

BN (Brown Norway)

BN/RijHsd

Developed in 1958 by Silvers and Billingham from a brown mutation maintained by King and Aptekman in a pen-bred colony (Billingham and Silvers 1959).

In 1963, from Microbiological Associates Inc., Bethesda, USA to Radiobiological Institute-TNO, Rijswijk, The Netherlands. In 1994, to Harlan Nederland through acquisition. Harlan became Envigo in 2015, then Envigo was acquired by Inotiv in 2021.

RESEARCH APPLICATIONS

Behavior, hydronephrosis, cancer research, myelocytic leukemia, aging, HgCl₂-induced nephritis.

CHARACTERISTICS

Animal model

The BN is an animal model for human acute myeloid leukemia (Colly and Hagenbeek, 1977). In this strain grows a transplantable myelocytic leukemia (BNML), which is a useful animal model for studying human acute myelocytic leukemia (Martens, *et al*, 1990).

Behavior

The BN strain is a docile rat. Poor performance in an active avoidance learning task, but good reference memory (Van Lujtelaar *et al*, 1988). Cannot be triggered into paradoxical sleep by dark pulse stimulation (Leung *et al*, 1992). Higher percentage of paradoxical sleep than LEW (Rosenberg *et al*, 1987). Low preference for ethanol and low capability to develop acute tolerance to ethanol hypnosis (York *et al*, 1994). Behavioral performance declined less rapidly with aging than in strain F344 (Spangler *et al*, 1994).

Drugs

Dimethylbenzanthracene induced a transplantable myeloid leukemia (Colly and Hagenbeek, 1977). Intermediate susceptibility to pentobarbital sodium with LD50 of 90 mg/kg (Shearer *et al*, 1973).

Genetics

Coat color genes

- *a, b, C, h¹*: non-agouti brown.

Histocompatibility

- *RT1ⁿ, RT2^a or RT2^b, RT3^b, RT8^b*.

Biochemical markers

- *Acon-1^a, Ac^p-2^a, Ahd-2^b, Akp-1^a, Alb^a, Amyl^b, Cryg-1^b, Es-1^a, Es-2^c, Es-3^d, Es-4^b, Es-6^b, Es-7^b, Es-8^a, Es-9^c, Es-10^b, Es-14^a, Es-15^c, Es-16^a, Es-18^b, Fh-1^a, Gc^a, Glo-1^a, Gox-1^b, Hbb^a, Igk-1^a, Lap-1^a, Mgd-1^b, Mup-1^a, Pg-1^a, Pgd^b, Svp-1^b*. (Bender *et al*, 1994).

Substrains vary with respect to Pep-3 and RT2. The original BN strain has been maintained with forced heterozygosity for RT2. Hence, BN strains vary in this RT2 blood group antigen. (Paul and Carpenter, 1981).

- BN/RijHsd = *Pep-3^a and RT2^a*
- BN/SsNOlaHsd = *Pep-3^b and RT2^b*





Immunology

Resistant to induction of experimental allergic encephalomyelitis (Gasser *et al*, 1975; McFarlin *et al*, 1975). However, resistance can be modulated by endogenous corticosteroids (Peers *et al*, 1995). Resistant to induction of autologous immune complex glomerulonephritis (Stenglein *et al*, 1975). Susceptible to the development of mercury-induced autoimmunity to renal basement membranes with the development of membranous glomerulonephritis (Henry *et al*, 1988). Susceptible to the autoimmune effects of mercury showing a decrease of peripheral RT6.2(+) T lymphocytes compared with strain LEW (Kosuda *et al*, 1994), but no release of hydrogen peroxide in peritoneal polymorphonuclear leukocytes and macrophages, in contrast with LEW (Contrino *et al*, 1992). Susceptible to the development of autoimmunity to skin-injected $HgCl_2$, in contrast to LEW (Warfvinge and Larsson, 1994). Develop a T-helper 2 cell-mediated autoimmune syndrome following treatment with mercuric chloride, gold or D-penicillamine which may be associated with the response of mast cells (Oliveira *et al*, 1995). Moderately sensitive to the development of experimental glomerulonephritis following injection of nephritogenic antigen from bovine renal basement membrane (Naito *et al*, 1991). Develops severe experimental allergic encephalomyelitis when immunized with rat spinal cord and carbonyl iron adjuvant (Levine and Sowinski, 1975). Linington *et al*, (1986) induced experimental allergic neuritis using T-cells and bovine P2 (a peripheral nerve myelin protein). Resistant to the induction of Heymann nephritis (Badalamenti *et al*, 1987). High

IgE response to Japanese cedar pollen antigen: may be a useful model for studying physiological and pathological changes in the nose after pollen challenge (Imaoka *et al*, 1993). Resident macrophages (ramified microglia) of the central nervous system are constitutively major histocompatibility complex class-II positive, in contrast with LEW (Sedgwick *et al*, 1993).

Following lethal irradiation and re-constitution with syngeneic bone marrow and given cyclosporin A for several weeks LEW rats will develop cyclosporin-induced autoimmunity after withdrawal of the cyclosporin. The condition resembles graft-versus host disease in terms of acute dermatitis and chronic scleroderma. However, BN rats do not develop this disease (Wodzig *et al*, 1993). Resistant to the induction of experimental autoimmune uveoretinitis and endotoxin-induced uveitis, which appears to be associated with the production of tumor necrosis factor (TNF) by retinal Muller glia and retinal-pigmented epithelium. LEW is susceptible. (Dekozak *et al*, 1994). Susceptible to the induction of proteinuria following treatment with the monoclonal antibody 5-6-1, like LEW and outbred Wistar, but unlike resistant outbred Sprague Dawley rats which were also resistant to glomerular damage (Gollner *et al*, 1995). Skin from neonatal males grafted onto syngeneic females induces tolerance to subsequent grafts of male skin. (Silvers and Connors, 1979). Low antibody response to phyto-hemagglutinin, concanavalin A and streptococcal group A carbohydrate (Koch 1976, Stankus and Leslie 1976, Williams *et al*, 1973). Good antibody response to a synthetic 20 amino acid peptide derived from the alpha helical

region of the RT1-D^u beta chain (Murphy *et al*, 1994). Low activity of NK cells compared with other rat strains (Reynolds and Holden, 1982).

Infection

Resistant to the induction of encephalitis by coronavirus, with a much shorter delay in lymphocyte proliferation following infection than in the susceptible LEW strain (Imrich *et al*, 1994). Partly resistant to *Trypanosoma cruzi* (Rivera-Vanderpas *et al*, 1983).

Life-span and spontaneous disease

Endocardial disease 7% at an average age of 31 months. The lesion consisted of a proliferation of fibroblast-like cells within the endocardium (Boorman *et al*, 1973). Tumors of epithelium 28% in males, 2% in females. Ureter tumors 20% in females, 6% in males. Estimated median lifespan more than 24 months in males and more than 25 months in females (Boorman and Hollander, 1974). Median lifespan 30.0 months in males and 31.2 months in females (Mos and Hollander, 1987). Median lifespan 28 months in males and 30 months in females (Burek and Hollander, 1977). Median lifespan 30.9 months for female retired breeders (Kort *et al*, 1984). Most common neoplastic lesions in males were urinary bladder carcinoma 35%, pancreas islet adenoma 15%, pituitary adenoma 14%, lymphoreticular sarcoma 14%, adrenal cortex adenoma 12%, medullary thyroid carcinoma 9%, and adrenal pheochromocytoma 8%. Four other types of tumors were observed. In females: pituitary adenoma 26%, ureter carcinoma 22%, adrenal cortical adenoma 19%, cervix sarcoma 15%, mammary gland

fibroadenoma 11% and islet adenoma 11%. Twelve other tumor types were observed (Burek and Hollander, 1977). Further details of an aging colony are given by Hollander (1976), Burek and Hollander (1977) and Burek (1978).

Vaginal and cervical tumors, mostly sarcomas but also seven squamous-cell carcinomas and four leiomyomas, were seen in 20% of animals that died naturally (Burek *et al*, 1976b). High incidence (31%) of hydronephrosis reported in 2-month-old BN/Rij (Cohen *et al*, 1970),

but little seen by Gray *et al* (1982) before 30 months, after which the disease progressed slowly. The BN/Rij rat has a mild severity of chronic progressive nephritis (Gray *et al*, 1982). Granular cell tumors are found in untreated BN/Rij rats (Hollander *et al*, 1976). Spontaneous paresis and paralysis associated with degenerative spinal cord and spinal nerve root lesions occurred in aging rats (Burek *et al*, 1976a). Induction of atherosclerosis can be induced by immunization with ovalbumin (Nishisono *et al*, 1999)

Miscellaneous

Characteristics of the BN strain have been described by Festing (1979) and Greenhouse *et al* (1990).

Physiology and biochemistry

Low plasma ceruloplasmin levels (Stolc, 1984).

Reproduction

Low litter size (4.8 young/litter).

REFERENCES

- Badalamenti J, Shea M, Cybulski AV, Quigg RJ, Salant DJ (1987) Heymann nephritis (HN) antigen in Lewis (LEW) and Brown Norway (BN) rats. *Fed Proc* 46, 1327.
- Bender K, Balogh P, Bertrand MF, den Bieman M, von Deimling O, Eghtessadi S, Gutman GA, Hedrich HJ, Hunt SV, Kluge R, Matsumoto K, Moralejo DH, Nagel M, Portal A, Prokop C-M, Seibert RT, van Zutphen LFM (1994) Genetic characterization of inbred strains of the rat (*Rattus norvegicus*). *J. Exp. Anim. Sci.* 36, 151-165.
- Billingham RE, Silvers WK (1959) Inbred animals and tissue transplantation immunity. *Transplant. Bull.* 6, 399-406.
- Boorman GA, Hollander CF (1974) High incidence of spontaneous urinary bladder and ureter tumors in the Brown Norway rat. *J. Natl. Cancer Inst.* 52, 1005-1008.
- Boorman GA, Zurcher C, Hollander CF, Feron VJ (1973) Natural occurring endocardial disease in the rat. *Arch. Pathol.* 96, 39-45.
- Bottger A, Den Bieman M, Lankhorst JE, Van Lith HA (1996) Strain specific response to hypercholesterolemic diets in the rat. *Lab. Anim.* 30, 149-157.
- Burek JD (1978) Pathology of aging rats. A morphological and experimental study of age-associated lesions in aging BN/Bi, WAG/Rij and (WAG x BN)F1 rats. CRC Press, Inc.
- Burek JD, Hollander CF (1977) Incidence of spontaneous tumors in BN/Bi rats. *J. Natl. Cancer Inst.* 58, 99-104.
- Burek JD, Van der Kogel AJ, Hollander CF (1976a) Degenerative myelopathy in three strains of aging rats. *Vet. Path.* 13, 321-331.
- Burek JD, Zurcher C, Hollander CF (1976b) High incidence of spontaneous cervical and vaginal tumors in an inbred strain of Brown Norway rats (BN/Bi). *J. Natl. Cancer Inst.* 57, 549-554.
- Cohen BJ, De Bruin RW, Kort WJ (1970) Heritable hydronephrosis in a mutant strain of Brown Norway rats. *Lab. Anim.* Care 20, 489-493.
- Colly LP, Hagenbeek T (1977) A rat model for human acute myeloid leukemia. In: *Experimental hematology today* (Baum SJ, Ledney DG, eds), pp 211-219. Springer Verlag, New York.
- Contino J, Kosuda LL, Marucha P, Kreutzer DL, Bigazzi PE (1992) The in vitro effects of mercury on peritoneal leukocytes (PMN and macrophages) from inbred Brown Norway and Lewis rats. *International Journal of Immunopharmacology* 14, 1051-1059.
- Dekozak Y, Naud MC, Bellot J, Faure JP, Hicks D (1994) Differential tumor-necrosis-factor expression by resident retinal cells from experimental uveitis-susceptible and uveitis-resistant rat strains. *J. Neuroimmunol.* 55, 1-9.
- Festing MFW (1979) Inbred strains. In: *The Laboratory Rat. Vol. I. Biology and Diseases* (Baker HJ, Lindsey JR and Weisbroth SH, eds). New York: Academic Press, pp 55-72.
- Gasser DL, Palm J, Gonatas NK (1975) Genetic control of susceptibility to experimental allergic encephalomyelitis and the Ag-B locus of rats. *J. Immunol.* 115, 431-433.
- Gollner D, Kawachi H, Oite T, Oka M, Nagase M, Shimizu F (1995) Strain variation in susceptibility to the development of monoclonal- antibody 5-1-6-induced proteinuria in rats. *Clin. Exp. Immunol.* 101, 341-345.
- Gray JE, Van Zwieten MJ, Hollander CF (1982) Early light microscopic changes of chronic progressive nephrosis in several strains of aging laboratory rats. *J. Gerontol.* 37, 142-150.
- Greenhouse DD, Festing MFW, Hasan S, Cohen AL (1990) Catalogue of inbred strains of rats. In: *Genetic monitoring of inbred strains of rats* (Hedrich HJ, ed). Stuttgart, New York: Gustav Fischer Verlag, pp. 410-480.
- Henry GA, Jarnot BM, Steinhoff MM, Bigazzi PE (1988) Mercury-induced renal autoimmunity in the MAXX rat. *Clin. Immunol. Immunopathol.* 49, 187-203.
- Hollander CF (1976) Current experience using the laboratory rat in aging studies. *Lab. Anim. Sci.* 26, 320-328.
- Hollander CF, Burek JD, Boorman GA, Snell KC, Laqueur GL (1976) Granular cell tumors of the central nervous system of rats. *Arch. Pathol. Lab. Med.* 100, 445-447.
- Imaoka K, Sakaguchi M, Inouye S (1993) Antibody-responses against Japanese cedar pollen allergen (Cry-j-I) in different strains of rats. *Exp. Anim.* 42, 61-65.
- Imrich H, Schwender S, Hein A, Dorries R (1994) Cervical lymphoid-tissue but not the central-nervous-system supports proliferation of virus-specific T-lymphocytes during coronavirus- induced encephalitis in rats. *J. Neuroimmunol.* 53, 73-81.
- Koch C (1976) Genetic control of antibody responses to PHA in inbred rats. *Scand. J. Immunol.* 5, 1149-1153.
- Kort WJ, Zondervan PE, Hulsman LOM, Weijma IM, Westbroek DL (1984) Incidence of spontaneous tumors in a group of retired breeder female Brown Norway rats. *J. Natl. Cancer Inst.* 72, 709-713.
- Kosuda LL, Housseinzadeh H, Greiner DL, Bigazzi PE (1994) Role of RT6(+) T-lymphocytes in mercury-induced renal autoimmunity - experimental manipulations of susceptible and resistant rats. *J. Toxicol. Environ. Health* 42, 303-321.
- Leung C, Bergmann BM, Rechtschaffen A, Benca RM (1992) Heritability of dark pulse triggering of paradoxical sleep in rats. *Physiol. Behav.* 52, 127-131.
- Levine S, Sowinsky R (1975) Allergic encephalomyelitis in the reputedly resistant Brown Norway strain of rats. *J. Immunol.* 114, 597-601.
- Linington C, Mann A, Izumo S, Uyemura K, Suzuki M, Meyermann R, Wekerle H (1986) Induction of experimental allergic neuritis in the BN rat. P2 protein-specific T cells overcome resistance to actively induced disease. *J. Immunol.* 137, 3826-3831.
- Martens ACM, Van Bekkum DW, Hagenbeek A (1990) The BN acute myelocytic leukemia (BNML): a rat model for studying human myelocytic leukemia (AML). *Leukemia* 4, 241-257.
- McFarlin DE, Hsu SC-L, Slemenda SB, Chou S C-H, Kibler RF (1975) The immune response against an encephalitogenic fragment of guinea pig basic protein in the Lewis and Brown Norway strains of rat. *J. Immunol.* 115, 1456-1458.
- Mos J, Hollander CF (1987) Analysis of survival data on aging rat cohorts: pitfalls and some practical considerations. *Mech. Ageing Dev.* 38, 89-105.
- Murphy G, Dalchau R, Parker KE, Sawyer GJ, Carter CA, Fabre JW (1994) T-cell recognition of an allogeneic RT1-dbu class-II MHC peptide. *Immunology Letters* 41, 195-199.
- Naito I, Kagawa M, Sado Y, Okigaki T (1991) Strain specific responses of inbred rats on the severity of experimental autoimmune glomerulonephritis - presence of a broad- spectrum of the susceptibility. *International Journal of Immunopathology and Pharmacology* 4, 145-154.
- Nishisono S, Kusaba M, Adan Y, Imaizumi K (1999) Induction of atherosclerosis in Brown Norway rats by immunization with ovalbumin. *Biosci. Biotechnol. Biochem.* 63, 379-383.
- Oliveira DBG, Gillespie K, Wolfreys K, Mathieson PW, Qasim F, Coleman JW (1995) Compounds that induce autoimmunity in the Brown Norway rat sensitize mast cells for mediator release and interleukin-4 expression. *Eur. J. Immunol.* 25, 2259-2264.
- Paul LC, Carpenter CB (1981) Heterogeneity of inbred BN strain rats for the RT2 locus. *Transplant. Proc.* 13, 1497.
- Peers SH, Duncan GS, Flower RJ, Bolton C (1995) Endogenous corticosteroids modulate lymphoproliferation and susceptibility to experimental allergic encephalo-myelitis in the Brown-Norway rat. *International Archives of Allergy and Immunology* 106, 20-24.
- Reynolds CW, Holden HT (1982) Genetic variation in Natural Killer (NK) activity in the rat. In: *NK cells and other natural effector cells*. (Herberman RB, ed). New York: Academic Press, pp 319-324.
- Rivera-Vanderpas MT, Rodriguez AM, Afchain D, Bazin H, Capron A (1983) *Trypanosoma cruzi*: variation in susceptibility of inbred rats. *Acta Tropica* 40, 5-10.
- Rosenberg RS, Bergman BM, Son HJ, Amason BGW, Rechtschaffen A (1987) Strain differences in the sleep of rats. *Sleep* 10, 537-541.
- Sedgwick JD, Schwender S, Gregersen R, Dorries R, Termeulen V (1993) Resident macrophages (ramified microglia) of the adult Brown Norway rat central-nervous-system are constitutively major histocompatibility complex class-II positive. *J. Exp. Med.* 177, 1145-1152.
- Shearer D, Creel D, Wilson CE (1973) Strain differences in the response of rats to repeated injections of pentobarbital sodium. *Lab. Animal Sci.* 23, 662-664.
- Silvers WK, Conners NH (1979) The behavior of H-Y-incompatible neonatal skin grafts in rats. *Transplant.* 28, 57-59.
- Spangler EL, Waggle KS, Hengemihle J, Roberts D, Hess B, Ingram DK (1994) Behavioral assessment of aging in male Fischer 344 and brown Norway rat strains and their F1 hybrid. *Neurobiology of Aging* 15, 319-328.
- Stankus RP, Leslie GA (1976) Rat interstrain antibody response and crossidiotypic specificity. *Immunogenet.* 3, 65-73.
- Stenglein B, Thoenes GH, Günther E (1975) Genetically controlled autologous immune complex glomerulonephritis in rats. *J. Immunol.* 115, 895-897.
- Stolc V (1984) Genetic polymorphism of ceruloplasmin levels in the rat. *J. Hered.* 70, 145-146.
- Van Luitelaar ELJM, Coenen AML (1988) Circadian rhythmicity in absence epilepsy in rats. *Epilepsy Res.* 2, 331-336.
- Warfvinge G, Larsson Å (1994) Contact stomatitis to mercury associated with spontaneous mononuclear cell infiltrates in Brown Norway (BN) rats with HgCl₂-induced autoimmunity. *J. Oral Pathol. Med.* 23, 444-445.
- Williams RM, Moore MJ, Benacerraf B (1973) Genetic control of thymus-derived cell function. III. DNA synthetic responses of rat lymph node cells stimulated in culture with concanavalin A and phytohemagglutinin. *J. Immunol.* 111, 1571-1578.
- Wodzicz KWH, Majoro GD, Vriesman RJC. V (1993) Susceptibility and resistance to cyclosporine-A-induced autoimmunity in rats. *Autoimmunity* 16, 29-37.
- York JL, Chan AWK (1994) Absence of acute tolerance to ethanol hyponis in F344 and BN/BiRij rats. *Alcohol* 11, 31-34.