cidate the precise genetic requirements for heterotic expression. On the other hand, if heterotic phenotype is considered to be superior growth rate, then such studies would reveal the mechanism or mechanisms of accomplishment of this superiority. This knowledge would appear to be equally as important as the knowledge of the genetic factors required for heterosis. Such information may ultimately lead to the elucidation of heterotic genotype (*10*).

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Maturation of a Stress-Activated Mechanism Inhibiting Induction of Tyrosine Transaminase

Abstract. *Rats of various ages were subjected to the stress of 30 minutes on a noisy reciprocating shaker 4 hours before their liver tyrosine transaminase and tryptophan pyrrolase activities were measured. Adrenalectomized infants and adults and hypophysectomized adults were also stressed. Intact, stressed infants exhibited an increase in tyrosine transaminase activity, while intact, stressed adults showed no change. In the stressed adrenalectomized adult, tyrosine transaminase activity markedly decreased, while adrenalectomized infants showed no change. Hypophysectomy largely, but not completely, abolished inhibition in the adults. Tryptophan pyrrolase activity, when present, was increased by stress in all age groups, but the increase was abolished by adrenalectomy and hypophysectomy. The results suggest stress-activation of a pituitary mechanism that inhibits or represses activation of tyrosine transaminase and that may not function during early postnatal life.*

Much evidence indicates that some hormones influence the synthesis of specific enzymes and that synthesis depends on activation of messenger RNA (mRNA). It is indeed possible that such action may underlie a variety of the physiological and biochemical changes produced by these hormones.

The classic work of Knox *et al.* has clearly established that, in the adult rat, exogenously administered adrenal cortical hormones increase the activities of certain liver enzymes participating in protein metabolism (*1*). These enzymes include α-ketoglutarate-tryptophan, tyrosine transaminase, and tryptophan pyrrolase. The effects of stress and of associated cortical hormone secretion on enzyme induction, however, have not been so thoroughly studied.

We have reported (*2*) that adult rats stressed for 30 minutes on a noisy reciprocating shaker did not respond with an increase in tyrosine transaminase activity despite marked adrenalcortical hormone secretion, and that this stress partially inhibited induction by cortisol of transaminase but not of tryptophan pyrrolase activity (*3*).

These observations led us to postulate stress-activation of not only adrenocorticotrophic-hormone (ACTH) secretion but also an additional mechanism (or mechanisms) that inhibited or repressed transaminase induction by the glucocorticoids. Results of additional studies indicated that this repressor mechanism is an adult phenomena that does not function during the early postnatal period (*4*). This report concerns the ontogenesis of this stress-activated inhibitory or repressor mechanism; we present evidence that it is largely abolished by hypophysectomy.

Sprague-Dawley rats bred in this laboratory were used for all experiments but those entailing hypophysectomy (*5*). Littermates of different ages were stressed on a noisy reciprocating shaker (*2, 4*); adrenalectomized and hypophysectomized rats were used 5 to 7 days after surgery. Activities of tyrosine transaminase and tryptophan pyrrolase were determined 4 hours later from portions of liver supernatant (*2*).

Figure 1 indicates that during the first 21 days of life the infant responded to stress with an increase in tyrosine transaminase activity, but that such activity was not increased in similarly stressed intact adults; the results on adults confirm our earlier report (*2*), and the relatively high levels of activity observed during the early postnatal period agree with the observations of Auerbach and Waisman (*6*).

Tryptophan pyrrolase activity was undetectable in either controls or stressed infants before 15 days of age; when it did appear at this time, it showed an increase in response to stress in the different age groups. In 15-day-old infants adrenalectomy prevented the increase in transaminase activity in response to stress, while the adrenalectomized adult, similarly stressed, exhibited a marked decrease in enzyme activity (Table 1). The increase in adult levels of transaminase in controls after adrenalectomy agrees with Knox's data (*1*), although the increase that we report is of a greater order of magnitude.

Adrenalectomy abolished the increase in tryptophan pyrrolase activity in response to stress. Our results thus suggest that in the adult rat this stress, which activates adrenal cortical hormone secretion (*2*), also activates another mechanism that blocks, inhibits, or represses the effects of the glucocorticoids on the induction of tyrosine transaminase, without affecting induction of tryptophan pyrrolase. This conclusion is supported by the observation that in the adult this stress substantially inhibits the transaminase-inducing effects of administration of cortisol (*3*) but not of tryptophan pyrrolase.

The repressor mechanism does not appear to function before 21 days of age, although it is also possible that hepatic tissue is refractory to its influence. The fact that hypophysectomy partially prevents the decrease and that hypophysectomy, together with adrenalectomy, completely prevents it (Table 1) suggests that pituitary factors may contribute to the mechanism. This effect is not an indirect action of ACTH, nor is it caused by adrenalin, noradrenalin, or thyroxine, because adrenalectomized rats exhibited no

Table 1. Average effects of age, adrenalectomy (adren.), and hypophysectomy (hyphys.) on activities (expressed as in Fig. 1) in liver of tryptophan pyrrolase and tyrosine transaminase in response to stress. Significances indicated in parentheses. NS, not significant; PP, 100μg of pyroxidoxal phosphate present.

Age (days)	N	Treatment	Activities (± SE)		
			Pyrrolase	Transaminase	
				−PP	+PP
15	4	None	1.8±.2	2.0±.6	6.3±.5
15	4	Stress	4.1±.6(<.05)	3.7±.7(NS)	11.5±.8(<.01)
15	8	Adren.	1.2±.2	2.1±.7	7.3±.8
15	8	Adren. + stress	1.2±.1(NS)	1.3±.5(NS)	6.9±.6(NS)
Adult	4	None	6.5±.7	.38±.1	7.2±1.3
Adult	4	Stress	19.1±3.5(<.05)	.31±.05(NS)	7.8±.4(NS)
Adult	16	Adren.	1.1±1.3	1.3±.3	12.2±1.3
Adult	16	Adren. + stress	1.1±.8(NS)	.28±.03(<.001)	3.8±.4(<.001)
Adult	12	Hyphys.	1.2±.2	2.5±.6	14.2±2.0
Adult	12	Hyphys. + stress	1.5±.3(NS)	1.9±.4(NS)	8.6±1.0(<.05)
Adult	7	Adren. + hyphys.		3.1±.8	9.1±.8
Adult	6	Adren. + hyphys. + stress		5.2±1.7(NS)	10.0±1.8(NS)

change in tyrosine transaminase activity 4 hours after administration of 5 to 10 units of ACTH or 1 μg of adrenalin or noradrenalin per gram of body weight; thyroxine at 1 μg/g did not decrease enzyme activity 4 hours after administration to intact rats.

Peraino and Pitot (*7*) have recently demonstrated repression by carbohydrate of induction of ornithine transaminase and threonine dehydrase by injection of glucagon or by dietary casein hydrolyzate. Possible endocrine involvements in this phenomenon have not been reported. The most likely candidate among the pituitary hormones for responsibility for the transaminase repression that we report would seem to be growth hormone because of its protein anabolic action; moreover, it is released under conditions of excitement and exercise (*8*) that accompanied the stress employed. As stress does not provoke ACTH secretion in the infant rat, aged less than 8 days (*9*), the elevation in transaminase activity before this age may represent substrate induction (*1*).

The nature and site of action of the stress-activated repressor mechanism in the adult have yet to be elucidated. It may act by inducing the formation of, or stabilizing, the enzymes that metabolize tyrosine transaminase, or by blocking induction of transaminase itself at the level of either mRNA or protein synthesis. Regardless of the site of action, however, our experiments suggest that (i) in response to this particular stress a mechanism is activated that opposes the transaminase-inducing effect of the adrenalcortical hormones; (ii) this mechanism is not present during the first three postnatal weeks; (iii) the mechanism involves the pituitary; and (iv) hormonal repression of enzyme synthesis or activity may play as important a role in physiological adaptation to some stresses as that attributed to enzyme induction.

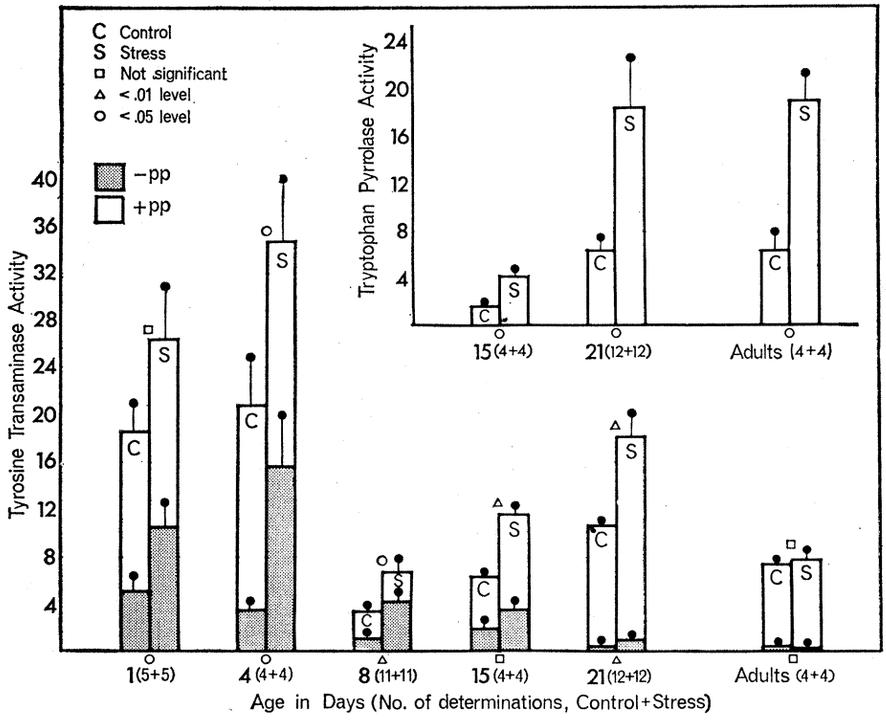

Fig. 1. Effects of age and stress on activities in liver of tyrosine transaminase and tryptophan pyrrolase. Transaminase activity expressed as micromoles of substrate per minute per gram of protein; pyrrolase units are micromoles of kyneurenine formed per hour per gram of protein. Solid circles represent standard errors. Transaminase was determined in presence (+) and absence (−) of 100 μg pyridoxal phosphate (*pp*). Number of determinations refers to number of littermate pools, each of 3 to 4 animals, in the 1-, 4-, and 8-day-old groups; in the older groups individual animals were used.

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