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Comparison of Uridine Diphosphate-Glucuronosyl Transferase and Other Drug Metabolizing Enzyme Activities between Two mutant strains of Wistar Rats with a Genetic Deficiency in Bilirubin or Androsterone Glucuronidation*

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In 1938, Gunn described that a mutant strain of Wistar rats (Gunn rats) exhibits hereditary hyperbilitunemia. It was reporter subsequently that Gunn rats lack the ability to glucuronidate billirubin (BL), due to the absence of BL UDP-glucuronosyltransferase (GT). Since Gunn rats have been maintained by crossbreeding with various rat strains, it is possible that Gunn rat colonies are not genetically identical except for jaundice locus.

Our Gunn rats were initially obtained from Albert Einstein College of Medicine, New York. Although matings among Gunn rats were unsuccessful, cross of Gunn rats with Wistar-Imamichi rats and subsequent inbreeding made it possible to provide jaundiced animals. Gunn described that the albino Gunn rats appeared relatively yellow in color owing to jaundice. In addition to this yellow color, our Gunn rat colony inherits the hooded coat pattern similar to Long-Evans rats which have black pigmentation on head and back stripe. The occurrence of a similar type of hooded Gunn rats was described previously.

Discontinuous variation in androsterone (AD) glucuronidation was demonstrated in Wistar rats, the high AD GT activity (HA) to low AD GT activity (LA) ratios being approximately 16 : 1. The genetic expression of HA phenotype is inherited as a single autosomal dominant trait, and HA and LA Wistar rats were selected and have been inbred respectively. Purification of AD GT enzyme from HA and LA Wistar rats has provided evidence that AD GT protein is absent in LA Wistar rats.

Our Gunn rat colony showed GT activity patterns typical of some albino Gunn rat population. BL GT activity was absent in our Gunn rats. Their low GT activities toward 2-aminophenol (AP) and 4-nitrophenol (NP) were restored to the high levels of LA Wistar rats by the addition of N-nitrosodiethylamine (NEN) or N-nitrodiethylamine (NEA).

Scragg *et al.* purified GTs from Gunn and Wistar rat livers and described that BL GT and possibly phenol (substrate : AP and 1-naphthol) GT were not present in the congenitally jaundiced Gunn rats. Thus, the reduced GT activities toward AP and NP and their restoration by addition of NEN or NEA may indicate the existence of a mutant GT(s)

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responsible for activation by NEN or NEA in our Gunn rats.

GT is bound to microsomes and exhibits latency, which may be due to restricted access of substrate to the enzyme and/or poorly active conformation of the membrane-bound enzyme. GT activity can be stimulated by several membrane-perturbing procedures. NEN and several alkylketones have been known to stimulate specifically GT activities toward AP and NP. From studies of modification of GT activities toward AP and NP, NEA in which the N-nitroso group of NEN is substituted for the N-nitro group is found to modify GT activities toward AP and NP in a manner similar to NEN in HA Wistar rats, though their molecular mechanism for the stimulation of the GT activities is not known. In the present study, NEA appears to stimulate the low Gunn rat NP GT activity more efficiently than does NEN in the presence of Triton. Since NEA is much less toxic than NEN, a potent carcinogen, it is apparent that NEA is a suitable compound for studying modification of GT activity.

Another interesting aspect is that our Gunn rats have high AD GT activity. Certain Gunn rat colony showed only 42% of AD GT activity, compared with the control Wistar rats. In another experiments, jaundice locus of Gunn rats was transferred to inbred RHA rats and their GT activities were compared with those of normal RHA rats. NP GT activity was reduced to about 30% in jaundiced RHA rats, however, their AD GT activity was not affected. These contradictory results may reflect the different genetic background in Gunn rat colonies except for jaundice locus. Two populations appear to exist in Wistar rat colonies, one with high and one with low AD GT activity. Although Gunn rats are a mutant strain of Wistar rats, it seems likely that our Gunn rats inherit comparatively high AD GT gene in contrast to LA Wistar rats. However, Crossbreeding study between Gunn and LA Wistar rats may provide further insight into the organization of GT gene family and the multiplicity of GT isoenzymes.