharmacology (Berl)* 210, 295-302.

Chantarujikapong, S. I., Scherrer, J. F., Xian, H., Eisen, S. A., Lyons, M. J., Goldberg, J., Tsuang, M., and True, W. R. (2001) A twin study of generalized anxiety disorder

symptoms, panic disorder symptoms and post-traumatic stress disorder in men. *Psychiatry Res.* 103, 133-145.

Chaouloff, F., Aguerre, S., and Mormede, P. (1998) GR 127935 and (+)-WAY 100135 do not affect TFMPP-induced inhibition of 5-HT synthesis in the midbrain and hippocampus of Wistar-Kyoto rats. *Neuropharmacology* 37, 1159-1167.

Charney, D. S. and Redmond, D. E., Jr. (1983) Neurobiological mechanisms in human anxiety. Evidence supporting central noradrenergic hyperactivity. *Neuropharmacology* 22, 1531-1536.

Chen, Z. Y., Jing, D., Bath, K. G., Ieraci, A., Khan, T., Siao, C. J., Herrera, D. G., Toth, M., Yang, C., McEwen, B. S., Hempstead, B. L., and Lee, F. S. (2006) Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science* 314, 140-143.

Cloninger, C. R., Van, E. P., Goate, A., Edenberg, H. J., Blangero, J., Hesselbrock, V., Reich, T., Nurnberger, J., Jr., Schuckit, M., Porjesz, B., Crowe, R., Rice, J. P., Foroud, T., Przybeck, T. R., Almasy, L., Bucholz, K., Wu, W., Shears, S., Carr, K., Crose, C., Willig, C., Zhao, J., Tischfield, J. A., Li, T. K., Conneally, P. M., and . (1998) Anxiety proneness linked to epistatic loci in genome scan of human personality traits. *Am. J. Med. Genet.* 81, 313-317.

Coover, G. D., Ursin, H., and Levine, S. (1973) Plasma-corticosterone levels during active-avoidance learning in rats. *J. Comp Physiol Psychol.* 82, 170-174.

DaSilva, J. K., Lei, Y., Madan, V., Mann, G. L., Ross, R. J., Tejani-Butt, S., and Morrison, A. R. (2011) Fear conditioning fragments REM sleep in stress-sensitive Wistar-Kyoto, but not Wistar, rats. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 35, 67-73.

De La Garza II, R. and Mahoney III, J. J. (2004) A distinct neurochemical profile in WKY rats at baseline and in response to acute stress: implications for animal models of anxiety and depression. *Brain Research* 1021, 209-218.

Driscoll, P. (1986) Roman high- and low-avoidance rats: present status of the Swiss sublines, RHA/Verh and RLA/Verh, and effects of amphetamine on shuttle-box performance. *Behav. Genet.* 16, 355-364.

Drolet, G., Proulx, K., Pearson, D., Rochford, J., and Deschepper, C. F. (2002) Comparisons of behavioral and neurochemical characteristics between WKY, WKHA, and Wistar rat strains. *Neuropsychopharmacology* 27, 400-409.

Dugovic, C., Solberg, L. C., Redei, E., Van, R. O., and Turek, F. W. (2000) Sleep in the Wistar-Kyoto rat, a putative genetic animal model for depression. *Neuroreport* 11, 627-631.

Duman, R. S. (2004) Role of neurotrophic factors in the etiology and treatment of mood disorders. *Neuromolecular. Med.* 5, 11-25.

Duman, R. S. and Monteggia, L. M. (2006) A neurotrophic model for stress-related mood disorders. *Biol. Psychiatry* 59, 1116-1127.

Ferguson, S. A. and Cada, A. M. (2003) A longitudinal study of short- and long-term activity levels in male and female spontaneously hypertensive, Wistar-Kyoto, and Sprague-Dawley rats. *Behav. Neurosci.* 117, 271-282.

Ferguson, S. A., Gough, B. J., and Cada, A. M. (2003a) In vivo basal and amphetamine-induced striatal dopamine and metabolite levels are similar in the spontaneously hypertensive, Wistar-Kyoto and Sprague-Dawley male rats. *Physiol Behav.* 80, 109-114.

Ferguson, S. A., Gray, E. P., and Cada, A. M. (2003b) Early behavioral development in the spontaneously hypertensive rat: a comparison with the Wistar-Kyoto and Sprague-Dawley strains. *Behav. Neurosci.* 117, 263-270.

Ferguson, S. A. and Cada, A. M. (2004) Spatial learning/memory and social and nonsocial behaviors in the Spontaneously Hypertensive, Wistar-Kyoto and Sprague-Dawley rat strains. *Pharmacology Biochemistry and Behavior* 77, 583-594.

Foa, E. B., Stein, D. J., and McFarlane, A. C. (2006) Symptomatology and psychopathology of mental health problems after disaster. *J. Clin. Psychiatry* 67 Suppl 2, 15-25.

Fox, N. A., Henderson, H. A., Marshall, P. J., Nichols, K. E., and Ghera, M. M. (2005a) Behavioral inhibition: linking biology and behavior within a developmental framework. *Annu. Rev. Psychol.* 56, 235-262.

Fox, N. A., Henderson, H. A., Marshall, P. J., Nichols, K. E., and Ghera, M. M. (2005b) Behavioral inhibition: linking biology and behavior within a developmental framework. *Annu. Rev. Psychol.* 56, 235-262.

Gendreau, P. L., Petitto, J. M., Gariepy, J. L., and Lewis, M. H. (1998) D2-like dopamine receptor mediation of social-emotional reactivity in a mouse model of anxiety: Strain and experience effects. *Neuropsychopharmacology* 18, 210-221.

Glowa, J. and Hansen, C. (1994) Differences in response to an acoustic startle stimulus among forty-six rat strains. *Behavior Genetics* 24, 79-84.

Gomez, F., Lahmame, A., de Kloet, E. R., and Armario, A. (1996) Hypothalamic-pituitary-adrenal response to chronic stress in five inbred rat strains: differential responses are mainly located at the adrenocortical level. *Neuroendocrinology* 63, 327-337.

Gould, T. D. and Gottesman, I. I. (2006) Psychiatric endophenotypes and the development of valid animal models. *Genes Brain Behav.* 5, 113-119.

Griebel, G., Cohen, C., Perrault, G., and Sanger, D. J. (1999) Behavioral Effects of Acute and Chronic Fluoxetine in Wistar-Kyoto Rats. *Physiology & Behavior* 67, 315-320.

Grillon, C., Avenevoli, S., Daurignac, E., and Merikangas, K. R. (2007a) Fear-Potentiated Startle to Threat, and Prepulse Inhibition Among Young Adult Nonsmokers, Abstinent Smokers, and Nonabstinent Smokers. *Biol. Psychiatry*.

Grillon, C., Duncko, R., Covington, M. F., Kopperman, L., and Kling, M. A. (2007b) Acute Stress Potentiates Anxiety in Humans. *Biol. Psychiatry*.

Guthrie, R. M. and Bryant, R. A. (2005) Auditory startle response in firefighters before and after trauma exposure. *Am. J. Psychiatry* 162, 283-290.

Gutiérrez-Mariscal, M., de Gortari, P., López-Rubalcava, C., Martínez, A., and Joseph-Bravo, P. (2008) Analysis of the anxiolytic-like effect of TRH and the response of amygdalar TRHergic neurons in anxiety. *Psychoneuroendocrinology* 33, 198-213.

Hamner, M. B. and Diamond, B. I. (1996) Plasma dopamine and norepinephrine correlations with psychomotor retardation, anxiety, and depression in non-psychotic depressed patients: a pilot study. *Psychiatry Research* 64, 209-211.

Henderson, A. S., Korten, A. E., Jorm, A. F., Jacomb, P. A., Christensen, H., Rodgers, B., Tan, X., and Easteal, S. (2000) COMT and DRD3 polymorphisms, environmental exposures, and personality traits related to common mental disorders. *Am. J. Med. Genet.* 96, 102-107.

Hineline, P. N. (1978a) Warmup in avoidance as a function of time since prior training. *J. Exp. Anal. Behav.* 29, 87-103.

Hineline, P. N. (1978b) Warmup in free-operant avoidance as a function of the response-shock = shock-shock interval. *J. Exp. Anal. Behav.* 30, 281-291.

Hirshfeld, D. R., Rosenbaum, J. F., Biederman, J., Bolduc, E. A., Faraone, S. V., Snidman, N., Reznick, J. S., and Kagan, J. (1992) Stable behavioral inhibition and its association with anxiety disorder. *J. Am. Acad. Child Adolesc. Psychiatry.* 31, 103-111.

Hirshfeld-Becker, D. R., Biederman, J., Henin, A., Faraone, S. V., Davis, S., Harrington, K., and Rosenbaum, J. F. (2007) Behavioral inhibition in preschool children at risk is a specific predictor of middle childhood social anxiety: a five-year follow-up. *J. Dev. Behav. Pediatr.* 28, 225-233.

Hopper, J. W., Frewen, P. A., van der Kolk, B. A., and Lanius, R. A. (2007) Neural correlates of reexperiencing, avoidance, and dissociation in PTSD: symptom dimensions and emotion dysregulation in responses to script-driven trauma imagery. *J. Trauma Stress.* 20, 713-725.

Jiao, X., Pang, K. C., Beck, K. D., Minor, T. R., and Servatius, R. J. (2011) Avoidance perseveration during extinction training in Wistar-Kyoto rats: An interaction of innate vulnerability and stressor intensity. *Behav. Brain Res.* 221, 98-107.

Jiao, X., Pare, W. P., and Tejani-Butt, S. (2003) Strain differences in the distribution of dopamine transporter sites in rat brain. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 27, 913-919.

Jiao, X., Pare, W. P., and Tejani-Butt, S. M. (2006) Antidepressant drug induced alterations in binding to central dopamine transporter sites in the Wistar Kyoto rat strain. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 30, 30-41.

Kagan, J., Reznick, J. S., and Gibbons, J. (1989) Inhibited and uninhibited types of children. *Child Dev.* 60, 838-845.

Kagan, J., Reznick, J. S., and Snidman, N. (1987) The physiology and psychology of behavioral inhibition in children. *Child Dev.* 58, 1459-1473.

Kalin, N. H. (2004) Studying non-human primates: a gateway to understanding anxiety disorders. *Psychopharmacol. Bull.* 38 Suppl 1, 8-13.

Kalin, N. H. and Shelton, S. E. (2003) Nonhuman primate models to study anxiety, emotion regulation, and psychopathology. *Ann. N. Y. Acad. Sci.* 1008, 189-200.

Kalin, N. H., Shelton, S. E., and Davidson, R. J. (2000) Cerebrospinal fluid corticotropin-releasing hormone levels are elevated in monkeys with patterns of brain activity associated with fearful temperament. *Biol. Psychiatry* 47, 579-585.

Kalin, N. H., Shelton, S. E., and Davidson, R. J. (2007) Role of the Primate Orbitofrontal Cortex in Mediating Anxious Temperament. *Biological Psychiatry* 62, 1134-1139.

Kalueff, A. V., Avgustinovich, D. F., Kudryavtseva, N. N., and Murphy, D. L. (2006) BDNF in anxiety and depression. *Science* 312, 1598-1599.

Karamustafalioglu, O. K., Zohar, J., Guveli, M., Gal, G., Bakim, B., Fostick, L., Karamustafalioglu, N., and Sasson, Y. (2006) Natural Course of Posttraumatic Stress Disorder: A 20-Month Prospective Study of Turkish Earthquake Survivors. *J. Clin. Psychiatry* 67, 882-889.

Kashdan, T. B., Elhai, J. D., and Frueh, B. C. (2006) Anhedonia and emotional numbing in combat veterans with PTSD. *Behaviour Research and Therapy* 44, 457-467.

Keltikangas-Jarvinen, L., Kettunen, J., Ravaja, N., and Naatanen, P. (1999) Inhibited and disinhibited temperament and autonomic stress reactivity. *Int. J. Psychophysiol.* 33, 185-196.

Kemppainen, S. and Pitkanen, A. (2000) Distribution of parvalbumin, calretinin, and calbindin-D(28k) immunoreactivity in the rat amygdaloid complex and colocalization with gamma-aminobutyric acid. *J. Comp Neurol.* 426, 441-467.

Kendler, K. S., Myers, J., and Prescott, C. A. (2002) The etiology of phobias: an evaluation of the stress-diathesis model. *Arch. Gen. Psychiatry* 59, 242-248.

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., and Walters, E. E. (2005) Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch. Gen. Psychiatry* 62, 617-627.

Lahdesmaki, J., Sallinen, J., MacDonald, E., Kobilka, B. K., Fagerholm, V., and Scheinin, M. (2002) Behavioral and neurochemical characterization of alpha(2A)-adrenergic receptor knockout mice. *Neuroscience* 113, 289-299.

Lahmame, A. and Armario, A. (1996) Differential responsiveness of inbred strains of rats to antidepressants in the forced swimming test: are Wistar Kyoto rats an animal model of subsensitivity to antidepressants? *Psychopharmacology (Berl)* 123, 191-198.

Laitman, B. M., DaSilva, J. K., Ross, R. J., Tejani-Butt, S., and Morrison, A. R. Reduced Gamma Range Activity at REM Sleep Onset and Termination in Fear-Conditioned Wistar-Kyoto Rats. *Neuroscience Letters* In Press, Accepted Manuscript.

Lanius, R. A., Williamson, P. C., Hopper, J., Densmore, M., Boksman, K., Gupta, M. A., Neufeld, R. W., Gati, J. S., and Menon, R. S. (2003) Recall of emotional states in posttraumatic stress disorder: an fMRI investigation. *Biol. Psychiatry* 53, 204-210.

Lei, Y. and Tejani-Butt, S. M. (2010) N-methyl-d-aspartic acid receptors are altered by stress and alcohol in Wistar-Kyoto rat brain. *Neuroscience* 169, 125-131.

Lei, Y., Yaroslavsky, I., and Tejani-Butt, S. M. (2009) Strain differences in the distribution of N-methyl-d-aspartate and gamma ([gamma])-aminobutyric acid-A receptors in rat brain. *Life Sciences* 85, 794-799.

Lemos, J. C., Zhang, G., Walsh, T., Kirby, L. G., Akanwa, A., Brooks-Kayal, A., and Beck, S. G. (2011) Stress-Hyperresponsive WKY Rats Demonstrate Depressed Dorsal Raphe Neuronal Excitability and Dysregulated CRF-Mediated Responses. *Neuropsychopharmacology* 36, 721-734.

Lind, K., Jonsson, M., Karlsson, I., Sjogren, M., Wallin, A., and Edman, A. (2006) Depressive symptoms and white matter changes in patients with dementia. *Int. J. Geriatr. Psychiatry* 21, 119-125.

Lopez-Rubalcava, C. and Lucki, I. (2000) Strain differences in the behavioral effects of antidepressant drugs in the rat forced swimming test. *Neuropsychopharmacology* 22, 191-199.

Lucki, I. and Nobler, M. S. (1985) The acute effects of antidepressant drugs on the performance of conditioned avoidance behavior in rats. *Pharmacology Biochemistry and Behavior* 22, 261-264.

Ma, S. and Morilak, D. A. (2004) Induction of FOS expression by acute immobilization stress is reduced in locus coeruleus and medial amygdala of Wistar-Kyoto rats compared to Sprague-Dawley rats. *Neuroscience* 124, 963-972.

Maes, M., Van, G. A., Delmeire, L., Kenis, G., Bosmans, E., and Song, C. (2002) Platelet alpha2-adrenoceptor density in humans: relationships to stress-induced anxiety, psychasthenic constitution, gender and stress-induced changes in the inflammatory response system. *Psychol. Med.* 32, 919-928.

Malkesman, O., Asaf, T., Shbiro, L., Goldstein, A., Maayan, R., Weizman, A., Kinor, N., Okun, E., Sredni, B., Yadid, G., and Weller, A. (2009) Monoamines, BDNF, Dehydroepiandrosterone, DHEA-Sulfate, and Childhood Depression-An Animal Model Study. *Adv. Pharmacol. Sci.* 2009, 405107.

Malkesman, O., Braw, Y., Zagoory-Sharon, O., Golan, O., Lavi-Avnon, Y., Schroeder, M., Overstreet, D. H., Yadid, G., and Weller, A. (2005) Reward and anxiety in genetic animal models of childhood depression. *Behavioural Brain Research* 164, 1-10.

Malkesman, O., Maayan, R., Weizman, A., and Weller, A. (2006a) Aggressive behavior and HPA axis hormones after social isolation in adult rats of two different genetic animal models for depression. *Behav. Brain Res.* 175, 408-414.

Malkesman, O. and Weller, A. (2009) Two different putative genetic animal models of childhood depression--A review. *Progress in Neurobiology* 88, 153-169.

Malkesman, O., Braw, Y., Maayan, R., Weizman, A., Overstreet, D. H., Shabat-Simon, M., Kesner, Y., Touati-Werner, D., Yadid, G., and Weller, A. (2006b) Two Different Putative Genetic Animal Models of Childhood Depression. *Biological Psychiatry* 59, 17-23.

Mann, R. and Bell, C. (1991) Neuronal metabolism and DOPA decarboxylase immunoreactivity in terminal noradrenergic sympathetic axons of rat. *J. Histochem. Cytochem.* 39, 663-668.

Martinowich, K., Manji, H., and Lu, B. (2007) New insights into BDNF function in depression and anxiety. *Nat Neurosci* 10, 1089-1093.

Mathew, R. J., Ho, B. T., Taylor, D. L., and Semchuk, K. M. (1981) Catecholamine and dopamine-[beta]-hydroxylase in anxiety. *Journal of Psychosomatic Research* 25, 499-504.

McAuley, J. D., Stewart, A. L., Webber, E. S., Cromwell, H. C., Servatius, R. J., and Pang, K. C. (2009) Wistar-Kyoto rats as an animal model of anxiety vulnerability: Support for a hypervigilance hypothesis. *Behav. Brain Res.*

McEwen, B. S. (2005) Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. *Metabolism* 54, 20-23.

Meloni, E. G. and Davis, M. (1999) Enhancement of the acoustic startle response in rats by the dopamine D1 receptor agonist SKF 82958. *Psychopharmacology (Berl)* 144, 373-380.

Milad, M. R., Quirk, G. J., Pitman, R. K., Orr, S. P., Fischl, B., and Rauch, S. L. A Role for the Human Dorsal Anterior Cingulate Cortex in Fear Expression. *Biological Psychiatry* In Press, Corrected Proof, -454.

Mineka, S. and Zinbarg, R. (1996) Conditioning and ethological models of anxiety disorders: stress-in-dynamic-context anxiety models. *Nebr. Symp. Motiv.* 43:135-210., 135-210.

Mineka, S. and Zinbarg, R. (2006) A contemporary learning theory perspective on the etiology of anxiety disorders: it's not what you thought it was. *Am. Psychol.* 61, 10-26.

Mineka, S. (2004) The positive and negative consequences of worry in the aetiology of generalized anxiety disorder: A learning theory perspective. [References]. pp. 24-48.

Mobbs, D., Petrovic, P., Marchant, J. L., Hassabis, D., Weiskopf, N., Seymour, B., Dolan, R. J., and Frith, C. D. (2007) When fear is near: threat imminence elicits prefrontal-periaqueductal gray shifts in humans. *Science* 317, 1079-1083.

Myers, K. M. and Davis, M. (2002) Behavioral and neural analysis of extinction. *Neuron* 36, 567-584.

Neumeister, A., Daher, R. J., and Charney, D. S. (2005) Anxiety disorders: noradrenergic neurotransmission. *Handb. Exp. Pharmacol.* 205-223.

North, C. S., Pfefferbaum, B., Tivis, L., Kawasaki, A., Reddy, C., and Spitznagel, E. L. (2004) The course of posttraumatic stress disorder in a follow-up study of survivors of the Oklahoma City bombing. *Ann. Clin. Psychiatry* 16, 209-215.

Nosek, K., Dennis, K., Andrus, B. M., Ahmadiyeh, N., Baum, A. E., Solberg Woods, L. C., and Redei, E. E. (2008) Context and strain-dependent behavioral response to stress. *Behav. Brain Funct.* 4, 23.

Novick, A., Yaroslavsky, I., and Tejani-Butt, S. (2008) Strain differences in the expression of dopamine D1 receptors in Wistar-Kyoto (WKY) and Wistar rats. *Life Sciences* 83, 74-78.

Nutt, D. J. and Malizia, A. L. (2004) Structural and functional brain changes in posttraumatic stress disorder. *J. Clin. Psychiatry* 65 Suppl 1, 11-17.

O'donnell, M. L., Elliott, P., Lau, W., and Creamer, M. (2006b) PTSD symptom trajectories: From early to chronic response. *Behav. Res. Ther.*

O'donnell, M. L., Elliott, P., Lau, W., and Creamer, M. (2006a) PTSD symptom trajectories: From early to chronic response. *Behav. Res. Ther.*

O'Mahony, C. M., Clarke, G., Gibney, S., Dinan, T. G., and Cryan, J. F. (2011) Strain differences in the neurochemical response to chronic restraint stress in the rat: relevance to depression. *Pharmacol. Biochem. Behav.* 97, 690-699.

Ohara, K., Nishii, R., Nakajima, T., Kokai, M., and Morita, Y. (2004) [Alterations of symptoms with borderline personality disorder after fronto-temporal traumatic brain injury. A case study]. *Seishin Shinkeigaku Zasshi* 106, 458-466.

Okamoto, K. and Aoki, K. (1963) Development of a strain of spontaneously hypertensive rats. *Jpn. Circ. J.* 27, 282-293.

Ottenweller, J. E., Servatius, R. J., and Natelson, B. H. (1994) Repeated stress persistently elevates morning, but not evening, plasma corticosterone levels in male rats. *Physiology & Behavior* 55, 337-340.

Overstreet, D. H., Rezvani, A. H., and Janowsky, D. S. (1990) Impaired active avoidance responding in rats selectively bred for increased cholinergic function. *Physiology & Behavior* 47, 787-788.

Overstreet, D. H., Rezvani, A. H., and Janowsky, D. S. (1992) Genetic animal models of depression and ethanol preference provide support for cholinergic and serotonergic involvement in depression and alcoholism. *Biological Psychiatry* 31, 919-936.

Palmer, A. A., Dulawa, S. C., Mottiwala, A. A., Conti, L. H., Geyer, M. A., and Printz, M. P. (2000) Prepulse Startle Deficit in the Brown Norway Rat: A Potential Genetic Model. *Behavioral Neuroscience* 114, 374-388.

Pardon, M.-C., Gould, G. G., Garcia, A., Phillips, L., Cook, M. C., Miller, S. A., Mason, P. A., and Morilak, D. A. (2002) Stress reactivity of the brain noradrenergic system in three rat strains differing in their neuroendocrine and behavioral responses to stress: implications for susceptibility to stress-related neuropsychiatric disorders. *Neuroscience* 115, 229-242.

Pardon, M. C., Joubert, C., Perez-Diaz, F., Christen, Y., Launay, J. M., and Cohen-Salmon, C. (2000) In vivo regulation of cerebral monoamine oxidase activity in senescent controls and chronically stressed mice by long-term treatment with Ginkgo biloba extrac3t (EGb 761). *Mechanisms of Ageing and Development* 113, 157-168.

Pardon, M. C., Ma, S., and Morilak, D. A. (2003) Chronic cold stress sensitizes brain noradrenergic reactivity and noradrenergic facilitation of the HPA stress response in Wistar Kyoto rats. *Brain Research* 971, 55-65.

Pare, A. M. T., Pare, W. P., and Kluczynski, J. (1999a) Negative Affect and Voluntary Alcohol Consumption in Wistar-Kyoto (WKY) and Sprague-Dawley Rats. *Physiology & Behavior* 67, 219-225.

Pare, W. P. (1992a) Learning behavior, escape behavior, and depression in an ulcer susceptible rat strain. *Integr. Physiol Behav. Sci.* 27, 130-141.

Pare, W. P., Blair, G. R., Kluczynski, J., and Tejani-Butt, S. (1999b) Gender differences in acute and chronic stress in Wistar Kyoto (WKY) rats. *Integr. Physiol Behav. Sci.* 34, 227-241.

Pare, W. P. and Kluczynski, J. (1997) Differences in the stress response of Wistar-Kyoto (WKY) rats from different vendors. *Physiol Behav.* 62, 643-648.

Pare, W. P. and Redei, E. (1993a) Depressive behavior and stress ulcer in Wistar Kyoto rats. *Journal of Physiology-Paris* 87, 229-238.

Pare, W. P. and Redei, E. (1993b) Sex differences and stress response of WKY rats. *Physiol Behav.* 54, 1179-1185.

Pare, W. P. and Tejani-Butt, S. M. (1996) Effect of stress on the behavior and 5-HT system in Sprague-Dawley and Wistar Kyoto rat strains. *Integr. Physiol Behav. Sci.* 31, 112-121.

Pare, W. P. (1989a) "Behavioral despair" test predicts stress ulcer in WKY rats. *Physiology & Behavior* 46, 483-487.

Pare, W. P. (1989b) "Behavioral despair" test predicts stress ulcer in WKY rats. *Physiology & Behavior* 46, 483-487.

Pare, W. P. (1989c) Stress ulcer susceptibility and depression in Wistar Kyoto (WKY) rats. *Physiology & Behavior* 46, 993-998.

Pare, W. P. (1992b) The performance of WKY rats on three tests of emotional behavior. *Physiology & Behavior* 51, 1051-1056.

Pare, W. P. (1993) Passive-avoidance behavior in Wistar-Kyoto (WKY), Wistar, and Fischer-344 rats. *Physiology & Behavior* 54, 845-852.

Pare, W. P. (1994) Open field, learned helplessness, conditioned defensive burying, and forced-swim tests in WKY rats. *Physiology & Behavior* 55, 433-439.

Pare, W. P. (1996) Enhanced retrieval of unpleasant memories influenced by shock controllability, shock sequence, and rat strain. *Biological Psychiatry* 39, 808-813.

Pare, W. P. and Schimmel, G. T. (1986) Stress ulcer in normotensive and spontaneously hypertensive rats. *Physiology & Behavior* 36, 699-705.

Pare, W. P., Tejani-Butt, S., and Kluczynski, J. (2001) The emergence test: effects of psychotropic drugs on neophobic disposition in Wistar Kyoto (WKY) and Sprague Dawley Rats. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 25, 1615-1628.

Pearson, K. A., Stephen, A., Beck, S. G., and Valentino, R. J. (2006) Identifying genes in monoamine nuclei that may determine stress vulnerability and depressive behavior in Wistar-Kyoto rats. *Neuropsychopharmacology* 31, 2449-2461.

Perez-Edgar, K., Roberson-Nay, R., Hardin, M. G., Poeth, K., Guyer, A. E., Nelson, E. E., McClure, E. B., Henderson, H. A., Fox, N. A., Pine, D. S., and Ernst, M. (2007) Attention alters neural responses to evocative faces in behaviorally inhibited adolescents. *Neuroimage.* 35, 1538-1546.

Redei, E., Pare, W. P., Aird, F., and Kluczynski, J. (1994) Strain differences in hypothalamic-pituitary-adrenal activity and stress ulcer. *Am. J. Physiol* 266, R353-R360.

Rittenhouse, P. A., Lopez-Rubalcava, C., Stanwood, G. D., and Lucki, I. (2002) Amplified behavioral and endocrine responses to forced swim stress in the Wistar-Kyoto rat. *Psychoneuroendocrinology* 27, 303-318.

Rosenbaum, J. F., Biederman, J., Bolduc-Murphy, E. A., Faraone, S. V., Chaloff, J., Hirshfeld, D. R., and Kagan, J. (1993) Behavioral inhibition in childhood: a risk factor for anxiety disorders. *Harv. Rev. Psychiatry.* 1, 2-16.

Rosenbaum, J. F., Biederman, J., Hirshfeld, D. R., Bolduc, E. A., Faraone, S. V., Kagan, J., Snidman, N., and Reznick, J. S. (1991) Further evidence of an association between behavioral inhibition and anxiety disorders: results from a family study of children from a non-clinical sample. *J. Psychiatr. Res.* 25, 49-65.

Rosenkranz, J. A. and Grace, A. A. (2001) Dopamine attenuates prefrontal cortical suppression of sensory inputs to the basolateral amygdala of rats. *J. Neurosci.* 21, 4090-4103.

Samanez-Larkin, G. R., Hollon, N. G., Carstensen, L. L., and Knutson, B. (2008) Individual differences in insular sensitivity during loss anticipation predict avoidance learning. *Psychol. Sci.* 19, 320-323.

Sands, S. A., Strong, R., Corbitt, J., and Morilak, D. A. (2000) Effects of acute restraint stress on tyrosine hydroxylase mRNA expression in locus coeruleus of Wistar and Wistar-Kyoto rats. *Molecular Brain Research* 75, 1-7.

Scholl, J. L., Renner, K. J., Forster, G. L., and Tejani-Butt, S. (2010) Central monoamine levels differ between rat strains used in studies of depressive behavior. *Brain Research* 1355, 41-51.

Schramm, N. L., McDonald, M. P., and Limbird, L. E. (2001) The {alpha}2A-Adrenergic Receptor Plays a Protective Role in Mouse Behavioral Models of Depression and Anxiety. *J. Neurosci.* 21, 4875-4882.

Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., and Rauch, S. L. (2003) Inhibited and uninhibited infants "grown up": adult amygdalar response to novelty. *Science* 300, 1952-1953.

Servatius, R. J., Jiao, X., Beck, K. D., Pang, K. C. H., and Minor, T. R. (2008) Rapid avoidance acquisition in Wistar-Kyoto rats. *Behavioural Brain Research* 192, 191-197.

Servatius, R. J., Ottenweller, J. E., Beldowicz, D., Guo, W., Zhu, G., and Natelson, B. H. (1998) Persistently exaggerated startle responses in rats treated with pyridostigmine bromide. *J. Pharmacol. Exp. Ther.* 287, 1020-1028.

Silver, R. C., Holman, E. A., McIntosh, D. N., Poulin, M., and Gil-Rivas, V. (2002) Nationwide longitudinal study of psychological responses to September 11. *JAMA* 288, 1235-1244.

Simmons, A., Strigo, I., Matthews, S. C., Paulus, M. P., and Stein, M. B. (2006) Anticipation of aversive visual stimuli is associated with increased insula activation in anxiety-prone subjects. *Biol. Psychiatry* 60, 402-409.

Smoller, J. W., Rosenbaum, J. F., Biederman, J., Kennedy, J., Dai, D., Racette, S. R., Laird, N. M., Kagan, J., Snidman, N., Hirshfeld-Becker, D., Tsuang, M. T., Sklar, P. B., and Slaugenhaupt, S. A. (2003) Association of a genetic marker at the corticotropin-releasing hormone locus with behavioral inhibition. *Biol. Psychiatry.* 54, 1376-1381.

Smoller, J. W., Yamaki, L. H., Fagerness, J. A., Biederman, J., Racette, S., Laird, N. M., Kagan, J., Snidman, N., Faraone, S. V., Hirshfeld-Becker, D., Tsuang, M. T., Slaugenhaupt, S. A., Rosenbaum, J. F., and Sklar, P. B. (2005) The corticotropin-releasing hormone

gene and behavioral inhibition in children at risk for panic disorder. *Biol. Psychiatry.* 57, 1485-1492.

Solberg, L. C., Baum, A. E., Ahmadiyeh, N., Shimomura, K., Li, R., Turek, F. W., Churchill, G. A., Takahashi, J. S., and Redei, E. E. (2004) Sex- and lineage-specific inheritance of depression-like behavior in the rat. *Mamm. Genome* 15, 648-662.

Solberg, L. C., Olson, S. L., Turek, F. W., and Redei, E. (2001) Altered hormone levels and circadian rhythm of activity in the WKY rat, a putative animal model of depression. *Am. J. Physiol Regul. Integr. Comp Physiol* 281, R786-R794.

Somers, J. M., Goldner, E. M., Waraich, P., and Hsu, L. (2006) Prevalence and incidence studies of anxiety disorders: a systematic review of the literature. *Can. J. Psychiatry* 51, 100-113.

Straube, T., Schmidt, S., Weiss, T., Mentzel, H. J., and Miltner, W. H. (2009) Dynamic activation of the anterior cingulate cortex during anticipatory anxiety. *Neuroimage.* 44, 975-981.

Sullivan, G. M., Coplan, J. D., Kent, J. M., and Gorman, J. M. (1999) The noradrenergic system in pathological anxiety: a focus on panic with relevance to generalized anxiety and phobias. *Biol. Psychiatry* 46, 1205-1218.

Suslow, T., Kugel, H., Rauch, A. V., Dannlowski, U., Bauer, J., Konrad, C., Arolt, V., Heindel, W., and Ohrmann, P. (2009) Attachment avoidance modulates neural response to masked facial emotion. *Hum. Brain Mapp.*

Taylor, D. P., Riblet, L. A., Stanton, H. C., Eison, A. S., Eison, M. S., and Temple, D. L. (1982) Dopamine and antianxiety activity. *Pharmacology Biochemistry and Behavior* 17, 25-35.

Tejani-Butt, S. M., Pare, W. P., and Yang, J. (1994) Effect of repeated novel stressors on depressive behavior and brain norepinephrine receptor system in Sprague-Dawley and Wistar Kyoto (WKY) rats. *Brain Res.* 649, 27-35.

Tejani-Butt, S., Kluczynski, J., and Pare, W. P. (2003) Strain-dependent modification of behavior following antidepressant treatment. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 27, 7-14.

Tyrka, A. R., Mello, A. F., Mello, M. F., Gagne, G. G., Grover, K. E., Anderson, G. M., Price, L. H., and Carpenter, L. L. (2006) Temperament and hypothalamic-pituitary-adrenal axis function in healthy adults. *Psychoneuroendocrinology* 31, 1036-1045.

Tyrka, A. R., Wier, L. M., Price, L. H., Rikhye, K., Ross, N. S., Anderson, G. M., Wilkinson, C. W., and Carpenter, L. L. (2008) Cortisol and ACTH responses to the Dex/CRH test: influence of temperament. *Horm. Behav.* 53, 518-525.

Vachette, C., Bourde, O., Gillon, J. Y., Pujol, J. F., and Renaud, B. (1993) Decrease in the reactivity of locus coeruleus neurons to hypotension after an increase in their tyrosine hydroxylase content: a subregional in vivo voltammetry study in the rat. *Eur. J. Neurosci.* 5, 261-268.

Vaswani, M., Linda, F. K., and Ramesh, S. (2003) Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 27, 85-102.

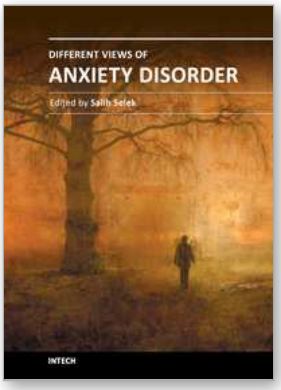
Walker, J. R., Su, A. I., Self, D. W., Hogenesch, J. B., Lapp, H., Maier, R., Hoyer, D., and Bilbe, G. (2004) Applications of a rat multiple tissue gene expression data set. *Genome Res.* 14, 742-749.

Will, C. C., Aird, F., and Redei, E. E. (2003) Selectively bred Wistar-Kyoto rats: an animal model of depression and hyper-responsiveness to antidepressants. *Mol. Psychiatry* 8, 925-932.

Yaroslavsky, I., Colletti, M., Jiao, X., and Tejani-Butt, S. (2006) Strain differences in the distribution of dopamine (DA-2 and DA-3) receptor sites in rat brain. *Life Sciences* 79, 772-776.

Zafar, H. M., Pare, W. P., and Tejani-Butt, S. M. (1997) Effect of acute or repeated stress on behavior and brain norepinephrine system in Wistar-Kyoto (WKY) rats. *Brain Res. Bull.* 44, 289-295.

Zinbarg, R. E. and Barlow, D. H. (1996) Structure of anxiety and the anxiety disorders: a hierarchical model. *J. Abnorm. Psychol.* 105, 181-193.




**Different Views of Anxiety Disorders**

Edited by Dr. Salih Selek

ISBN 978-953-307-560-0
Hard cover, 370 pages
**Publisher** InTech
**Published online** 12, September, 2011
**Published in print edition** September, 2011

Anxiety, whether an illness or emotion, is a term with historical roots even in the Bible, but it was not popular until the modern age. Today, we can group, diagnose and treat several anxiety disorders to an extent, but the assessment of symptoms and severity, dealing with resistant conditions, new treatment modalities and specific patient population, such as children, are still the challenging aspects of anxiety disorders. This book intends to present anxiety disorders from a different view and discuss a wide variety of topics in anxiety from a multidimensional approach. This Open Access book addresses not only psychiatrists but also a broad range of specialists, including psychologists, neuroscientists and other mental health professionals.



INTECH
open science | open minds

**InTech Europe**
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

**InTech China**
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821