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Genetic determinants of individual differences in avoidance learning: Behavioral and endocrine characteristics

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Abstract. Bidirectional genetic selection for good and poor active avoidance learning in a shuttle box has been carried out in three independent laboratories using remarkably similar discrete-trial training procedures. The resulting strains are known as the Roman High and Low Avoidance (RHA and RLA), the Syracuse High and Low Avoidance (SHA and SLA) and the Australian High and Low Avoidance (AHA and ALA) strains, respectively. An additional unidirectionally selected strain, known as the Tokai High Avoider (THA) strain was developed in Japan using a free-operant Sidman avoidance procedure in a Skinner box. This paper reviews the selection of the Syracuse strains, enumerates the various behavioral and endocrine characteristics of the strains, and compares them to the other similarly selected strains. The behavioral work suggests that genetic selection from diverse breeding stocks has resulted in common characteristics that differentiate the strains in the emotional, not learning, domain. The endocrine data, however, are somewhat at odds. The Syracuse strains differentiate one way with respect to endocrine function, and the Roman strains differentiate in the opposite way. We suggest, therefore, that the endocrine correlates are not tightly linked to the avoidance genotype. Genetic analysis of all of the selected strains for both the avoidance phenotype and the endocrine correlates will be needed to test this hypothesis.

Key words. Genetic selection; Syracuse High and Low Avoidance strains; Roman High and Low Avoidance strains; Australian High and Low Avoidance strains; Tokai High Avoider strain; rats; open-field behavior; passive avoidance; CER suppression; stress-induced analgesia; behavioral contrast; pituitary-adrenal axis; plasma and adrenal corticosterone.

Introduction

Although our preliterate ancestors were undoubtedly aware of the existence of individual differences (one must assuredly assume they were aware of sex differences), it was not until late in the 18th century that scientists made the first systematic quantitative observations of individual differences by determining an astronomer's 'personal equation' for making measurements of stellar transits. The measurements were done by noting the time on a clock when a star entered the visual field of the telescope and by counting the number of 1-sec ticks of the clock until the star had just reached a critical line in the telescopic field and then counting the number of ticks required for the star to cross that critical line. The difference between the two numbers was the transit time. It turned out that there were rather large individual differences in these measurements, which clearly involved both visual and auditory reaction times and probably attention and vigilance as well. Not only did two individuals differ from each other, but the difference between them varied over time, suggesting that the 'personal equation' of one or both individuals was not invariant[1]. However, not until the invention of chronometric instruments and the establishment of Wundt's experimental psychology laboratory in the latter half of the 19th century was it possible to measure an individual's reaction time directly. Thus, the systematic and scientific study of individual differences became the province of psychology, although many biomedical researchers continue to investigate individual differences in humans at a number of levels. For example, Wilder's law of initial value[83] attempted to relate variation in the magnitude of response to a stimulus, such as a drug, to the basal or initial level of activity in that response system. As such, the law of initial values is applicable to many fields such as physiology, pharmacology, radiotherapy, and neuroscience.

Under the influence of the theory of evolution Galton attempted to understand individual differences in human intellectual capacity in terms of Darwin's notions of variation, selection and fitness. This led, unfortunately, to the highly profitable but often scurrilous mental testing movement in the United States and Great Britain[42, 51, 73]. With the rediscovery of Mendel's principles of heredity in 1900, the way was open for biologists to establish the genetic mechanisms (often involving major, i.e. single, genes) underlying binary structural characteristics, although the analysis of polygenic as well as single-gene inheritance of *quantitative* characteristics was also advancing. Psychologists and biologists began to manipulate the genotypes of their animals, using selective breeding and cross-breeding for behavioral[40, 79], physiological[60, 80], or neurochemical[61] characteristics, as well as the morphological characteristics which had been the first to be investigated. Because behavioral and physiological characteristics tend to be continuously variable and poylgenic in nature, the relatively new field of quantitative genetics developed[25, 28, 29]. Concurrently with these developments, the field of behavioral genetics came formally into existence with a series of important publications[33, 41, 62, 66], to name just a few. The Behavior Genetics Association was formed in 1970, and publication of its journal, *Behavior Genetics* began the following year.

As noted by Fuller and Simmel[32], most of the current work in behavioral genetics is being done by psychologists working in psychology departments, and, with respect to selective breeding for behavioral characteristics, the behavioral methods depend heavily on the knowledge and procedures developed during the heyday of stimulus-response (S-R) behaviorism. Ironically, the S-R behaviorists largely ignored individual differences in learning and performance[43, 77] and treated between-subject variation as a source of error in their pseudo-quantitative equations (e.g., Hull's oscillatory potential, $_{S}O_{R}$). The radical behaviorists, with their emphasis on using data from a single individual to establish an effect[26], also typically ignored the often dramatic individual differences in various forms of operant conditioning. With respect to free-operant avoidance learning, for example, it was common knowledge around the Walter Reed Army Institute of Research in the late 1950s that rats being trained to lever-press on a Sidman avoidance schedule were put in the Skinner boxes as technicians were leaving for the day with the avoidance schedule in effect for the entire night. If an animal learned to avoid, it was alive the next morning; if not, it was not! Meyer, Cho and Wesemann[57] provided a systematic account and analysis of the problem of using the lever-press as an avoidance response in discrete-trial procedures with rats, although Berger and Brush[7] subsequently noted that at least some of the difficulties were procedural in nature. Ironically, Pavlov's Conditioned Reflexes[63] had had an enormous influence on the behaviorist movement in the United States[76], yet his extensive work[64, 65] on individual differences in the temperaments of dogs went almost unnoticed.

Today, behavioral genetics is part of the mainstream of psychology, as indexed by the number of introductory texts that address such issues as heredity or behavioral genetics or related concepts, and the extensiveness of the coverage of such issues in those texts (see Fuller and Simmel[32] for examples). Furthermore, despite the absurdly exaggerated claims about the degree of genetic contribution to human intelligence and other personality and psychopathological characteristics of humans[45, 48], it is now widely accepted that the behavior of most species is the product of the often complex interaction between genes and environmental experiences (see Govind[36] for a lovely analysis of that interaction in a crustacean familiar to many of us for gastronomic reasons).

To that end this paper will review a series of experiments that have addressed the general question of individual differences in responses to aversive stimulation and that use selective breeding of rats for variation in active avoidance learning. In particular, this paper will review the derivation of the Syracuse High and Low Avoidance strains and the behavioral and endocrine correlates of the two strains. Comparisons will also be made to two additional sets of bidirectionally selected strains derived by Bignami in Italy[6] and by Bammer in Australia[4], and to a unidirectionally selected strain developed by Shigeta in Japan[74].

Selective breeding for avoidance learning

Derivation of the Syracuse strains

Background research. An experiment on the original Kamin effect[49, 50] which is the U-shaped retention function following incomplete avoidance training in the shuttle box, encountered a large percentage of animals that failed to reach a learning criterion of 10 consecutive avoidance responses[75]. This criterion was required to test whether the U-shaped retention function occurred during an extinction test, to exclude the possibility that stress-induced temporal changes in shock sensitivity mediated the U-shaped retention function. Despite the large loss ratio, the experiment was positive in the sense that the U-shaped retention function was found during extinction testing of those animals that met the acquisition criterion, which suggested that the U-shaped retention effect was not mediated by changes in shock sensitivity. The acquisition data suggested that animals of the Long-Evans stock, which were used in those experiments, were not efficient enough at learning the shuttle-box avoidance task to support experiments on the retention function. This led to a search for dependent variables early in acquisition that might reliably predict successful learning or failure to learn, in the hope that more efficient procedures could be developed. One such variable was escape latency, which in those experiments differed between learners and non-learners on the first trial, increased to different maxima on trial five or six and then decreased to different asymptotes on subsequent trials. On all measures the escape latencies of non-learners were significantly greater than those of learners[12], but the maximum escape latency on trial five or six was the best predictor of subsequent likelihood of learning to avoid.

However, in subsequent experiments[13, 15] it became clear that this variable may have been fortuitously predictive of subsequent learning success in that earlier experiment. The question of why some animals learned rapidly to avoid shock in the shuttle box, whereas others rarely if ever avoided at all, remained mysterious. Indeed, the results of our early experiments suggested that Driscoll was correct when he noted years later that 'the *biggest* problem involved in using 'normal' rats and mice is that such animals *do not exist* and, in reality... laboratories are merely using undefined genetic material; i.e. introducing an unknown quantity into their research' (italics in original, p. 463)[22].

The above research, together with many reports of strain differences in avoidance learning as well as differences in avoidance and other behaviors between different shipments from a commercial breeder of rats of a given strain or between different commercial breeders of the 'same' strain[2, 27, 31, 37, 46, 47, 52–54, 82], led us to conclude that the difference(s) between animals that learn and do not learn to avoid in a shuttle box may be genetically determined, at least in part.

Selective breeding of the Syracuse strains. To explore this idea we began selective breeding for good and poor shuttle-box avoidance learning in 1965, at about the time Bignami published the first report of successful selective breeding of the Roman strains for high and low rates of shuttle-box avoidance learning[6]. The parental stock of the Syracuse High and Low Avoidance strains (SHA/Bru and SLA/Bru, respectively), were Long-Evans rats derived from animals obtained originally from Rockland Farms, Rockland County, New York, via breeding colonies that were established from that source first at Huntingdon Farms, West Conshohocken, Pennsylvania, and subsequently transferred to the animal farm maintained by the University of Oregon Medical School (see Brush, Froehlich and Sakellaris[17] for details). In 1971 the strains were transferred to Syracuse University and in 1981 to Purdue University, where they currently reside. At Syracuse University the animals had to be moved to newly remodelled facilities shared by other researchers so that the M-pulmonis, with which the strains were infected, had to be eliminated by caesarian delivery and fostering to germ-free dams. Since then the strains have been gnotobiotic in the sense of being free of the pathogens that typically infect colonies of rodents (see Brush et al.[15] for details).

Selection criteria. All animals were trained in automated shuttle boxes in which the warning signal (WS) was light and white noise presented at either end of the two compartments, the shock was 0.25 mA, the WS-shock interval was 5 sec, the maximum trial duration was 35 sec, and the intertrial interval (ITI) was 2 min during the initial 10 pretest trials (WS alone) and 1 min during the immediately following 60 trials of avoidance training. An animal could escape from the shock (and terminate the WS) by running to the opposite compartment. The same response during the WS-shock interval terminated the WS and avoided the shock on that trial.

Animals were selected for breeding if they met both of two criteria: a) few short latency (< 5-sec) responses to the WS during the 10 pretest trials and b) either good or poor performance during the 60 trials of avoidance training (see Brush et al.[17] for details). In general, the best performers of the high avoidance line and the worst performers of the low avoidance line were selected for breeding. The actual performance of the selected breeders was, of course, dependent on the distribution of avoidance responses, and figure 1 illustrates this point. Clearly, there was opportunity for greater selection pressure upward than downward, given the relatively poor performance of the original breeding stock (see the 0th generation of figure 2). From the beginning of selection, two replicate families, each based on full-sib matings, were maintained in each selection line. However, by the 5th and 6th generations fertility was markedly reduced in both lines, especially in the SLA/Bru lines (see figure 3 of Brush et al.[17]). To preserve the lines after approximately two years' investment of time and effort, the two families in each selection line were crossed, and non-sib mating was the breeding system in effect in all subsequent generations. Selection continued for 21 and 25 generations in the SLA/Bru and SHA/Bru lines, respectively, at which time declining fertility dictated free mating, with avoidance of full- and half-sib mating, within each line for several generations.

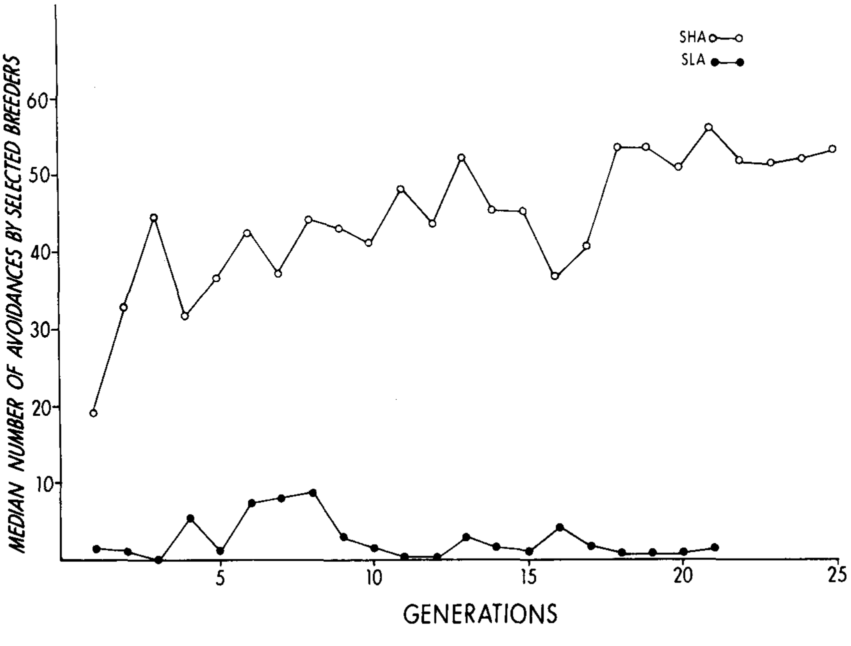

Figure 1. Median number of avoidance responses made by selected breeders as a function of generations of original selection. (From Brush, 1985. Copyright, 1985, Lawrence Erlbaum Associates. Reprinted by permission of the publisher).

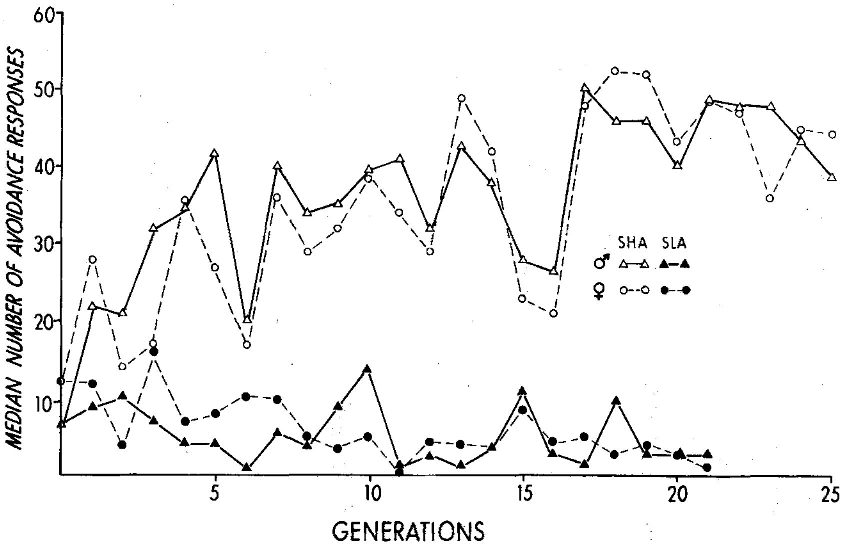

Figure 2. Median number of avoidance responses as a function of generations of original selection. (From Brush, 1985. Copyright, 1985, Lawrence Erlbaum Associates. Reprinted by permission of the publisher).

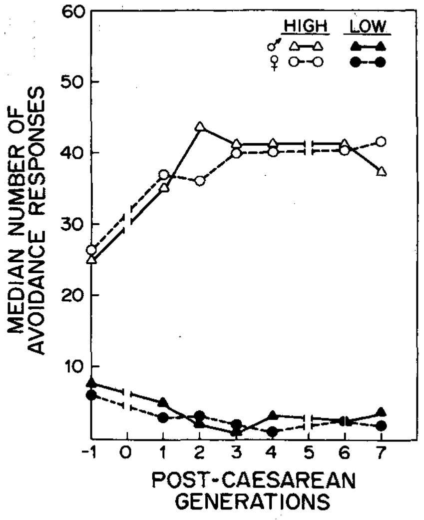

Figure 3. Median number of avoidance responses as a function of the last pre- and first seven post-caesarian generations. (From Brush et al., 1985. Copyright, 1985, American Psychological Association. Reprinted by permission of the authors and publisher).

After approximately 2.5 years of free mating, selection pressure was resumed, caesarian derivation occurred (only two litters within each strain), and selection pressure was continued after derivation. Figures 2 and 3 present the outcome of selection before and after caesarian derivation. Clearly, the data of both figures suggest that shuttle-box avoidance learning is heritable in the sense of responding to selection pressure. Indeed, realized heritability (h^2)[25], in the original selection was estimated to be 0.16 in each strain[17], a value comparable to that found in other selection studies in the affective domain[4, 20].

Derivation of the Roman and Australian strains

The Roman strains. Bignami[6] reported the first successful selective breeding experiment with rats in which the selected phenotypes were good or poor avoidance learning in a shuttle box. The resulting strains are known as the Roman High and Low Avoidance strains (RHA and RLA, respectively). The parental stock were Wistar-derived rats obtained from a commercial supplier in Italy. Full-sib mating was avoided except for two generations (S_2 and S_3) in the RLA strain, after which the inbred animals became extinct. No control strain was kept, but Wistar rats from the original supplier were tested periodically.

Selection criteria. Training consisted of 5 daily sessions of 50 trials each. The WS was a light presented at the middle of the shuttle box, thus requiring the animals to approach the fear-elicting stimulus to avoid the shock. The scrambled shock was 1.6 mA AC, and the WS-shock interval was 5 sec. The ITI was 30 sec, and ITRs were punished by electrification, throughout the ITI, of the grid on the side from which the rat had escaped or avoided. No pretest was given. Selection was based on the number of avoidance responses during the first two sessions and on good or poor retention from each session to the next. Selection was highly effective, with the RHA and RLA animals avoiding in 68% and 20% of the 250 trials by the 5th selected generation. A reciprocal cross of S_3 animals showed heterosis (hybrid vigor) and moderate inverse maternal effects, with hybrid animals born of and raised by RLA dams making more avoidance responses than those from RHA dams. Cross fostering, in a separate experiment, was without effect. Broadhurst and Bignami[11] tested animals of the Roman strains for 50 trials in a single session using a centrally located buzzer as the WS, an 8-sec WS-shock interval, a shock intensity of 0.25 mA, and a variable ITI that averaged 60 sec. ITRs were not punished. RHA and RLA animals avoided in 73% and 14% of the trials, respectively. However, avoidance and escape latencies were significantly shorter in RHA than RLA animals, and ITRs were also greater in RHA than RLA animals. Colonies of the Roman strains, established from breeding stock obtained from Broadhurst, have been maintained by Satinder at Lakehead University in Canada[67], by Driscoll and Bättig at the Institut für Verhaltenswissenschaft in Zurich[23], and by Guenaire and Delacour in Paris, France[38, 39]. The Satinder animals are designated RHA/Lu and RLA/Lu and the Driscoll/Bättig animals as RHA/Verh and RLA/Verh. As noted by Driscoll and Bättig[23], the subsidiary colonies maintained selection pressure using slightly different apparatus and procedures, resulting in subtle differences among the three colonies, but the selected phenotypes remain robust in all three colonies.

The Australian strains. In 1978 Bammer[4] reported on the first six generations of selective breeding of Sprague-Dawley rats for high and low levels of avoidance responding in a shuttle box (see also Bond[8]). The resulting strains are known as the Australian High and Low Avoidance strains (AHA and ALA, respectively). The breeding program was apparently designed to minimize inbreeding, but Bammer reported that inbreeding was greater in the AHA than ALA strains and may have contributed to the reduced fertility of the AHA animals.

Selection criteria. In avoidance training the WS was a tone (possibly 2800 Hz, loudness and loci or locus unspecified; see Bond[8]), the shock was 1 mA, and the WS-shock interval was 5 sec. ITI was not specified by Bammer, but Bond, using the AHA and ALA animals, employed a constant 30-sec ITI. During the first five generations of selection, training consisted of 50 trials distributed over 5 days, but beginning with the 6th generation, the trials were massed in a single session to permit assessment of the effects of drugs without the complication of tolerance effects. Escape latencies of ALA animals were significantly greater than those of AHA animals. Realized heritability over the first five generations of selection was 0.18 and 0.27 for the AHA and ALA strains, respectively.

Derivation of the Japanese strain

These animals were derived from Jcl-Wistar rats, using full-sib mating at 12–13 weeks of age from the onset of selection[74]. The resulting unidirectionally selected strain is known as the Tokai High Avoider (THA) strain (Shigeta is at the Tokai University School of Medicine).

Selection criteria. The selection criterion was an avoidance rate of more than 95% avoidance in the last five of 10 sessions of Sidman avoidance training in a Skinner box. The shock-shock (S-S) interval was 5 sec, the response-shock (R-S) interval was 30 sec, shock duration was 0.5 sec, and shock intensity was 3.0 mA (100 V, DC). The daily training sessions were 60 min in duration and began when the animals were 7 weeks of age. Selective breeding began in 1981 and by 1990 the strain had reached the 27th generation of selection[74].

Phenotypic correlates

An important issue for any selection experiment is the characterization of the selected phenotype(s). Such characterization is accomplished by identifying other characteristics that are associated with the selected phenotype(s). We can distinguish between 'important' and 'trivial' correlates. For example, suppose that one were to selectively breed for fast and slow learning of a multiple-unit maze, as in Tryon's original experiment[79]. Suppose further that Tryon had been more successful than he was, and that the maze-bright animals were superior to the maze-dull animals, generally, in any learning task in which they were tested. Performance in these other situations would be an 'important' set of correlates, and the existence of those correlates would suggest that selection had resulted in phenotypes that differed in general learning ability.

Suppose, on the other hand, that Tryon's results were as they are, i.e., that the strain difference in maze learning ability is specific to the particular maze and does not generalize to many other learning situations. Suppose further, that the difference in maze-learning ability is because the maze-dull animals cannot see (because of retinal degeneration), whereas the maze-bright animals can see (no retinal degeneration). This, in my view, would be a 'trivial' phenotypic correlate and of little interest, unless one were investigating the genetics of retinal development and/or degeneration, but if one were, it seems unlikely that selection would have been based on maze-learning ability.

Thus, *important* correlates are those that elucidate the nature of the selected phenotype(s) by characterizing the associated behavioral or other features of the animals, as in the generalized learning ability in the illustration above. *Trivial* ones are those that may be associated with the selected phenotype(s) but are correlated with it/them for largely irrelevant reasons, as in the blind maze-dull illustration above. (It should be noted that Tryon's maze-dull animals are not blind! The illustration is purely heuristic). The distinction we draw here assumes that one is interested in 'important' phenotypic correlates having some relationship to the goal of the selective breeding, e.g., learning, as opposed to 'trivial' phenotypes having to do with irrelevant sensory or motor capacities.

Phenotypic correlates of the Syracuse strains

Trivial correlates. A number of *trivial* correlates have been eliminated. The strains do not differ in level of locomotor activity, in latency of escape or avoidance responses, or in sensitivity to electric shock; they can both see and hear equally well, as indexed by the magnitude of their acoustic-induced startle reflex and their ability to make visual pattern discriminations[15–17].

Important correlates. There are a number of *important* correlates of the two selected phenotypes.

a) *Behavioral correlates.* SLA/Bru animals appear to be more emotional or emotionally reactive than animals of the SHA/Bru strain. This inference is based on a number of observations. For example, SLA/Bru animals defecate more than SHA/Bru animals during avoidance training and during open-field testing (see Archer[3], Broadhurst[9], Denenberg[21], and Suarez and Gallup[78] for various interpretations of this measure). For example, the mean (± SE) daily defecation frequency during 3 days of open-field testing was 2.5 ± 0.2 for SLA/Bru animals and only 1.6 ± 0.1 for SHA/Bru rats[15]. In addition, this measure in phenotypic SHA/Bru animals from segregating generations tends to habituate over days, whereas that of SLA/Bru animals does not. If one accepts the emotionality interpretation of this measure, then the SLA/Bru animals are more emotional or emotionally reactive in the open-field situation than are the SHA/Bru animals.

In a previously unpublished experiment rats of the S_{12} selected generation in the SHA/Bru strain were trained over 13 days using a modified Sidman avoidance schedule in the shuttle box. The R-S interval was 40 sec, and instead of an S-S interval, shock, when it occurred, was continuous until terminated by an escape response. Males of the 12th selected generation were compared with males of the unselected parental stock. As illustrated in figure 4, the SHA/Bru animals were superior to the parental stock from about the 4th day of training. Indeed, the distribution of animals of the parental strain divided biomodally into a majority of animals that failed to learn (Long-Evans (NL)) and a small minority of those that did learn (Long-Evans (L)). It can be seen from the figure that the selectively bred animals (S_{12}) learned nearly as rapidly as the self-selected learners of the parental stock. Both the genetically selected and self-selected animals reached the same asymptote of performance.

In addition, SLA/Bru rats acquire conditioned suppression (CER) faster than SHA/Bru animals at low and medium shock intensities[16]. Following baseline training on a 1-min VI schedule and 2 days of pretesting of the CS, conditioning began at the rate of 4 trials per day (2-min CS-US interval, 0.5-sec shock US), using a series of increasing shock intensities as indicated in figure 5, which plots the mean daily suppression ratio during pretest and as a function of days of conditioning and shock intensity. The plotted suppression ratio is the mean of the ratios, B/(A + B), of the 4 trials on each day, where B is the number of responses during the 2-min CS and A is the number of responses in the immediately preceding 2 min. It is clear from the figure that SLA/Bru animals condition faster and at lower shock intensities than SHA/Bru animals and that females condition faster than males. Differences in shock sensitivity can account for the sex difference but not the strain difference in conditioning[15]. Baseline response rates (all non-CS times) were also differentially affected in the two strains: SLA/Bru animals were relatively suppressed early in conditioning and SHA/Bru animals were relatively activated, even at shock intensities which did not support conditioning in those animals[16].

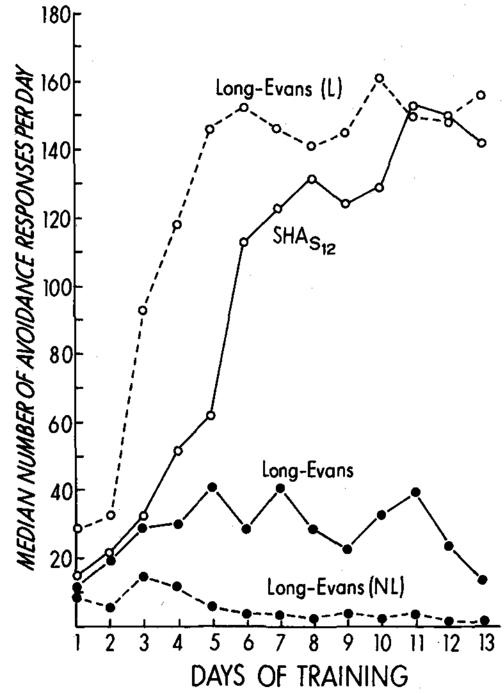

Figure 4. Median number of avoidance responses as a function of days of training for SHA/Bru S_{12} males and males of the parental stock (Long-Evans) subdivided into those which learned (Long-Evans (L)) and those which did not learn (Long-Evans (NL)).

SLA/Bru animals also learn a passive avoidance response faster than SHA/Bru animals[16]. In this experiment the animals were trained to press a lever for continuous food reward (FR-1-food). The schedule was then changed to a conjoint FR-1-food/FR-20-punishment, so that every response was rewarded and every 20th response was punished by a 0.5-sec shock. When shock intensity was 0.64 mA, the animals of the two strains did not differ; both learned to suppress bar pressing equally rapidly (after 4–6 shocks). However, when shock intensity was 0.21 mA, SHA/Bru animals continued pressing, and actually tended to increase their rate of responding, whereas SLA/Bru animals suppressed responding after an average of 17 shocks.

In addition, males of the SLA/Bru strain exhibit a stress-induced analgesia that is orders of magnitude greater than that induced in SHA/Bru males[19, 58, 59]. The procedure involved obtaining baseline tail-flick latencies prior to administration of shock to the tail. Tail-flick latencies were obtained again after every 20th shock or after every 20 min of restraint; the 1.0-mA, 5-sec shocks were administered on a variable interval schedule which averaged 1 min. Figure 6 illustrates this effect in one experiment in which we attempted to block the stress-induced analgesia by prior treatment with 7.0 mg/kg naltrexone; this attempt and others, including bilateral adrenalectomy, were not successful, suggesting that the profound

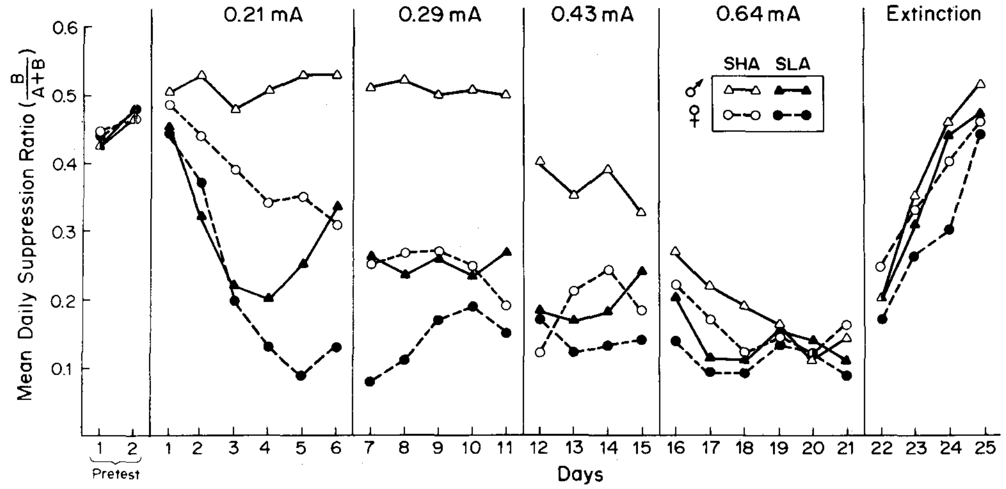

Figure 5. Mean daily suppression ratios as a function of pretest day, day of conditioning and shock intensity in male and female rats of the SHA/Bru and SLA/Bru strains. (From Brush et al., 1988. Copyright 1988, American Psychological Association. Reprinted by permission of the authors and publisher).

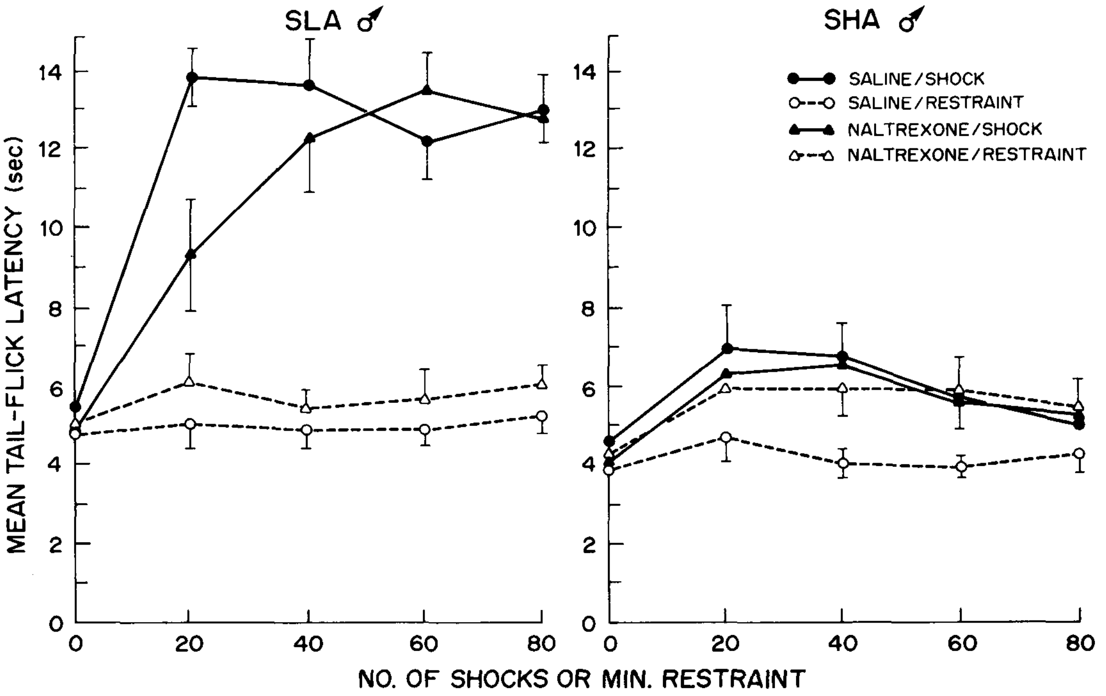

Figure 6. Mean ±S.E. tail-flick response latency as a function of number of shocks or duration of restraint in male rats of the SLA/Bru and SHA/Bru strains that received either 7.0 mg/kg naltrexone or saline, S.C., 20 min before testing. (From Nagase et al., 1985. Copyright, 1985, Pergamon Press. Reprinted by permission of the authors and publisher).

stress-induced analgesia in the SLA/Bru animals is not mediated by endogenous opioids[59].

In addition to the above, Flaherty and Rowan[30] found that males of the Syracuse strains differed in the magnitude of successive negative incentive contrast (see fig. 7). Specifically, males of the two strains were given daily 5-min access to either 32% or 4% sucrose for 10 days. Beginning on day 11 all animals were given access to 4% sucrose. The down-shifted animals of both strains showed a negative contrast effect by drinking less of the 4% sucrose than unshifted controls. However, the magnitude of this effect was significantly greater in SLA/Bru than SHA/Bru animals. Furthermore, when, on day 12, the animals were injected with 8 mg/kg of chlordiazepoxide, a well established anxiolytic involving the GAGA/BZP receptor complex, 30 min prior to the test session, the contrast effect was eliminated in SLA/Bru animals but was not altered in SHA/Bru animals (see fig. 7). Again, these results suggest that the strains differ in emotionality or emotional reactivity and that this difference may have a physiological substrate involving the GABA/BZP receptor systems of the brain.

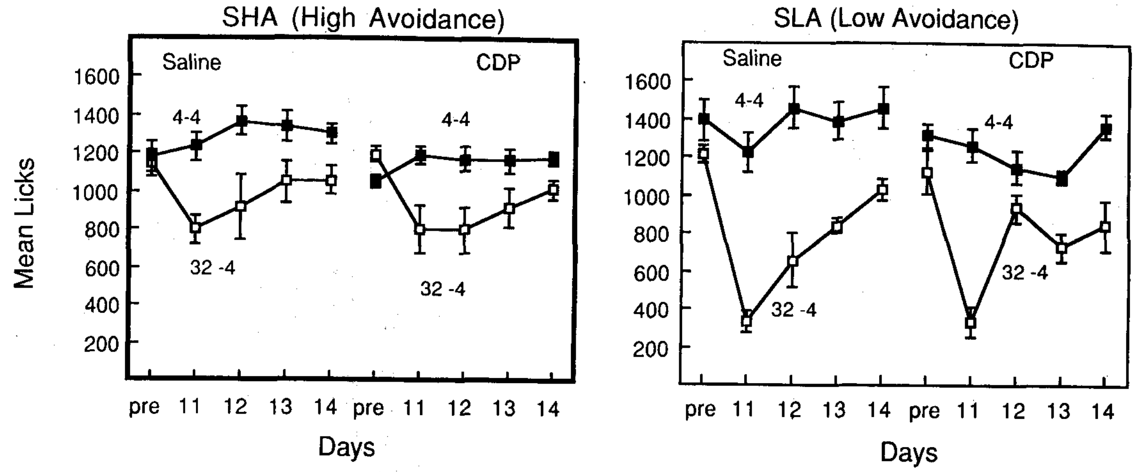

Figure 7. Mean ± SE lick frequency of male SHA/Bru and SLA/Bru shifted and unshifted rats on the terminal acquisition day (pre) and four post-shift days. The saline and chlodiazepoxide (8 mg/kg) were administered on the second post-shift day only (day 12). (From Flaherty and Rowan, 1989. Copyright, 1989, Academic Press. Reprinted by permission of the authors and publisher).

b) *Endocrine correlates.* At a morphological level, the body weights of 90-day-old SLA/Bru males are greater than those of SHA/Bru males, whereas the females of the two strains do not differ in body weight. Adrenal gland weights, on the other hand, both absolutely and relative to body weight are 40–50% greater in SLA/Bru than SHA/Bru animals of both sexes, and this difference is greater in females than males. Morphometry of the adrenal glands indicated that the difference in weight is confirmed by an overall difference in volume of the total gland and of all three cortical regions, but not in the volume of the medulla[18]. Interestingly, despite having smaller adrenal glands, basal and stress-induced increases in adrenal corticosterone are greater in SHA/Bru than SLA/Bru animals. These findings suggest that there may be a genetically determined enzymatic defect in steroid synthesis in the SLA/Bru animals and that the increase in adrenal size in these animals relative to those of the SHA/Bru strain may be the result of compensatory ACTH release. The fact that the strain difference in adrenal gland weight is present as early as 21 days of age is consistent with such an interpretation[18].

Comparison of the Syracuse strains with the other selected strains

Selection criteria and procedures

The three bidirectionally selected sets of strains, Syracuse, Roman and Australian, used roughly similar shuttle boxes, a 5-sec WS-shock interval, and 30-sec to 1-min intertrial intervals. The WSs were variously auditory, visual or compound auditory-visual, and intertrial responses were punished in the Romans but not in the others. The shocks were of varied intensities and durations, which may be more important than some of the other procedural variations in determining the nature of the selected phenotypes. As is customary in psychological research, the genetic stocks from which the selected strains were derived were mostly albino stocks of either Wistar or Sprague-Dawley origin. Only the Syracuse strains were derived from non-albino, hooded, stock, although it must be acknowledged that Long-Evans rats originated from a cross between a black or brown rat and an albino strain. The animals contributing to the Syracuse strains have bred true for coat color (color of pigmentation and hooded pattern) for many generations, although this was not true of Long-Evans stock supplied by several commercial breeders of 'hooded rats' for many years. All of the bidirectionally selected strains relied on discrete-trial active avoidance learning in a two-way shuttlebox. In contrast, the unidirectionally selected THA strain was derived from Wistar stock using a non-discriminated free-operant lever-press avoidance procedure. It will be interesting to see how these animals are similar to or different from the other bidirectionally selected high-avoidance strains based on shuttle-box learning. Only preliminary data on these animals is available at the present time[73].

Behavioral correlates

Animals of the Roman colonies which will be discussed here (Lu and Verh), share many behavioral correlates of the selected phenotypes. Some might be categorized as 'trivial' as in the above discussion of the Syracuse strains. For example, RHA animals display greater locomotor activity in a variety of situations, including intertrial responding during shuttle-box avoidance training, in some open-field situations[23, 67], and in complex mazes[5, 56]. Thus it may be that some of the difference in active shuttle-box avoidance behavior in the Roman strains may be attributed to different levels of locomotor activity. In contrast, the animals of the Syracuse strains do not differ in intertrial responding in the shuttle box, either during pretest or during training, and they do not differ in ambulation or rearing in an open field. Thus differences in activity level may be sufficient to account partially for the differences in avoidance learning in the Roman strains, but such differences are clearly not necessary to obtain genetically selected difference in avoidance learning, as exemplified by the Syracuse strains.

Similarly, Driscoll et al.[24] and Satinder and Hill[71] found that the RHA animals of their colonies (Verh and Lu, respectively) have lower flinch (Lu) and/or jump (Lu, Verh) thresholds to electric shock than the RLA animals. In addition, Satinder[68] found that his RHA/Lu animals also had a lower aversion threshold, as measured by instrumental escape responding, than the RLA/Lu rats. In contrast to these results, the animals of the Syracuse strains do not differ in either detection threshold[15] or aversion threshold (Brush and Pellegrino, 1987, unpublished observations). Thus the poor avoidance behavior of the RLA animals may be attributed partly to their reduced sensitivity to or the aversiveness of electric shock relative to those of the RHA strain, although in the case of the Verh rats, Driscoll et al.[24] have noted that there were no differences in sensitivity to shock at levels used for avoidance testing. Satinder[68, 69] attempted to surmount his difficulties by using different shock intensities for animals of the two strains. Specifically, he found the aversion threshold for each animal and used that shock intensity during avoidance training which had previously adequately supported escape responding in that individual. Even with this adjustment, the phenotypic difference in avoidance learning in the two-way shuttle box persisted in his animals. Thus, something more than differential sensitivity to or aversiveness of electric shock must be postulated to account for the superior avoidance learning of RHA over RLA animals. Satinder pursued this problem further and manipulated the complexity of the avoidance task. He found that the phenotypic difference between the strains persisted even in the simplest one-way active avoidance task. The Syracuse strains have not been tested in one-way avoidance, but the data presented above in figure 4 indicate that the SHA/Bru animals do rather well in a free-operant avoidance task. Thus the Roman strains appear to differ from each other in both activity level and sensory and aversion thresholds to electric shock, whereas the Syracuse strains do not differ on either of these measures. Nonetheless, the phenotypes in both the Roman and Syracuse strains appear to be sufficiently robust to suggest that these correlated characteristics of the Roman strains may not be adequate to account for the difference in avoidance behavior.

Much less is known about the phenotypic correlates of the Australian strains and the Tokai strain. Bond[8] reported that the AHA and ALA strains did not differ in their escape latency on the first shock trial, suggesting no difference in sensitivity or aversiveness of the 1-mA shock between the strains. However, it must be acknowledged that this is a rather insensitive index. In addition 'intertrial crossings proved to be a significant covariate [of avoidance responding]' (Bond[8], p. 325), but the direction of the covariation was unspecified. One presumes that the correlation was positive with greater intertrial responding being associated with greater frequency of avoidance responding. The animals were subsequently tested in a one-way active task and again the AHA animals were superior to the ALA rats.

Shigeta et al. have found, paradoxically, that shock thresholds were higher in both male and female THA rats than in unselected Wistar control animals. In addition, THA animals were less active than Wistars in the open field[73].

Defecation frequency. As noted above, SLA/Bru animals defecate more frequently than SHA/Bru animals during avoidance training and during open-field testing. Initially, the Roman strains were thought not to differ in frequency of defecation in the open field[11, 44, 71]. Those studies used the Roman animals from the original colony or the one maintained at Lakehead University. Subsequent work by Gentsch et al.[34, 35] indicates that the RLA/Verh rats defecate more frequently during open-field testing than do the RHA/Verh animals. Thus, the strain difference in emotionality, as indexed by this measure, appears to be consistent in the Syracuse and Roman/Verh strains, with the low avoidance animals being more emotional or emotionally reactive than the high avoidance animals. There have been no reports regarding the Australian strains on this measure. Shigeta et al.[73] found no differences in defecation frequency between the selected THA and unselected Wistar rats.

Free-operant avoidance learning. As noted above, the SHA/Bru rats of the 12th selected generation performed very well on a Sidman avoidance schedule in the shuttle box. There have been no reports of studies using this procedure with the Roman or Australian strains, but rats of the THA strain, which was selected using a Sidman procedure in a Skinner box are reported to do well in a two-way shuttle avoidance task[73]. Thus, selection for high levels of either discrete-trial or free-operant avoidance learning appears to generalize well to the opposite form.

Pavlovian aversive conditioning. The Syracuse strains clearly differ in the rate of acquisition of conditioned suppression (see figure 5), with SLA/Bru animals showing much faster conditioning at low and medium shock intensities than SHA/Bru rats[16]. Similarly RLA/Verh rats showed a stronger conditioned taste aversion, based on apomorphine, than RHA/Verh animals, and the conditioned aversion was more resistant to extinction in RLA/Verh than RHA/Verh rats[55]. In addition, Imada[44] also found evidence of greater shock-induced suppression of drinking in RLA than RHA animals from the original colony in London. In contrast, Bond[8] found that AHA rats made more frequent anticipatory responses to the CS in a Pavlovian paradigm in a shuttle box than ALA animals. Thus it appears that when Pavlovian aversive conditioning is indexed by suppression of behavior, low avoidance animals of the Syracuse and Roman strains are superior to their high-avoidance counterparts, whereas the reverse may be true if conditioning is indexed by active responding. Clearly additional research manipulating these dimensions of behavior and conditioning is needed to clarify this issue. No information is available on this form of conditioning in THA animals.

Passive avoidance learning. Consistent with the above results on inhibitory aversive Pavlovian conditioning, SLA/Bru rats are superior to SHA/Bru animals in an operant punishment (passive avoidance) paradigm, at least at low shock intensities. At high shock intensities animals of the two strains do not differ[16]. Driscoll (personal communication) has also reported superior passive avoidance performance in RLA/Verh than in RHA/Verh rats based on studies conducted in four different laboratories. In contrast, however, Satinder[69] reported finding no difference in passive avoidance learning between RLA/Lu and RHA/Lu animals. Bond[8], on the other hand, found that ALA animals were superior to AHA rats in acquisition of a one-trial step-through passive avoidance response. No information is available about such learning in the THA strain. Thus, we are left with somewhat conflicting results regarding this phenotypic correlate, but, for the most part, it appears that active and passive avoidance learning are negatively correlated in the Roman, Syracuse and Australian strains.

Stress-induced analgesia and incentive contrast. These paradigms have only been studied in the Syracuse strains, so no information is available regarding these correlates in the other selected strains.

Endocrine correlates

The pituitary-adrenocortical axis, its basal and stress-induced activity and feedback effects have been associated with avoidance learning and aversive conditioning for many years. So it was not surprising that the Syracuse strains differ in several measures of activity in this endocrine system. In particular, it was not surprising that the SLA/Bru animals, thought on behavioral grounds to be more emotional than SHA/Bru rats, have larger adrenal glands than SHA/Bru animals. Nor was it surprising that the hypertrophy was entirely cortical. However, the finding that SLA/Bru animals have lower basal and stress-induced adrenal corticosterone, both absolutely and relative to gland weight, than SHA/Bru rats was not consistent with expectations. The absence of differences in plasma corticosterone concentration in the Syracuse strains, in the face of differences in adrenal content and concentration, suggest there may be differences in half-life or distribution volume between the two strains[18].

However, these effects are quite different from those seen in the Roman strains. For example, Gentsch et al.[34] found that RLA/Verh male rats have significantly smaller (lighter) adrenal glands than RHA/Verh males. Paradoxically, after a 10-min exposure to a novel environment (open field) RLA/Verh animals had a higher plasma concentration of corticosterone than did the RHA/Verh animals. Gentsch et al.[35] confirmed these strain differences for plasma corticosterone concentration under a variety of mild stress conditions, e.g., following an i.p. injection, being placed in novel environments such as a new cage, an open field or shuttle box. Following more severe stressors such as etherization, immobilization, or inescapable foot shock, no strain differences were found, probably because of ceiling effects. More recently, Walker et al.[81] reported that basal plasma corticosterone concentrations were the same in RHA/Verh and RLA/Verh rats, although plasma ACTH concentrations were higher in RHA/Verh than RLA/Verh animals. Stress-induced increases in plasma corticosterone were greater in RLA/Verh than RHA/Verh following open-field exposure but not following etherization, again probably because of ceiling effects. In addition Walker et al.[81] found evidence suggesting that the anterior pituitary of RLA/Verh rats is more sensitive to CRH than that of RHA/Verh animals. Thus, it appears that in the Roman strains, the low avoidance animals have a pituitary-adrenal axis that is more active or responsive to mild stressors than is the case in the high avoidance strain. The difference in size of the adrenal glands, the high avoidance strain having the larger glands, suggests that reduced negative feedback from reduced release of corticosterone, may have resulted in compensatory growth from augmented ACTH release, a conclusion consistent with the Walker et al.[81] data on basal ACTH concentrations in plasma. Although ACTH determinations have not been made on the Syracuse strains, they appear to be the exact opposite of the Roman strains. That is, in the Syracuse strains the low avoidance animals have big adrenal glands which are relatively inactive, whereas in the Roman strains, the high avoidance animals have big adrenal glands which are relatively inactive. No information about the endocrine characteristics of the Australian strains or the THA strain is available.

Conclusions

On the basis of data from the Syracuse and Roman strains, those which have been studied most extensively, one is tempted to conclude that selection for differences in active two-way shuttle-box avoidance learning has resulted in divergent strains that differ not so much in learning ability as in emotionality or emotional reactivity. However, this is a dangerous conclusion, because of the vague definition of what we mean by those terms: emotionality and emotional reactivity. Behaviorists and behavior geneticists have argued about these terms for years[3, 10, 21] and hard conclusions about the definitions of these terms are not yet available. However, the research reviewed here, involving mostly, but not exclusively, the Syracuse and Roman strains, suggests genetic selection studies can help to elucidate what we might mean by these terms. In this review, we have focused on the Syracuse strains and attempted to compare them with other strains genetically selected using similar criteria. Much of the behavioral work suggests that such selection from diverse breeding stock has resulted in common characteristics that differentiate the strains in the emotional, not learning, domain. The endocrine data, on the other hand, are contradictory. Given that the Syracuse strains differentiate one way and the Roman strains differentiate in the opposite way, we suggest that the endocrine correlates are not tightly linked to the avoidance genotype. Genetic analysis of all of the selected strains for both the avoidance phenotype and the endocrine correlates will be needed to unravel this issue.

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