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Stimulus Processing and Associative Learning in Wistar and WKHA Rats

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Abstract

This study assessed basic learning and attention abilities in WKHA (Wistar-Kyoto Hyperactive) rats using appetitive conditioning preparations. Two measures of conditioned responding to a visual stimulus, orienting behavior (rearing on the hindlegs) and food cup behavior (placing the head inside the recessed food cup) were measured. In Experiment 1, simple conditioning but not extinction was impaired in WKHA rats compared to Wistar rats. In Experiment 2, non-reinforced presentations of the visual cue preceded the conditioning sessions. WKHA rats displayed less orienting behavior than Wistar rats, but comparable levels of food cup behavior. These data suggest that WKHA rats exhibit specific abnormalities in attentional processing as well as learning stimulus-reward relationships.

Keywords

attention-deficit hyperactivity disorder; classical conditioning; attention; orienting

Introduction

The WKHA (Wistar-Kyoto Hyperactive) rat strain exhibits neurochemical alterations and changes in locomotor activity levels that make it a potentially interesting model of attentional dysfunction in humans. Hendley and Ohlsson (1991) developed the WKHA strain from successive selective inbreeding of offspring derived from a cross of the SHR (Spontaneously Hypertensive Rat; characterized by hyperactivity and hyper-responsivity to stress) and WKY (Wistar Kyoto; a normo-tensive, normo-active control) in an attempt to develop a strain with a similar behavioral profile to the SHR in terms of hyperactivity without the potentially confounding influence of hypertension. The resulting WKHA strain is normo-tensive with a hyperactive phenotype while the WKHT (Wistar-Kyoto Hypertensive) strain is hypertensive with a normo-active phenotype (Hendley, 2000; Hendley & Ohlsson, 1991).

WKHA rats exhibit changes in mesolimbic and mesocortical dopaminergic function including increases in dopamine (DA) uptake (Hendley & Fan, 1992; Hendley, 2000). Hyperactivity was significantly correlated with these increases, complementing previous findings of locomotor hyperactivity following selective DA depletion (Simon et al., 1980). These data provide an intriguing parallel to polymorphisms of the DA transporter protein and D4 DA receptor observed in some samples of individuals with ADHD (Solanto, 2001). Very few studies, however, have characterized basic cognitive function in WKHA rats. For example, there has been no assessment of conditioning abilities or the effects of altered attention on learning. Likewise, there has been no assessment of how changes in locomotor activity may be manifest

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in task-related measures of learning or attention. Indeed, the utility of this strain to model attention deficits in humans is currently understudied (Ferguson, 2001; Paule et al., 2000).

The present experiments were thus designed to characterize basic learning and attentional function in the WKHA strain, the interaction between cognitive function and hyperactivity, and the potential use of WKHA rats as a model of attention disorders. Attentional processing in WKHA and normo-active rats (Wistar) was examined in the context of associative learning. Contemporary learning theories maintain that alterations in processing of conditioned stimuli (CSs) reflect changes in attention to those cues (Mackintosh, 1975; Pearce & Hall, 1980), often resulting in alterations in learning. For example, animals increase attentional processing of stimuli that are surprising or inconsistent predictors of future events, and decrease processing of stimuli that provide little or no relevant information (e.g., Pearce & Hall, 1980). Increased attentional processing commonly enhances subsequent learning, while decreases in attention retard subsequent learning about that stimulus. A series of studies has now established that distinct brain systems are involved in increasing and decreasing attention to CSs, including midbrain dopaminergic systems (Han et al., 1997; McDannald et al., 2004a, 2004b) as well as central cholinergic systems (Bucci et al., 1998; Chiba et al., 1995; Baxter et al., 1997).

Since disorders such as attention-deficit/hyperactivity disorder (ADHD) and schizophrenia are marked by difficulty in filtering out extraneous information and focusing on target stimuli (Thaker et al., 2002; Serra et al., 2001; Nigg, 2001), examining attentional processing of CSs in WKHA rats may provide a means to explore the neurobiological basis of these deficits. Given the constellation of neurochemical alterations and reported changes in general activity in WKHA rats, it was thus hypothesized that attentional processing of CSs would be altered in WKHA rats, leading to deficits in learning and extinction. The results of this study provide insight into the ability of WKHA rats to form simple associations and alter attention appropriately to conditioned stimuli.

EXPERIMENT 1

In Experiment 1, rats were trained in a simple appetitive conditioning task to evaluate the ability of WKHA rats to learn simple associations compared to normo-active rats (Wistar). The acquisition phase was then followed by extinction sessions to assess responding in the absence of reward. Since children with ADHD continue to respond at a high rate during extinction trials (Douglas & Parry, 1994), and deficits in extinction are often considered a core deficit in ADHD (Johansen & Sagvolden, 2004), the extinction sessions in Experiment 1 were intended to determine whether WKHA rats exhibit similar increases in responding during extinction. In addition to monitoring conditioned orienting and food cup behavior during presentations of the CS, the amount of behavior exhibited just prior to the onset of the CS was monitored as a measure of task-relevant changes in activity and baseline responding.

Previous studies have compared the behavior of WKHA rats to one or more of several rat strains, including SHR, WKHT, WKY, and Wistar rats. In this study, it was important to choose a comparison strain that was a) genetically related to the WKHA strain, b) commonly used in behavioral studies, and c) without behavioral or neurochemical abnormalities that set it apart from other commonly used strains. It has been suggested, for example, that WKY rats may exhibit behavioral abnormalities themselves, including hypo-activity, compared to other commonly used albino strains (Drolet et al., 2002). Our own data also indicate that WKY rats do not process stimuli like other common albino strains as evidenced by reductions in attention and learning compared to other common strains (Chess et al., 2003). Likewise, the SHR and WKHT rats exhibit hypertension, which can adversely affect cognitive function unrelated to hyperactivity (e.g., Thyrum et al., 1995; Majeski et al., 2004). For these reasons, it was determined that the WKY, SHR, and WKHT rats were not likely to be useful comparison strains in the present study. Instead, the performance of WKHA rats was compared to Wistar rats in

the simple conditioning procedures used in Experiment 1. Indeed, more recent studies indicate that Wistar rats may be the most appropriate comparison strain in studies of WKHA rats (Drolet et al., 2002).

Materials and Methods

Subjects

Eleven male WKHA rats were bred and provided at 3 months of age by Dr. Edith Hendley (University of Vermont). Eight 3-month old male Wistar rats were obtained at the same time through Charles River Laboratories (Montreal, Canada). Once in our facility, all rats were housed individually and maintained on a 12:12 light-dark cycle. Both strains were housed in the same colony room and given 10 days to acclimate to the environment, with free access to food (Purina standard rat chow) and water. Over the course of another 10 days, body weights were gradually reduced to 85% of the initial ad libitum weights. At the start of behavioral training, all rats were between 3–4 months old and of similar weights (300–350g). Throughout the study, rats were monitored and cared for in compliance with AAALAC guidelines and the University of Vermont IACUC.

Conditioning Apparatus

Experiments were conducted using standard operant conditioning chambers (24 x 30.5 x 29 cm; Med Associates, St. Albans, VT) connected to a computer and enclosed in sound-attenuating chambers (62 x 56 x 56 cm) outfitted with an exhaust fan to provide air flow and background noise. The operant chambers consisted of aluminum front and back walls, clear acrylic sides and top, and grid floors. A dimly illuminated food cup was recessed in the center of one end wall; a 6-W jeweled panel light, which was the source of a visual CS, was located 5 cm above the opening to the recessed food cup. Surveillance cameras located inside each of the surrounding chambers were connected to a VCR and used to videotape the rats' behavior.

Conditioning Procedures

Rats were first trained to eat from the food cups. Two 45-mg food pellets (Noyes), which served as the unconditioned stimulus (US) throughout the experiment, were randomly delivered eight times within a single 30-minute session. All rats then received ten daily acquisition sessions each lasting 30 minutes and consisting of six 10-second presentations of the visual stimulus (conditioned stimulus, CS) co-terminating with the delivery of two food pellets. At the end of each session, animals were weighed and fed to maintain target weights. After the last acquisition session, six extinction sessions were introduced each consisting of 6 light-alone trials. Inter-trial intervals (ITIs) during acquisition and extinction sessions were variable and averaged 5 minutes.

Behavioral Observations

Behavior was scored from videotaped recordings of the experiment every 1.25 seconds during the 5-second period preceding the CS ("pre-CS"), the 10 seconds during the CS ("during-CS"), and 5 seconds after the CS terminated and food was delivered ("post-CS"). Food cup behavior was defined as nose poke entries into the food cup, head-jerk behavior around the food cup, or standing motionless in front of the food cup as described previously (Bucci et al., 1998; Holland, 1984). Rearing behavior was observed according to methods described by Holland (1977) and was defined as standing on the hind-legs with both forepaws off the ground. Grooming was not considered an instance of rearing, even if both forepaws were off the ground. Previous work has shown that rats typically exhibit mostly rearing behavior during the first 5 sec of a 10-sec visual CS and mostly food cup behavior during the second 5 sec of a 10-sec visual CS in appetitive conditioning preparations (Holland, 1977). Observations made during

the present experiments confirmed that pattern (data not shown) and thus rearing and food cup behavior were measured during the first and second half of the during-CS period, respectively. The index of response frequency was percent food cup or rear behavior, calculated as the number of times the subject was observed carrying out the target behavior divided by the total observations recorded during an observation period. The observer was unaware of the strain of each rat when scoring the videotapes. A secondary observer (also blind to strain) scored a subset of the data to assess inter-rater reliability. The two observers agreed on 98% of all observations.

Analysis of Conditioning Data

Nonparametric statistics were used for all analyses because it is unlikely that the data met standard assumptions of normality and homogeneity of variance since rats could only exhibit 0, 1, 2, 3, or 4 instances of a behavior during each of the observation periods. This type of analysis has been used previously with similar data (e.g., Bucci & Burwell, 2004; Bucci et al., 1998; Gallagher et al., 1990). Mann-Whitney U statistics were calculated for food cup and rearing scores across all sessions or trials, as appropriate. Wilcoxon T statistics were used to compare performance between the first trial and last trial of a training phase. An alpha level of 0.05 was used for all analyses.

Open Field Test

At the completion of the associative learning procedures, rats were provided free access to food in the home cage and allowed 10 days to return to free-feeding weights. Rats were then placed individually in a 43.2 X 43.2 cm open field composed of plexiglass walls and floor. The chamber was equipped with 16 photobeams mounted on the sides of the chamber at two different heights. Rats were allowed to freely explore the chamber for 15 minutes, during which the distance traveled was monitored by a computer and Open Field Activity Software (Med Associates, St. Albans, VT).

Analysis of Open Field Activity Data

The distance traveled during the 15-min open field session was divided up into 3-min blocks. Differences between strains were analyzed using a repeated measures analysis of variance (ANOVA), with Strain as the between-subjects and Block as the within-subjects variable. All analyses were conducted using an alpha level of 0.05.

Results

Acquisition

One of the Wistar rats was eliminated from the study because it exhibited no evidence of conditioning. For the remaining Wistar rats and the WKHA rats, food cup behavior during presentation of the visual stimulus increased from the first to the last session as shown in Figure 1A [Wilcoxon $T(7)=0$, $p<0.02$ (Wistar); $T(11)=0$, $p<0.02$ (WKHA)]. Despite the fact that rats in both groups learned the light-food relationship, the amount of food cup behavior exhibited by Wistar and WKHA strains during presentation of the CS differed significantly. WKHA rats exhibited lower levels of food cup behavior compared to Wistar rats [Mann-Whitney $U(7,11)=16$, $p<0.04$], suggesting that WKHA rats were slower to learn the association between the light and food. The amount of orienting behavior during presentations of the light also differed between the two groups of rats during presentation of the CS, as shown in Figure 1B. WKHA rats exhibited significantly less rearing than Wistar rats [$U(18)=15.5$, $p<0.04$], primarily during the first few sessions. During acquisition there was no significant difference in pre-CS food cup behavior or orienting behavior, i.e., during the 5 sec interval before the light was presented ($p>0.4$ and $p>0.3$, respectively). Likewise, there was no difference in the amount of food cup

behavior exhibited after the CS was terminated and food was delivered (post-CS), suggesting that motivation levels were comparable between the two strains. The mean post-CS food cup behavior for Wistar and WKHA rats was $74.9\% \pm 3.6$ and $67.6\% \pm 2.7$, respectively ($p>0.1$).

Extinction

Prior to the first extinction trial, Wistar and WKHA rats exhibited comparable levels of food cup behavior during presentation of the CS [data point “A” (mean of last 3 acquisition sessions) in Figure 2A; $p>0.9$]. Both Wistar and WKHA rats gradually reduced conditioned responding from the first extinction session to the last session as evidenced by decreasing food cup behavior in Figure 2A [$T's=0$, $p's<0.01$]. In addition, the overall amount of food cup behavior was comparable in Wistar and WKHA rats ($p>0.2$). Likewise, orienting behavior was comparable by the end of the acquisition session (data point “A” is the mean of last 3 acquisition sessions; $p>0.5$) and did not differ between Wistar and WKHA rats during extinction ($p>0.5$), as shown in Figure 2B. There were no significant differences in pre-CS food cup behavior or orienting behavior during extinction ($p>0.7$ and $p>0.9$, respectively).

Locomotor Activity

Activity levels during the 15-minute open field test are presented in Figure 3A. There was no significant main effect of Strain on the total distance traveled between Wistar and WKHA rats ($p>0.7$). Nevertheless, there was a trend towards a significant Strain X Block interaction [$F(4,64)=2.3$, $p=0.07$] such that WKHA rats tended to exhibit less activity during the early 3-min blocks and greater activity levels during the final blocks.

Discussion

The results of Experiment 1 indicate that WKHA rats exhibit deficits in conditioning to a visual CS compared to normo-active, normo-tensive rats. In addition to decreased food cup behavior, WKHA rats also exhibited lower levels of conditioned orienting behavior when the light was presented, indicative of decreased attentional processing of the CS. In contrast, during the extinction phase of the experiment food cup behavior and orienting behavior did not differ between WKHA and Wistar rats, indicating that under other circumstances associative processes are unaltered in WKHA rats. Likewise, food cup behavior during acquisition was comparable between the groups after the CS was terminated and food was delivered. Together, these data indicate that alterations in food cup or orienting behavior do not merely reflect performance deficits or differences in motivation. Interestingly, these alterations in stimulus processing and conditioning were observed despite the fact that pre-CS behavior was not different between the two strains, and there was only a marginal difference in habituation of locomotor activity in the open field test.

Although other behaviors were not systematically studied in this experiment, it may be that WKHA rats exhibit less food cup and orienting behavior during conditioning because they are unable to ignore extraneous stimuli also present in the training chamber (e.g., a speaker, houselight, etc.) and focus processing resources on the behaviorally-relevant, conditioned stimulus. If so, then behaviorally-irrelevant cues (i.e., non-reinforced) might be expected to garner more processing resources in WKHA rats than in normal rats. This possibility was explored further in Experiment 2.

EXPERIMENT 2

In this experiment, a new set of Wistar and WKHA rats first received non-reinforced presentations of the visual cue used in Experiment 1 (pre-exposure phase). Normo-active rats initially exhibit high levels of orienting behavior to a non-reinforced cue, which rapidly habituates as the rat comes to learn that the cue does not signal a biologically significant event.

This is thought to reflect a decrease in attention to behaviorally-irrelevant stimuli (Gallagher et al., 1990; Kaye & Pearce, 1984). When the same stimulus is later paired with food during the conditioning phase, the orienting response re-emerges and conditioned food cup behavior increases, indicative of renewed interest in the stimulus (Gallagher et al., 1990). It was hypothesized that if WKHA rats have difficulty ignoring irrelevant stimuli, then unconditioned orienting to the light may remain high in WKHA rats compared to Wistar rats during the pre-exposure phase. Alternatively, if less unconditioned orienting behavior is exhibited by WKHA compared to Wistar rats, especially during the first few trials, this would indicate that WKHA rats attend to novel, behaviorally-irrelevant cues less than Wistar rats.

Materials and Methods

Subjects

A new set of three-month old male WKHA (n=10) and Wistar (n=12) rats were used in Experiment 2. Animals were obtained and maintained exactly as described in Experiment 1. The *Apparatus*, *Behavioral Observations*, *Open Field Test*, and *Analyses* were carried out exactly as described in Experiment 1.

Behavioral Procedures

This task included two phases, the first of which consisted of two daily sessions of non-reinforced light presentations (pre-exposure phase). Rearing behavior exhibited during the pre-exposure phase was referred to as “unconditioned orienting.” The second phase consisted of six daily sessions of light-food pairings as in Experiment 1 (training phase); rearing behavior exhibited during the conditioning phase was referred to as “conditioned orienting.” All sessions lasted approximately 30 minutes each with a variable ITI averaging 5 minutes.

Results

Pre-exposure Phase

During the pre-exposure phase of the experiment (Figure 4), strain differences were apparent in unconditioned orienting behavior during presentations of the visual stimulus. First, WKHA rats exhibited significantly less unconditioned orienting compared to Wistar rats [$U(10,12)=13$, $p<0.001$] during the pre-exposure phase. Secondly, Wistar rats [$T(12)=6.5$, $p<0.03$] but not WKHA rats ($p>0.2$) exhibited habituation of the unconditioned orienting response as evidenced by decreased rearing from trial 1 to trial 12. There were no differences in pre-CS unconditioned orienting behavior during the pre-exposure phase ($p's>0.9$).

Conditioning Phase

Once the visual cue was reinforced, Wistar rats continued to exhibit significantly more rearing behavior (conditioned orienting) during presentations of the CS across conditioning sessions compared to WKHA rats, as presented in Figure 5A [$U(10,12)=27$, $p<0.03$]. Interestingly, the direction of this effect was opposite to a difference observed in pre-CS orienting, in that WKHA rats exhibited significantly more rearing than Wistar rats during the pre-CS period [$U(10,12)=25$, $p<0.02$]. Food cup behavior during presentations of the CS was comparable between strains during the conditioning phase of the experiment, as shown in Figure 5B ($p>0.6$). There was again a significant difference in pre-CS behavior, but in this case Wistar rats exhibited more food cup behavior than WKHA rats before the light was presented [$U(10,12)=14$, $p<0.01$]. Notably, in both cases the observed differences in pre-CS behavior were opposite to the responding patterns observed during presentation of the CS, and so it was unlikely that differences in orienting or food cup behavior during presentation of the light were simply due to pre-CS differences.

Locomotor Activity

Locomotor activity during the open field test in Experiment 2 is depicted in Figure 3B. As in Experiment 1, there was no significant main effect of strain on locomotor activity levels ($p>0.2$). There was a significant interaction between strain and block [$F(4,80)=3.13$, $p=0.03$] in that WKHA rats exhibited greater activity levels than Wistar rats during the final blocks of the session.

General Discussion

The present experiments were designed to examine basic stimulus processing and learning abilities in WKHA rats, a strain currently under scrutiny as a potential animal model of ADHD and other attention disorders in humans. Experiments 1 and 2 examined the ability of WKHA rats to process unconditioned and conditioned stimuli and acquire stimulus-reward relationships in simple classical conditioning paradigms. A second goal was to determine if reported increases in locomotor activity in WKHA rats translated to alterations in task-related measures of activity, such as responding before presentation of a conditioned stimulus (i.e., pre-CS responding). In Experiment 1, WKHA rats exhibited deficits in both attentional processing and conditioning to a visual cue that predicted food reward. Extinction of conditioned food cup behavior, however, was unaltered in WKHA rats. Both strains also exhibited comparable levels of orienting behavior during extinction. In Experiment 2, WKHA rats exhibited less attention to a behaviorally-irrelevant cue as indicated by abnormally low levels of unconditioned orienting. Once the cue was paired with food, however, WKHA rats were able to learn the stimulus-reward association at the same level as control rats. These alterations in attentional function and learning were present despite the lack of consistent changes in pre-CS responding or differences in post-CS responding between the two strains.

The results of both Experiments 1 and 2 indicate that WKHA rats exhibit impairments in attentional processing of environmental stimuli compared to Wistar rats. The amount of orienting behavior directed towards a stimulus, in this case rearing on the hind-legs during presentation of a visual stimulus, is thought to reflect attentional processing of that cue (e.g., Kaye & Pearce, 1984; Gallagher et al., 1990). Alterations in processing were apparent regardless of whether the stimulus was behaviorally-relevant (i.e., paired with food), as in Experiment 1, or irrelevant (e.g., non-reinforced) as in Experiment 2. Importantly, the frequency of orienting behavior was reduced in WKHA rats even during the first few trials of the pre-exposure phase of Experiment 2. Normally orienting behavior is quite high during those trials (Gallagher et al., 1990) since the visual cue is novel and the subject has not yet learned that the stimulus does not predict biologically-significant future events.

Not surprisingly, the deficit in attentional processing of the visual cue was reflected in lower levels of conditioned food cup behavior in WKHA rats in Experiment 1. Indeed, food cup responding in WKHA rats was lower than that exhibited by Wistar rats. This is predicted by contemporary learning theories which maintain that reduced processing of a conditioned stimulus often leads to impaired conditioning to that cue (Pearce & Hall, 1980; Kaye & Pearce, 1984; Lubow & Moore, 1959). In Experiment 2, however, food cup behavior was comparable in WKHA and Wistar rats during the conditioning phase of the experiment. The only difference between this experiment and Experiment 1 was the inclusion of two days of stimulus pre-exposure prior to conditioning; nevertheless, the introduction of this pre-exposure phase drastically altered the performance of WKHA rats. Previous studies have demonstrated that pre-exposure to a non-reinforced stimulus can retard subsequent learning to that stimulus, an effect known as latent inhibition (Lubow & Moore, 1959). It is thought that non-reinforced presentations of a stimulus lead to reductions in attentional processing, which impair subsequent learning when the stimulus is later paired with food. Although Experiment 2 was not designed to assess latent inhibition per se, it is interesting to question whether the pre-

exposure phase produced a latent inhibition effect in the Wistar group but not the WKHA group. Wistar rats initially displayed high levels of orienting behavior (i.e., high degree of processing) which decreased over the course of several trials (i.e., decreased processing) as observed previously (Gallagher et al., 1990). WKHA rats, on the other hand, exhibited less processing of the cue during the pre-exposure phase as evidenced by consistent, low levels of orienting behavior throughout the entire pre-exposure phase. Thus, in WKHA rats the stimulus would not have undergone the usual alterations in attention that presumably occurred in the Wistar rats.

There are several other possible alternative explanations for the stimulus processing and conditioning deficits exhibited by WKHA rats. First, WKHA rats could be less motivated by food than Wistar rats. This does not seem likely, however, since WKHA and Wistar rats exhibited comparable levels of post-CS food cup behavior in Experiment 1. Secondly, WKHA rats may be impaired in their ability to perform the orienting response or food cup response. However, comparable performance during the extinction phase of Experiment 1, as well as comparable levels of food cup behavior during the conditioning phase of Experiment 2 argues against this possibility. In addition, it is possible that a strain difference in general activity could underlie differences in conditioned responding. This also does not seem likely, since only minor differences were observed in the open field test in Experiment 2 and they did not translate in any consistent fashion to differences in pre-CS responding, which is arguably a better (e.g., more task-relevant) measure of baseline activity. Thus, it is likely that the observed alterations in conditioned responding in WKHA rats do reflect strain-related deficits in attentional processing and learning.

Developing valid models of attentional dysfunction in humans, particularly ADHD, is currently an area of great research interest (Ferguson, 2001; Paule et al., 2000). Existing models, such as the SHR strain are constrained by the possible confounding influence of hypertension (Ferguson, 2001; Sagvolden, 2001). Thus, it has been difficult to interpret observed alterations in cognitive function in SHR rats since hypertension is known to negatively affect cognition (Thyrum et al., 1995; Majeski et al., 2004). The WKHA strain has appeared to be an attractive alternative, as it is normo-tensive but still retains alterations in catecholaminergic function reminiscent of those observed in ADHD (Hendley & Fan, 1992; Hendley, 2000). Indeed, it has been suggested that WKHA rats may provide a “naturalistic” animal model of ADHD (Hendley, 2000).

ADHD is characterized by a variety of behavioral and cognitive alterations (reviewed by Nigg, 2001), including changes in reinforcement sensitivity, inattention, as well as hyperactivity and impulsivity. Some researchers have argued that deficits in executive inhibitory control are at the core of ADHD (Barkley, 1997) while others maintain that symptoms arise primarily from motivational inhibition impairments (e.g., Newman & Wallace, 1993). For example, deficits in extinction are associated with ADHD, supporting the notion that individuals with ADHD may react more strongly to situations where expectations of reward are violated (Johansen & Sagvolden, 2004; Johansen et al., 2002; Douglas & Parry, 1994). The lack of differences in orienting behavior or food cup behavior during extinction in Experiment 1 suggests that WKHA rats may not share this behavioral phenotype with ADHD. Likewise, WKHA rats did not exhibit alterations in responding during extinction using operant conditioning procedures (Sagvolden et al., 1992). The present findings complement those of Sagvolden et al. (1992) and also increase the interpretability of their results by providing insight into the basic learning abilities of WKHA rats and examining levels of pre-CS responding and general motivation.

Previous studies have reported increased locomotor activity in WKHA rats compared to SHR, WKHT or WKY strains (Hendley & Ohlsson, 1991; Sagvolden et al., 1992; Courvoisier et al., 1996), suggesting that WKHA rats may model the hyperactivity observed in ADHD. However,

a more recent study indicates that WKHA rats are not hyperactive when compared to more commonly used, non-hypertensive albino rats, such as Wistars (Drolet et al., 2002). Indeed, there is evidence that WKY rats, for example, are actually hypoactive and not representative of other common normo-tensive strains (Drolet et al., 2002; Chess et al., 2003). The present findings replicate those of Drolet et al., (2002) in finding that locomotor activity did not differ between WKHA rats and Wistar rats when measured by total distance traveled in an open field chamber during a 10 min (Drolet et al., 2002) or 15 min (present study) test period. However, when the test session was broken down into smaller epochs, our data indicate that activity in the open field does not habituate as quickly in WKHA rats compared to Wistar rats, although this effect only reached statistical significance in Experiment 2. This analysis was not reported by Drolet et al. (2002), so it is possible that similar results may have been obtained in that study as well. Regardless, the present findings, along with those of Drolet et al., (2002) call into question whether or not WKHA rats are hyperactive when compared to more common strains.

Other theories of ADHD emphasize deficits in cognitive suppression, including attentional orienting deficits mediated by posterior cortical systems (Rafal & Henik, 1994; Nigg, 2001). Previous studies in rats (reviewed by Holland, 1997) have produced substantial data supporting the existence of two separable attentional processing systems: an incremental and a decremental system. The ability to increase attentional processing of a stimulus relies heavily on a system involving the posterior parietal cortex (Bucci et al., 1998; Bucci & Chess, 2003; Bucci et al., 1995) and specific cholinergic (Chiba et al., 1995; Baxter et al., 1997, 1999) and dopaminergic pathways (Han et al., 1997; McDannald et al., 2004a, 2004b). The results of Experiments 1 and 2 suggest that the ability to increase attentional processing may be impaired in WKHA rats, and that WKHA rats, in general, process cues less than Wistar rats. Indeed, WKHA rats exhibited impaired orienting to the light whether it was paired with food from the outset (Experiment 1) or later came to predict the delivery of food (second phase of Experiment 2). In addition, Wistar rats but not WKHAs exhibited elevated levels of orienting once the light was paired with food in the conditioning phase of Experiment 2. This notion is consistent with alterations in dopaminergic (Hendley & Fan, 1992; Hendley, 2000) and possibly cholinergic functioning (Kwok et al., 2002) in WKHA rats.

Although WKHA rats may not share all of the behavioral characteristics of ADHD, this strain may serve as a useful model of attentional processing deficits associated with ADHD and other clinical disorders. Moreover, given the intense debate regarding the fundamental basis for the behavioral deficits associated with ADHD, it is doubtful that any single animal model could encompass all aspects of ADHD. The present results clearly indicate that WKHA rats exhibit impairments in their ability to process and attend to environmental stimuli. These alterations in attention and learning in WKHA rats are not confounded by performance-related abnormalities such as changes in pre-CS responding, suggesting that WKHA rats may provide a unique model of attention and learning impairments.

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Figure 1.

Food cup and orienting behavior during presentation of the CS in the acquisition phase in Experiment 1. Food cup behavior (panel A) increased in both strains over the course of consistent, repeated pairings of a visual cue and food. However, WKHA rats exhibited less overall food cup responding compared to Wistar rats. WKHA rats also exhibited less

conditioned orienting behavior (panel B) compared to Wistar rats, particularly at the outset of conditioning. All data are mean $\pm$ SEM.

Figure 2.

Food cup and orienting behavior during presentation of the CS during the extinction phase of Experiment 1. Food cup responding decreased in both Wistar and WKHA rats over the course of extinction (panel A), and was comparable in WKHA and Wistar rats. Orienting behavior

did not differ between WKHA and Wistar rats during extinction (panel B). All data are mean $\pm$ SEM.

Figure 3.

Distance traveled in the open field test in Experiments 1 (panel A) and 2 (panel B). WKHA and Wistar rats did not differ in overall locomotor activity exhibited during the 15 minute exposure to the open field chamber, although activity was slower to habituate in WKHA rats in Experiment 2. Data are mean $\pm$ SEM.

Figure 4. Orienting behavior during non-reinforced presentations of the visual cue in Experiment 2. Unconditioned orienting was greater in Wistar rats relative to WKHA rats during non-reinforced exposure to the visual cue. The orienting response habituated in Wistar rats but not WKHA rats. Trials 1–6 occurred on Day 1, trials 7–12 occurred on Day 2. All data are mean $\pm$ SEM.

Figure 5.

Food cup and orienting behavior during presentation of the CS during the conditioning phase of Experiment 2. When the visual cue was reinforced, Wistar rats displayed increased conditioning orienting compared to WKHA rats (panel A). In contrast, food cup behavior (panel B) was comparable in WKHA rats compared to Wistar rats. All data are mean $\pm$ SEM.