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## The Roman Lines/Strains of Rats

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### INTRODUCTION

The Swiss sublines of Roman high (RHA/Verh) and low (RLA/Verh) avoidance rats, descended from the RHA and RLA rats founded by Bignami[1] from Wistar stock, have been selected and bred since 1972 on the basis of their divergent performance in active, two-way avoidance (shuttle box) behavior.[2–4] The initial acquisition of two-way avoidance has been shown to be strongly dependent upon emotional factors (see Refs. 4–6). RHA/Verh rats, which acquire avoidance quickly, do so mainly because they are less emotionally reactive, coping actively with that test in comparison to RLA/Verh rats which, as passive copers, show

much freezing (immobility) behavior. The two rat lines are also known to differ in many other respects, both at the behavioral and neuroendocrine/neurochemical levels. When exposed to a novel environment (or various other stressors) RLA/Verh rats show more pronounced emotional responses such as more defecation, immobility or self-grooming activity, a comparatively higher activation of the hypothalamo-pituitary-adrenal (HPA) axis, and especially higher plasma prolactin (PRL) levels than do RHA/Verh rats.[2,3,7–12] A large number of neurochemical differences have been reported, a few of which will be mentioned in this review.

## STRESS AND PROLACTIN

A factor that may be important for stressor-induced PRL secretion is the "controllability" of the stressor.[13] Those investigators discovered that, when RHA/Verh rats can control their emotional response by actively exploring the environment, stress-induced PRL secretion was rapidly reduced, that not being the case for RLA/Verh rats exposed to the same treatment. The mediator in this control was believed to be dopamine (DA), as DA is a major PRL-inhibiting factor. Rats from the RHA/Verh line have shown a more pronounced activation of the mesocortical DAergic system under stress conditions, associated with increased locomotor activity and with an activation of cognitive processes in an attempt to cope with stressors.[3,14,15] If this increased DA activity also occurs in the tuberoinfundibular system controlling PRL secretion this could explain why, when RHA/Verh rats can master a stressful situation through locomotor activity, they are better able to reduce PRL secretion.[13]

## GLUCOCORTICOID RECEPTORS

Corticosteroid action in the brain is mediated by specific glucocorticoid receptors (hippocampal type I and pituitary type II), which are critically involved in HPA axis regulation. Differences have been reported in adult male RHA/Verh and RLA/Verh rats under baseline conditions, with the latter line having lower levels of both types. This may result in a reduced feedback efficacy for RLA/Verh rats.[8] Indeed, recent experiments have suggested a partial dysregulation of the HPA axis in RLA/Verh rats, which exhibited a more pronounced response to a corticotropin-releasing factor (CRF) challenge under dexamethasone suppression, much as one observes in a large majority of depressed patients.[13] Future studies dealing with changes in glucocorticoid receptors under stress conditions would certainly provide valuable information on these topics.

## CORTICOSTERONE, ACTH, CRF, AND VASOPRESSIN

Both ACTH and corticosterone responses to CRF have been investigated in a number of studies. Ovine CRF was shown to induce a significantly larger increase in plasma ACTH in RLA/Verh rats, both *in vivo* and *in vitro*,[8] this effect being apparently age dependent.[11] Studying the expression of CRF and vasopressin (VP), both of which are neurohormones exerting a synergistic action on ACTH release, it was found under basal conditions that RLA/Verh rats had higher VP mRNA levels in the parvicellular neurons of the paraventricular nucleus (PVN),

there being no difference in CRF mRNA levels. It was suggested that differences in basal VP expression in CRF neurons of the PVN may participate in the mechanisms underlying the hyperactivity of the HPA axis in the RLA/Verh rats.[10] VP also appears to play a part in mediating some aspects of the behavioral and physiological responses observed during conditioned, stressful environmental challenges, exerting its action at the central nucleus of the amygdala (CEA). Low doses of arginine-8-VP (AVP) injected into the CEA of conscious RLA/Verh rats enhanced stress-induced bradycardia and immobility in that line, whereas high doses of AVP or oxytocin attenuated the same responses. Neither stress responses nor drug effects were seen in RHA/Verh rats, suggesting that differences in CEA receptor densities and/or VP innervation may contribute to the differences in behavioral coping strategies characterizing the two lines of rats.[16]

## ALTERING BEHAVIORAL RESPONSES TO STRESSORS THROUGH ENVIRONMENTAL MANIPULATION

As previoulsy mentioned, exposure to various stressors induces a more pronounced emotional response in RLA/Verh rats, such as higher levels of defecation,[2,4,12,16,17] immobility,[2,4,6,17] and self-grooming activity[6,11,12] than in RHA/Verh rats. In comparison to this style of "passive coping," rats of the RHA/Verh line are "active copers," exploring more and taking more risks[9,12,13,17] (as, for example, more quickly entering the brightly lit compartment of a black/white box test after having been initially placed in the dark compartment,[6] being willing to drink strange, and sometimes even aversive, liquids,[18] and eagerly seeking out novelty, for example, in a hole board test with strange objects placed under the holes[9]) than do RLA/Verh rats. Some of these behavioral differences are summarized in TABLE 1. In addition, a series of studies has shown that emotional, or fearful, responses to various stressors, including HPA axis responses[6–8,10,11,13] as well as stressor-induced decrements in exploratory behavior, can be enduringly altered by neonatal handling in rats.[19] Changes induced by neonatal handling on the behavioral and hormonal responses seen in the Roman lines, as summarized in TABLE 1, are also listed there. Neonatal handling in all cases consisted of 1–21-day-old rats being placed individually in plastic cages (on paper towels) twice daily for 10 min. After the first 5 min and at the end of the 10-min period, each pup was gently handled for 3 sec. Nonhandled rats were left undisturbed until weaning at 21 days of age. The rats were later tested as adults.[4,9,19]

## THE MESOCORTICAL DOPAMINE PROJECTION

The mesocorticolimbic DAergic system consists of two major projections, both of which originate in the ventral tegmental area of the brainstem. The mesoaccumbens projection terminates in the ventral striatum (nucleus accumbens) whereas the mesocortical projection largely innervates the medial prefontal cortex. The latter system is involved in the regulation of goal-directed behavior and in the locomotor and rewarding effects of psychostimulants and other drugs of abuse, as well as in the (previously infered) regulation of emotional states and cognitive and attentional processes. As mentioned earlier, RHA/Verh rats show a more pronounced activation of the mesocortical DAergic system under stress conditions, which has been interpreted as an activation of cognitive processes in an

**TABLE 1.** Differences between RHA/Verh (RHA) and RLA/Verh (RLA) Rats, and the Effects of Neonatal Handling Thereon, in Some Behaviors Related to Emotionality, Novelty Seeking, and Hormonal Stress Responses[a]

| Emotionality Measure | Interline Difference | Effect of Neonatal Handling on | |
|---|---|---|---|
| | | RHA | RLA |
| New cage | | | |
| • Defecation | RHA < RLA | ↓ | ⇓ |
| Fear conditioning | | | |
| • Defecation | RHA < RLA | == | ↓ |
| Labyrinth | | | |
| • Activity | RHA > RLA | ↑ | ⇑ |
| • Entries into lit center | RHA > RLA | ↑ | ⇑ |
| • Defecation | RHA < RLA | ↓ | ⇓ |
| Black/white box | | | |
| • Initial crossing latency | RHA < RLA | == | == |
| • Self-gromming latency | RHA > RLA | ⇑ | ↑ |
| • Defecation | RHA == RLA | ↓ | ⇓ |
| Hyponeophagia | | | |
| • Latency to start eating | RHA < RLA | == | ⇓ |
| • Time spent self-grooming | RHA < RLA | == | ⇓ |
| • Defecation | RHA < RLA | == | == |
| Hole board exploration and preference for new objects and/or spaces | RHA > RLA | ↑ | ⇑ |
| Hormonal stress responses | | | |
| • ACTH | RHA < RLA | == | == |
| • Corticosterone | RHA < RLA | == | ↓ |
| • PRL | RHA < RLA | == | ↓ |

[a]Arrows and double arrows indicate magnitude and direction of the effects of neonatal handling on those paradigms as follows: ==: no difference; ↑ or ↓: significant increase or decrease; ⇑ or ⇓: very significant increase or decrease.

attempt to cope with the stressors.[3,14,15] Under these same conditions (tail pinch, loud noise, restraint, etc.), RLA/Verh rats showed much freezing behavior, self-grooming and defecation, whereas the RHA/Verh rats increased their locomotor activity or "fought with the stressor" more (e.g. tail clamps) when applicable.[14,15]

It can be seen, therefore, that the pattern of an individual's stress response is determined not only by the event (stressor) but also by the ability or inability of the individual to cope with it, depending upon the adequacy of their (usual) coping style.[20] Two other neurotransmitter systems which undoubtedly play important roles in the process of differential stress responses are the serotonergic system and the $GABA_A$/Benzodiazepine Receptor/$Cl^-$ complex, both of which are being continuously studied in the Roman rat lines,[4,21–23] and which will be subjects of a later review.

## THE MESOACCUMBENS DOPAMINE PROJECTION AND DRUGS

The mesoaccumbens projection has proven to be of particular interest in connection with the effects of cocaine and morphine in RHA/Verh and RLA/Verh

rats.[24] An acute challenge with low doses of either drug caused significant locomotor activation in RHA/Verh rats only, as well as a significantly larger activation of the DAergic mesolimbic (mesoaccumbens) projection, also only in that line of rats, as reflected by increments in DA output in the shell area of the n. accumbens. That area, considered to be part of the "extended amygdala," is more involved in motivation and emotivity than is the core area, which is rather involved in motor functions. Within the framework of the incentive motivational theories of behavior, it has been proposed that the repeated administration of drugs of abuse is associated with abnormal motivational learning due to a persistent, that is, nonadaptive, increment in DA release in the shell of the nucleus accumbens,[25] facilitating the acquisition and maintenance of two interactive processes; incentive learning (the association between drug stimulus and reward) and habit learning (the association between drug-related stimuli and drug-seeking behavior).[24,25] The results obtained with RHA/Verh rats, therefore, are important in the light of their novelty-seeking type of behavior. Based on their affinity for alcohol and other substances[18] and their stronger reaction (stimulatory) to other drugs that exert their effects largely through the DAergic system (see Refs. 15 and 24), as well as other aspects of their behavior in, for example, hole board,[9,19] hyponeophagia and conflict,[12] and DRL (impulsiveness)[26] tests, we enter the realm of what may be classified as "sensation seeking" behavior.

## SENSATION SEEKING IN RHA/VERH RATS

Sensation seeking (SS) in humans is characterized by high levels of exploratory and novelty ("thrill") seeking behaviors and disinhibition (impulsive activity, alcohol and drug use, conspecific aggression, etc.).[27] Subjects who score high on Zuckerman's SS scale also show visual evoked potential (VEP) augmenting, whereas non-SS types of individuals are VEP reducers. Briefly, VEP amplitudes are recorded from the cerebral cortex (scalp in humans) as a function of stimulus intensity. As the light flash stimulus increases, the normal psychophysical expectation is that the amplitude of the evoked response would also increase. This occurs, however, only in SS subjects.[27] After having demonstrated this phenomenon in humans and cats, on both of which the association between VEP augmenting and the appropriate behavioral criteria were found to be very strong, the suspected genetic aspects of the SS-VEP relationship were investigated in the Roman rat lines, whose well-known behavioral differences appeared to make them good subjects for such a study.

Indeed, as with SS humans and cats, the slopes of $P_1$ amplitudes as a function of flash intensity (5 flashes) were significantly greater in RHA/Verh rats (which were thereby augmenters) than in either RLA/Verh or locally obtained Wistar rats, the latter two groups both showing almost identical, flat amplitude-intensity functions (thereby classifying them as reducers).[28] These findings showed that (a) the relationship between SS behavior and VEP augmenting vs reducing (A/R) is also present in rats (as with cats and humans), (b) A/R is a cortical and not a subcortical phenomenon, and (c) A/R and related SS behaviors are heritable, the latter finding being further supported by steadily increasing amounts of data obtained with humans.[27] The association between A/R and such SS characteristics as preferences for rewarding substances,[18] and behavioral and CNS sensitivity to psychostimulants and addictive drugs[24] leads us into the important topic of alcohol consumption.

## RAT MODELS AND ALCOHOL CONSUMPTION

Human studies have implied that a direct effect of stress on alcohol-related problems is highly questionable.[29] Anyway, as even those rats that enjoy drinking alcohol (the great majority do not) will not voluntarily do so to the state of becoming either drunk or addicted, there is no really effective model of alcoholism in rats (forced drinking with liquid diets, a stressor in itself, is certainly not an acceptable model for the human condition). The various bidirectionally selected lines of rats that prefer/do not prefer alcohol (e.g., AA/NA, P/NP, etc.), therefore, are rather models of "social drinking" than of alcoholism. This puts ethanol (E) preference in rats into a different, albeit still interesting, light. Through a well-formulated study combined with a comprehensive consideration of the literature, Razafimanalina *et al.*[18] have set up some genuine breakthroughs in this field. First, they eliminated emotionality differences as a crucial factor in E preference by showing that a report on "more anxious" P rats vs "less anxious" NP rats was not reconcilable with a report on "more emotional" rats selected for low saccharin (S) preference versus "less emotional" rats selected for high S preference,[30] because rats selected for E preference are almost invariably known to also consume more S.[18] Second, as both E and S preferring rats do not prefer quinine (Q) solutions to water, and as RHA/Verh rats (which had been bred in Bordeaux for several generations) prefered all three (E, S, and Q) to water, they concluded that rats selectively bred for divergence in E preference cannot be directly compared to rats selectively bred for high and low shuttle box avoidance.[18] Finally, this left the E-, S-, and Q-preferring RHA/Verh rats in a position that perhaps no selectively bred rats have been in to date, particulary in comparison to their RLA/Verh counterparts, which demonstrate a total aversion to all three compounds. The peculiar preferences of the former were thereby interpreted as apparent attempts to increase their levels of sensory stimulation.[18] This provides, also in the opinion of those authors, further evidence in the direction of these two lines of rats being a good model for studying the SS trait, in addition to their obvious usefulness in studying the effects of stress from a genetic/developmental standpoint.[11,13,19]

## INBREEDING IN PREPARATION FOR MOLECULAR-MAPPING STUDIES

One of the future projects decided upon has been to try to identify the genetic bases responsible for the divergent emotionality profiles seen in these rats. Toward this end, an inbreeding program was initiated in 1993, derived through brother/sister mating from the hitherto outbred lines (the latter also being continued in parallel, of course). In line with previous, similar programs,[31,32] a first step in the molecular mapping of a trait would be to find markers that distinguish the two inbred Roman strains. To date, 128 markers have been analyzed, and 26 of those have been found to be polymorphic between the strains. In order to cover the genome at sufficient density to detect loci that contribute 5% or more to the phenotypic variance of a trait, at least 80 markers are required. It has been estimated that another 330 markers must be analyzed to achieve that goal.

## BEHAVIORAL TESTING WITH THE INBRED ROMAN STRAINS

In the meantime, the inbred strains have undergone much behavioral testing, starting in 1995 at about the sixth generation, with the main purpose of deter-

mining their adherence to the well-established behavioral profiles of the outbred lines. Similar results have been found so far in the hole board apparatus, with the inbred RHA/Verh/I (RHA/I) rats exploring more and showing more novelty seeking when new objects were introduced beneath the holes than their inbred RLA/Verh/I (RLA/I) counterparts did. Results in the shuttle box (two-way, active avoidance acquisition) have been virtually identical to those found with the outbred lines, further confirming the continuity of the basis of selection. As in previously mentioned studies,[17,19] young RHA/I and RLA/I rats have shown the same behavioral patterns in both a hexagonal tunnel maze (the labyrinth referred to in Table 1—here the RLA/I rats also showed less entries into the illuminated central arena, decreased locomotor activity, and increased defecation compared to RHA/I rats) and in a conditioned fear test as the outbred lines have.[33] RLA/I rats have also been found to be more sensitive than RHA/I rats were to the narcotic effects of intraperitoneal injections of ethanol, confirming earlier studies with the outbred lines.

## DIFFERENCES IN THE ACOUSTIC STARTLE RESPONSE

One of the most valuable findings has been with a test that will most certainly be part of the battery of tests involved in the molecular mapping project, that being the acoustic startle paradigm. In that study,[34] RHA/I and RLA/I rats received 40 acoustic stimuli followed by 10 electric footshocks and another 30 acoustic stimuli. RLA/I rats showed significantly higher startle response amplitudes, before and after the shocks, than did RHA/I rats (all adult males), indicating a stronger emotional reaction to the acoustic stimuli, as well as a stronger response to the footshocks. It was concluded that RLA/I rats show more pronounced emotional reactions to fearful stimuli.

## DIFFERENCES IN THE ELEVATED PLUS-MAZE

In another test that will undoubtedly be used, rats of both strains were exposed to an elevated plus-maze. One group of each strain was tested during the dark phase of the light-dark cycle under very dim (red) light conditions and another group of each during the light phase under lighted conditions. Each rat was placed in the maze facing an enclosed arm and tested for 5 min. The results can be seen in FIGURES 1 and 2, with strain differences being found in several of the measures, as well as a lighting effect on grooming behavior in RHA/I rats (FIG. 2). FIG. 1 shows that the RLA/I rats were more "fearful" in regard to one commonly measured item, that being entries into the open arms, whereas there were no significant differences between the strains in time spent in the open arms. FIGURE 2, however, shows that the RLA/I rats were also more "fearful" in regard to distance travelled in the open arms, in latency to start grooming, and the total time spent self-grooming. A principal lesson to be learned here is that many more behaviors can be measured with this test than the usually measured "time spent in and number of entries into open/closed arms," for example, the additional three items shown in FIGURE 2. Another would be (not measured here) rearing behavior in both the open and closed arms.[19] Several other well-founded criticisms and warning-notes have been sounded from various quarters that should at least dissuade investigators from relying on this test as the only one to be used to measure fearfulness or emotionality (not to mention "anxiety").[19,35,36]

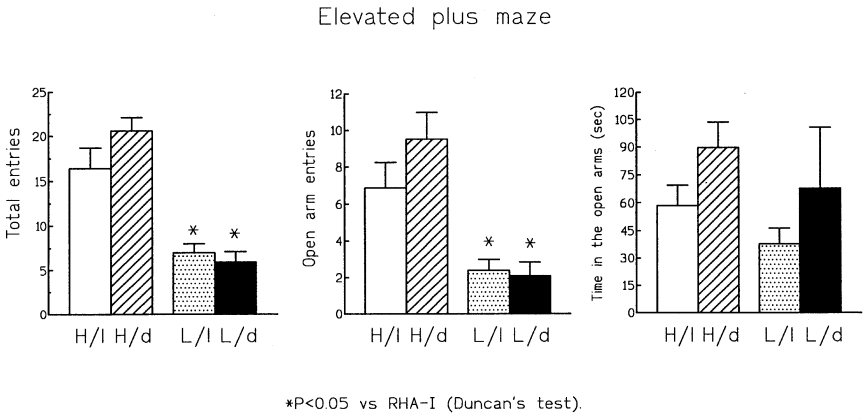


**FIGURE 1.** Elevated plus maze results in three commonly used criteria of measurement. H=RHA/I rats, L=RLA/I rats, l=light phase, lighted maze, d=dark phase, dimly lit maze.

## CONCLUSION

RHA/Verh and RLA/Verh rats, originally selected and bred for rapid versus poor acquisition of a two-way active avoidance response, differ in emotional reactivity, sensitivity to stressors, and in their coping strategies in other testing situations, as well. These differences are associated with certain neuroendocrine and neurochemical characteristics, and it has been demonstrated that neonatal handling can have long-lasting effects on several of these behavioral and physiological attributes, particularly in the direction of reducing the emotional responses of

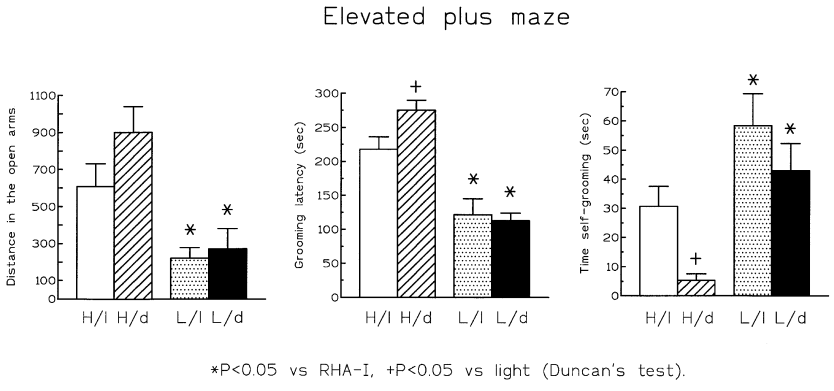


**FIGURE 2.** Elevated plus maze results in three additional (unconventional, innovative) criteria of measurement. Same symbols as FIGURE 1. (See text for explanations.)

RLA/Verh rats. Newer elements in this collaborative project have been an awareness of the importance of novelty (sensation) seeking in the RHA/Verh phenotype and the production of inbred strains in parallel. These should enable the undertaking of a molecular genetic analysis based on divergent emotional responses to stressors, when the latter are considered in conjunction with eventual dispositions in simultaneously measured characteristics of the $F_2$ generation crosses.

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