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The locus ceruleus: a possible neural focus for genetic differences in emotionality

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*Summary.*The Maudsley Reactive and Non-Reactive strains have been developed as a model for the study of individual variations in stress-reactivity, and many differences in biobehavioral systems have been found between them. This review discusses limitations of the 'emotionality' construct in accounting for differences between the Maudsley strains and offers an alternative, theoretical approach. Amaral and Sinnamon[1] have proposed that the locus ceruleus (LC) plays a stress-attenuating role in mediating behavioral, physiological and neuroendocrine response to prepotent, emergency-provoking stimuli and, building upon this formulation, it is proposed that the LC has been an important focus for gene action in the Maudsley model. It is suggested that the LC of the Non-Reactive strain is more strongly activated by stressful stimuli than the LC of Reactive rats, and is the basis of many of the behavioral and physiological differences between them. Behavioral and biochemical evidence consistent with this proposition is reviewed. Identification of the LC as a target for gene-action in the Maudsley model has an important advantage. It substitutes variations at a specific anatomic location in the brain for a loosely defined construct like emotionality, and the hypothesis is amenable to empirical tests by a variety of experimental approaches.

Key words. Genetics; stress; emotionality; locus ceruleus; Maudsley strains.

Introduction

The Maudsley rat strains are a well-known experimental model for the investigation of individual differences in stress-reactivity. The Maudsley Reactive (MR) and Maudsley Non-Reactive (MNR) strains were selectively bred for variation in open-field defecation (OFD) (MR: high-defecating; MNR: low-defecating) by P. L. Broadhurst of the University of London in the late 1950s and early 1960s[14,15]. The voluminous biobehavioral literature on the strains is summarized in Eysenck and Broadhurst[22] and Broadhurst[17]. The strains were transferred to the United States when the selection experiment was successfully completed[25,40], and a more recent review of the status of North American stocks of the Maudsleys is provided in Blizard[6].

The previous work on the Maudsleys can be divided into several phases. In the initial stages of the experiments it was of primary importance to establish reliable differences in OFD between the strains. This was accomplished very early in the selection program and fixed in the strains by brother/sister mating (inbreeding)[14]. Calvin Hall had already selected for differences in OFD at Case Western Reserve University in the United States[24], and there existed ample evidence from strain comparisons among rats and mice that this psychophysiological characteristic was a genetic variable[41]. The significance of the Maudsley model was that the use of inbreeding fixed the genes responsible for variation in OFD within the strains. As a result, when the selection procedure was discontinued, the differences in OFD between the strains persisted both in the British stocks and in other independent colonies where rigorous inbreeding was continued[9,26]. While a line of rats or mice is commonly designated as an inbred strain when it has been brother/sister mated for 20 or more generations, it is now recognized that 60 or more generations of inbreeding produce a much higher probability of genetic fixation and consequently, a much lower probability of genetic drift[5,27]. For this reason, it is highly recommended that standardized inbreeding procedures be rigorously followed wherever an independent colony of an inbred strain is established.

The second phase of research on the Maudsley strains involved the biobehavioral characterization of the strains in a variety of test situations[17,22]. To mention but a few of the many findings, MR rats were shown to perform active-avoidance conditioning less efficiently than MNR rats[18,32], develop a more pronounced conditional emotional response than MNR rats[36] and respond with greater increases in running speed following frustrative non-reward than MNRs[34]. These findings clearly showed that selection for differences in OFD was associated with alterations in behavior in a wide variety of test situations involving the organism's response to stress.

A third phase of research on the Maudsley strains has centered on strain differences in the central and peripheral noradrenergic system and on alterations in cardiovascular function[7,8,10,11,30,37]. This research has been primarily conducted on Maudsley rats derived from the Harrington collection of inbred strains maintained at the University of Northern Iowa[25] which are identified by the suffix Har, as in MR/Har.

Limitations of the emotionality construct

Open-field defecation was used as a selection criterion to differentiate the Maudsley strains because it was considered a valid index of emotionality, defined by Broadhurst as a hypothetical construct with drive-like properties which energizes a variety of different behaviors[12]. The many differences which have been found between the Maudsley strains in behavioral response to stressful situations have been cited as support for the validity of OFD as an index of emotionality[17,22]. Unfortunately, many of the tasks which have been shown to differentiate the Maudsley strains are complex and engage many different neural systems and, without further analysis, it is difficult to attribute these strain differences to variations in a single unitary construct such as emotionality. For example, while differences in active-avoidance conditioning such as those that have been found between the Maudsley strains are consistent with their differing in emotionality, as defined above, it is also consistent with their differing in sensory, motor or integrative systems. Such a situation could come about when using inbred strains because, while inbreeding fixes the different alleles underlying the trait of interest (in this case, open-field defecation), unrelated alleles are also randomly fixed within each strain and could result in systematic differences between the groups.

In addition, even without the interpretive problems outlined above, it is not clear how group differences in emotionality might impact on performance of a specific experimental task. It has been amply demonstrated that there is a curvilinear relationship between motivation and performance of many tasks[13] and the prediction of how group differences in emotionality might interact with motivation to influence performance of a specific behavioral task is far from straightforward. This issue was faced by Broadhurst and collaborators in the design of some of their experiments involving strain comparisons[16, 18]. Nevertheless, the issue of how group differences in emotionality might interact with task performance still remains when considering the many behavioral differences which have been found between the Maudsley strains. In addition to the above, Archer has also discussed other problems connected with the construct of emotionality[2].

As noted, the previous research on the Maudsley strains has provided researchers with a large number of observations about how the strains differ in behavioral, pharmacological, neuroendocrine and physiological characteristics. However, this research has not been carried out with a hypothetical view of the way in which variations in the nervous system might mediate group differences in behavior. This is partly because the construct of emotionality has never been linked to a particular set of neural events clearly enough to permit its experimental evaluation. While this state of affairs may have been understandable during the initial stages of characterization of the Maudsley model, our understanding of the nervous system has greatly increased in the past 20 years and it is surely time to attempt to integrate what we know of group differences between the Maudsley strains with current concepts of nervous system function.

A neural mediator for differences between the Maudsley strains

Because of the conceptual confusion connected with previous usage it is suggested that it is timely to dispense with the concept of emotionality in preference for an attempt to understand differences between the Maudsley strains in terms of defined variations in the nervous system. As defined above, emotionality energizes a variety of behavioral processes and this makes the arousal system a prime candidate for its neural substrate. An alteration of the arousal system would be likely to have a global effect on a variety of behavioral processes and is consistent with the widespread differences which are seen between the Maudsley strains in stressful situations. A change in the reticular activating system might be expressed in terms of individual alterations in the threshold at which an arousal response is generated by afferent stimuli, or possibly by changes in the magnitude or pattern of the arousal response to a specific supra-threshold stimulus. In either case, this would be likely to affect the way in which the brainstem reticular system modulates the electrical activity of the various areas of the brain and spinal cord to which it projects.

The reticular activating system consists of a non-specific neural system that extends medially through the brainstem[19]. Originally, it was described as a diffuse network of cells among which specific nuclei were not defined. However, more recently, specific components have been described[28]. One of these, the locus ceruleus, is an important part of the central noradrenergic system. It is located in the anterior pons and contains cell bodies of noradrenergic neurons which project to may different regions of the brain and spinal cord. Thus, the widespread connections of the LC suggest a global rather than specific role for this nucleus in its interactions with other parts of the nervous system. Although the nucleus only occupies a small volume in the anterior pons, its projections are extensively arborized[20] and lesions of the LC have a major impact on noradrenaline(NA) concentrations in brain regions such as cortex. For example, the studies of Kobayashi et al. demonstrated that cortical NA concentrations fell by 70% following electrolytic lesions of the LC[29]. The diffuse nature of the projections of the LC are also present in its synaptic connections. On the projections of the LC, varicosities are seen which resemble those seen on peripheral sympathetic post-ganglionic nerves. Furthermore, as is the case in the peripheral sympathetic nervous system, these varicosities do not form the classical close synaptic contact with adjacent cells, but are arranged so that neurotransmitter released from these varicosities spreads diffusely in its local environment[21]. This characteristic, as well as the extensive arborization of its projections, seems to suggest a global rather than specific signal role for the LC in its interactions with other brain regions.

The locus ceruleus as a stress-attenuator

Amaral and Sinnamon[1] have proposed that the anatomic connections of the LC and its neurophysiological effects are consistent with its enhancing signal-to-noise ratio in the nervous system. Their view is based on observations showing that electrical stimulation of the LC inhibits the spontaneous activity of hippocampal and cerebellar units but facilitates transmission of other afferent signals[23, 35]. In this view, suppression of spontaneous activity by the LC reduces the noise or non-signal component of nervous activity while enhancement of transmission of afferent signals augments the signal value of a particular neural event. Taken together, both influences would be expected to bias the organism to respond to prepotent environmental events which require swift or emergency response. This view of the LC led Amaral and Sinnamon to propose that one role of the LC may be to exert a stress-attenuating role in the nervous system to permit the organism to carry out an adaptive response.

Variations in the locus ceruleus as a mediator of strain differences in the Maudsley strains

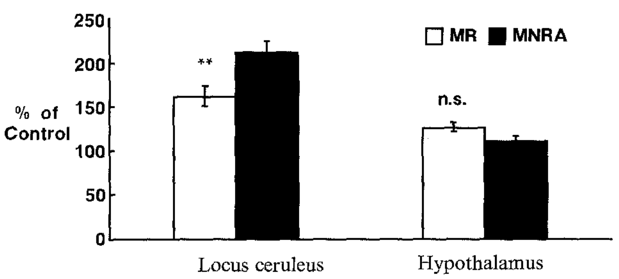
Amaral and Sinnamon's suggestion that the locus ceruleus exerts a stress-attenuating role when considering the organism's response to prepotent environmental stimuli identifies it as a possible mediator of differences between the two Maudsley strains. In applying this view of the LC to the Maudsley model it is postulated that alleles capable of influencing the function of the LC have been selected for in the Maudsley Reactive and Non-Reactive strains and fixed by inbreeding within them. It is proposed that strain-dependent variations in the LC are responsible for many of the behavioral and physiological differences that are seen between them. Formulation of this hypothesis has the advantage that the behavioral and other differences between the Maudsley strains are related to strain-dependent variations in the anatomy or function of a defined locus in the nervous system. The hypothesis predicts that there would be differences in the manner in which the LC responds to stress in the two strains.

a) *Strain-dependent biochemical variations in the locus ceruleus following stress.* To test the hypothesis that genetic differences between the Maudsley strains are mediated by variations in the LC, comparisons of LC-response to chronic stress were made by measuring tyrosine hydroxylase (TH) activity in the LC of the Maudsley strains under control and chronically stressed conditions[8]. This index was selected because the LC has been shown to be exquisitely sensitive to the effects of chronic stress to the extent that large increases in TH-activity are seen in this nucleus following exposure of experimental animals to repetitive stress, and these increases in enzyme-activity are sustained in time well beyond the application of the stressful stimulus[39, 43]. The signal for increased synthesis of TH-molecules in noradrenergic neurons is believed to be the depletion of NA which accompanies stress[42], an hypothesis supported by the observation that the magnitude of depletion and temporal recovery of tissue NA that follows reserpine administration is inversely correlated with the magnitude of TH-elevation[33]. Thus, measurements of TH-activity were used in this experiment to provide an indirect estimate of the magnitude of cerulear activation and the associated depletion of transmitter.

Amaral and Sinnamon's proposal that activation of the LC enhances signal-to-noise ratio in the nervous system is a key feature of their hypothesis that the LC exerts a stress-attenuating role. In this context, the superior performance of Non-Reactive rats in active avoidance conditioning is consistent with their possessing an improved signal-to-noise processing capability relative to Reactive rats. It was therefore predicted that Non-Reactive rats selected for decreased reactivity to stress would exhibit greater cerulear activation, a greater NA-depletion and, associated with the latter, a larger synthesis of TH-molecules in the LC. Groups of Reactive and Non-Reactive male rats were exposed to a daily stress consisting of 50 min exposure to intermittent footshock and were sacrificed approximately 24 h after the 9th daily stress exposure. As predicted, exposure to this stressful regime produced a significantly greater elevation of cerulear TH-activity in MNRA/Har than MR/Har male rats (fig.). The greater elevation of cerulear TH in MNRA/Har rats was seen in three independent experiments, thus establishing it as a highly reliable strain difference. It is proposed that exposure to footshock produced greater neuronal activity in the cerulear pathway of Non-Reactive rats, a correspondingly greater depletion of neuronal NA levels, and as outlined above, a stronger stimulus for enzyme induction in the LC of Non-Reactive rats. TH-activity in hypothalamus did not exhibit the same strain- dependent elevation after stress and because the LC does not project extensively to the hypothalamus this finding suggests an element of specificity in the response of the central noradrenergic system in the Maudsley strains.

There is no information at present as to how strain-dependent variations in neuronal activity in the LC might be mediated. These could result from genetically-controlled alterations in the projections to the LC[4]. Alternatively, the intrinsic activity of LC neurons might differ in such a way as to affect their ability to respond to an activating stimulus. In any case, the important conclusion to be derived from the present results is that the biochemical evidence provides support for the hypothesis that the cerulear pathway is differentially activated by stress in the two Maudsley strains and provides strong encouragement for pursuing additional experimental tests of its validity.

Tyrosine hydroxylase activity



Effects of chronic stress on tyrosine hydroxylase activity in two brain regions.

N=12–21 per group. ** $p < 0.01$ vs Non-Reactive; (After Blizard, Freedman and Liang[8]).

b) *Strain-dependent variations in the peripheral sympathetic nervous system.* Amaral and Sinnamon identified several other effects of cerulear function which are relevant to the theory which is being discussed. It has been suggested that descending projections from the LC to the spinal cord exert an inhibitory influence on the peripheral sympathetic nervous system. This is consistent with the observation that LC lesions lead to elevated blood-pressure and death within 24 h, a phenomenon which may depend on increased sympathetic tone and peripheral vasoconstriction[38]. The hypothesis that the LC exerts a stress-attenuating role is consistent with this observation because the peripheral sympathetic nervous system (PSNS) is activated during stress, and concomitant cerulear activation would be likely to attenuate the response of the PSNS.

It is relevant to this aspect of cerulear function that the Maudsley strains have been shown to differ in the response of the PSNS to acute stress. Male rats of Reactive and Non-Reactive strains were implanted with abdominal aortic cannulae and after six days of post-operative recovery were exposed to several different acute stresses: handling, exposure to the open-field and immobilization[10]. The response of the PSNS was estimated by measuring plasma catecholamines from blood samples obtained under basal (resting) and each of the stress conditions described above. Reactive rats exhibited significant increases in plasma NA and adrenaline (A) after all three stressors, whereas Non-Reactive rats did not exhibit a significant increase in NA after any of the stressors, and only showed a significant increase in A after immobilization and open-field tests (table).

The difference in the response of the two strains to stress does not appear to be a difference in the time-course of the response. Samples were taken after different periods of exposure to the various stressors (for handling, after 30 s; for the open field, after a 2-min exposure to the open-field; for immobilization, after 5 min) and Non-Reactive rats did not exhibit a significant increase in plasma NA after any of these stressors. On the other hand, the strain difference appears to be restricted to the peripheral sympathetic nervous system. Non-Reactive rats exhibited significant increases in plasma A following the open-field and immobilization manipulations in the same manner as Reactive animals.

The fact that three different acute stresses, ranging from mild (handling) to severe (immobilization), did not produce an increase in plasma NA in Non-Reactive rats but produced significant increases in Reactive animals suggests a diminished response of the PSNS to stress in Non-Reactive rats.

Plasma catecholamines under resting conditions and in response to stress in the Maudsley Reactive and Maudsley Non-Reactive strains

	Basal		Handling		Open-field		Immobilization	
	NA	A	NA	A	NA	A	NA	A
MR/Har	676.3 ±42.8	489.2 ±44.7	1279 ±118	1383 ±138	1437 ±58.4	1450 ±73.7	2045 ±153	1666 ±164
MNR/Har	1174 ±185	619 ±66.9	974 ±144	816 ±73.6	1247 ±124	1331 ±137	1473 ±120	1406 ±127

Maudsley Reactive and Maudsley Non-Reactive male rats were chronically cannulated in the abdominal aorta and blood-samples obtained after a postsurgery recovery period of approximately 6 days under basal conditions and after exposure to three manipulations (handling, open-field and immobilization). The plasma catecholamines noradrenaline (NA) and adrenaline (A) were measured by radiometric assay. MR/Har rats exhibited significant increases in plasma NA and A above basal levels after all three stresses but MNR/Har rats only exhibited significant increases in plasma A after immobilization and open-field exposures. See text for additional discussion and Blizard et al.[10].

The diminished response of Non-Reactive animals to stress is consistent with their having a greater cerulear activation than Reactive rats because, as proposed above, the LC is believed to exert an inhibitory influence on the peripheral sympathetic nervous system.

It has also been found that the Maudsley strains differ in their peripheral sympathetic nervous system under resting conditions. Non-Reactive rats were originally found to have higher tissue levels of catecholamines (primarily noradrenaline) than MR/Har rats in heart, spleen and adrenal glands[30, 37] and this was later extended to other peripheral tissues such as submaxillary gland, small intestine and colon[7]. The pattern of results indicate that there is a substantial difference between the peripheral sympathetic nervous systems of the Maudsley strains which is distributed in a widespread manner across many peripheral organs. Subsequent studies of the concentration of catecholamines in the blood-stream of chronically-cannulated Maudsley rats revealed that males of both Non-Reactive strains and higher concentrations of noradrenaline in the blood than MR/Har rats[11]. It has been argued that plasma levels of catecholamines reflect the release rate from peripheral sympathetic neurons and the higher plasma levels of Non-Reactive rats suggests that there is a higher peripheral release of noradrenaline in Non-Reactive vs Reactive rats.

Higher sympathetic tone in Non-Reactive rats would be likely to produce a down-regulation of post-synaptic receptors in this strain and in support of this hypothesis it was found that Non-Reactive rats had a lower density of cardiac beta receptors than Reactives[31]. This provides additional evidence that the basal sympathetic tone of Non-Reactive rats is elevated and that the increased sympathetic tone has physiological significance.

The differences in the resting or basal tone of the PSNS of the Maudsley strains are opposite to those which have been demonstrated in response to acute stress. Non-Reactive rats have a diminished PSNS-response to acute stress but increased resting PSNS-tone. In this presentation, we have emphasized the significance of the diminished PSNS-reactivity of Non-Reactive rats for the present theory but the differences which exist in the resting state should not be forgotten as they may also reflect the influence of tonic cerulear alterations which could be relevant to understanding strain differences in the phasic response of the LC.

Conclusion

Amaral and Sinnamon[1] argued that the LC exerts a stress-attenuating role in the nervous system whose influence would be seen in facilitating the behavioral response to stressful situations and also in attenuating the response of the peripheral sympathetic nervous system to stress. Utilizing this framework, it has been hypothesized that the LC has been a target for gene action in the Maudsley model. As elaborated, three different lines of evidence support this hypothesis. First, the biochemical response of the LC to chronic stress differs in the Maudsley strains: we have argued that the greater elevation of TH in the LC of Non-Reactive rats following chronic stress reflects a more profound activation of the cerulear pathway by stress in Non-Reactive animals. Secondly, the marked behavioral differences in stressful situations which have been demonstrated in the Maudsley strains is also consistent with variation in the LC. It has been argued that cerulear activation enhances the signal-to-noise ratio in the nervous system and biases the animal to respond to prepotent stimuli. The greater activation of the LC hypothesized to exist in Non-Reactive rats is thus compatible with their more efficient performance in active avoidance conditioning[18, 32] where animals are required to attend to and respond efficiently to a warning stimulus. Thirdly, the diminished reactivity to stress of the peripheral sympathetic nervous system of Non-Reactive rats is consistent with a greater activation of LC because, as discussed earlier, the LC is believed to exert an inhibitory influence on the PSNS.

The possibility that the LC is a focus of gene action in the Maudsley model has important heuristic value. It permits the various behavioral, biochemical, physiological and endocrinological differences between the strains to be understood as being the result of a gene-action at a particular locus in the nervous system. The hypothesis does not preclude the possibility that other CNS-loci may have been altered by gene-action. Indeed, it seems unlikely that the many behavioral and physiological differences which have been found between the strains can be explained by variation at a single locus in the nervous system. Nevertheless, the hypothesis has an important advantage: it substitutes a specific anatomic location in the brain for a loosely defined construct (emotionality) and is thus amenable to empirical evaluation. The LC has been the subject of intense investigation in recent years and the accumulation of knowledge about the LC endows great flexibility on future experimental approaches[3, 4]. Reciprocally, if future research continues to support involvement of the LC in the mediation of genetic differences between the Maudsleys, this model may assist in the elucidation of the biological function of this important noradrenergic nucleus.

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Short Communications

Long-term depressor effects of noradrenaline and dopamine neurons transplanted into the third ventricle of the brain of salt-loaded hypertensive rats

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Summary. Neural tissues including A 6 group noradrenaline neurons in the locus ceruleus or A 10 group dopamine neurons in the substantia nigra were transplanted into the third ventricle at the preoptic-anterior hypothalamic level of rats made hypertensive by salt loading. Either transplant exerted a long-lasting depressor effect.

Key words. Neural transplants; catecholamine neurons; third ventricle; salt hypertension; depressor effects.

In the course of a previous study in which we assessed the effects on gonadotropin secretion of the transplantation of catecholamine (CA) neuron-rich brain tissue into the third ventricle (IIIV) at the level of the preoptic area (POA)[1], it was occasionally found that rats with such transplants had a blood pressure considerably lower than that in control rats without transplants (unpublished observation). There is ample evidence that brain catecholamine plays a role in decreasing arterial blood pressure[2–10]. It seems that the POA-anterior hypothalamic area (AHA) contributes to the depressor system[11,12], the function of which is stimulated by CA transmission and is probably mediated by the nucleus tractus solitarius (NTS)[13]. Electrical stimulation of the AHA lowered blood pressure[14,15]. In addition, the administration of CA, either noradrenaline (NA) or dopamine (DA), in the POA-AHA and NTS induced a decrease in blood pressure in