BIOBIOGRAPHICAL SKETCH

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NAME **GEORGE R. BREESE, Ph.D.**	POSITION TITLE John R. Andrews Distinguished Professor Departments of Psychiatry and Pharmacology
eRA COMMONS USER NAME (credential, e.g., agency login) George_Breese	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Butler University, Indianapolis, Indiana	B.S.	1959	Pharmacy
Butler University, Indianapolis, Indiana	M.S.	1961	Pharmacology & Hospital Pharmacy
University of Tennessee, Memphis, Tenn.	Ph.D.	1965	Pharmacology
National Institute of Mental Health, Bethesda Maryland	Rapt fellow	1968	Pharmacology

A. PERSONAL STATEMENT:

Clinical data have demonstrated that stress induces craving and neural changes in brain of abstinent alcoholics—changes not observed in social drinkers. To model these negative symptoms to stress in alcoholics during abstinence, we documented that during absence from chronic intermittent alcohol (CIA) exposure stress-induced anxiety-like behavior (anxiety) was facilitated. Further work from our laboratory subsequently demonstrated that the central amygdala (CeA) was critically involved in this facilitation of stress induced anxiety. Based upon these earlier studies, *the hypothesis proposed is that facilitation of stress-induced anxiety after chronic intermittent alcohol (CIA) exposure involves activation of basolateral amygdala (BLA) neurons that synapse on neural outputs in the lateral (CeL) and medial (CeM) neural sub-regions of the CeA which in turn input on periaqueductal gray (PAG) neurons.* Further explored is based upon testing this hypothesis will be work to define the *influenced CRF, vasopressin (VP) and oxytocin (OXY) input have on output of CeA neurons to influence PAG or other CeA terminal sites.* This effort has been possible by introducing optogenetic and Dreadd systems to the laboratory. We feel that defining the influence neural inputs to and from the CeA have in stress-induced anxiety after CIA exposure will provide a better biological basis for the stress-induced negative affect and craving observed during abstinence in alcoholics because these paths have not been critically defined. Because of this work, the laboratory is currently exploring changes in cytokine-mRNAs in various brain sites to identify the association of brain regions in which neuroimmune function contributes to ethanol withdrawal-induced anxiety. A particular interest is defining if VP, like CRF, is involved in functions of the CeA—a strategy which permits integrating efforts to understand the brain regions and pathways in brain that contribute to the anxiety that follows ethanol withdrawal. Based upon my 50 yrs of research experience, I have rarely observed such important research opportunities arise that can provide such critical understanding of an issue directly relevant to the clinically involved negative symptoms observed to stress in alcoholics.

B. POSITIONS AND HONORS

Positions

1962-1964 USPHS Trainee & Teaching Assistant, Dept. of Pharmacology, UT Med. Unit (Memphis).

1964-1965 USPHS Predoctoral Fellow, Dept. of Pharmacology, UT Medical Units (Memphis).

1965-1966 Instructor in Pharmacology, Dept. of Pharmacology, Univ Arkansas Medical School

1966-1968 RAPT Fellow, NIMH, National Institutes of Health, Bethesda, Maryland.

1968-1972 Assistant Professor of Psychiatry & Pharmacology, UNC School of Med. (Chapel Hill).

1972-1976 Associate Professor of Psychiatry & Pharmacology, UNC School of Med. (Chapel Hill).

1977-present Professor of Psychiatry & Pharmacology, UNC School of Med. (Chapel Hill).

1968-present Scientist BDRC & Neuroscience Center, University of North Carolina (Chapel Hill).

1990-present Scientist, Head Neuropharmacology Laboratory, Bowles Center for Alcohol Studies, University of North Carolina, School of Medicine (Chapel Hill).

Honors

1981 Among the 1000 Most Cited Contemporary Scientists from 1965-1981 (ISI)

1981-2014 Listed as highly cited researcher by ISI (>18,892 citations).

2001 ASPET Award for Experimental Therapeutics.

2008. Distinguished Alumni Award; Butler University, Indianapolis, Ind.

2008 John R. Andrews Distinguished Professorship.

C. Contributions to Science

My earliest contributions were associated with involvement of monoamine function associated with peripheral and central action of various drugs. In the process of exploring central acting drug actions on norepinephrine (NE) metabolism, the metabolite for NE in brain was identified to be distinct from the major metabolite for norepinephrine in the periphery. This discovery allowed evaluating NE metabolism that occurred in brain in the urine—an approach not previously undertaken. This approach was a major objective upon coming to the University of North Carolina.

Schanberg SM, Breese GR, Schildkraut KK, Gordon EK, Kopin IJ.(1968) 3-methoxy-4-hydroxy-phenylglycol sulfate in brain and cerebrospinal fluid. Biochem Pharmacol. 17:2006-2008.

Schanberg SM, Schildkraut JJ, Breese GR, Kopin IJ. (1968) Metabolism of normetanephrine-H3 in rat brain--identification of conjugated 3-methoxy-4-hydrophenylglycol as the major metabolite. Biochem Pharmacol. 17:247-254.

- Upon coming to UNC School of medicine, my next initiative was to develop an approach by which NE, dopamine (DA), or both neural systems could be destroyed. This was initially accomplished with drugs and intracisternal injection of 6-hydroxydopamine (6-OHDA), a known neurotoxin on peripheral NE neurons. This strategy was subsequently successful as noted in the manuscripts to follow.

Breese GR, Traylor TD (1970) Effect of 6-OHDA on brain norepinephrine and dopamine evidence for selective degeneration of catecholamine neurons. J Pharmacol Exp Ther. 174:413-420.

Breese GR, Traylor TD (1971) Depletion of brain noradrenaline and dopamine by 6-hydroxydopamine. Br J Pharmacol. 42:88-99.

- From the development of this approach to reduce brain NE & DA individually in brain a variety of manuscripts followed to examine their involvement in drug actions and various behaviors. Examples are provided below.

Cooper BR, Howard JL, Grant LD, Smith RD, Breese GR.(1974) Alteration of avoidance and ingestive behavior after destruction of central catecholamine pathways with 6-hydroxydopamine. Pharmacol Biochem Behav. 2:639-649.

Breese GR, Cooper BR, Hollister AS.(1975) Involvement of brain monoamines in the stimulant and paradoxical inhibitory effects of methylphenidate. Psychopharmacologia. 44:5-10.

Breese GR, Smith RD, Cooper BR. (1975) Effect of various 6-hydroxydopamine treatments during development on growth and ingestive behavior. Pharmacol Biochem Behav. 3:1097-1106.

Hollister AS, Breese GR, Mueller RA. (1979) Role of monoamine neural systems in L-dihydroxy-phenylalanine-stimulated activity. J Pharmacol Exp Ther. 208:37-43.

Breese GR, Duncan GE, Napier TC, Bondy SC, Iorio LC, Mueller RA. (1987) 6-hydroxydopamine treatments enhance behavioral responses to intracerebral microinjection of D1- and D2-dopamine agonists into nucleus accumbens and striatum without changing dopamine antagonist binding. J Pharmacol Exp Ther. 240:167-176.

➢ A summary of the role of 6-OHDA reduction of DA or NE in brain in behavior and drug action was summarized in an early review.

Breese GR, Cooper BR. Smith RD, (1974) Biochemical and behavioral alterations following 6-OHDA administration into brain. in Proceedings of the 3rd Catecholamine symposium. These findings outline here were instrumental in reversing the previous thinking that NE release, not DA release, support the majority of the actions examined. To be reviewed subsequently will be the work performed with DA loss in neonate rats and the relevance of this exposure to clinical disease.

➢ At the same time this latter work was underway, myself in collaboration with others at UNC and Abbott laboratory reported that thyrotropin-releasing hormone (TRH) had actions in brain distinct from its support of thyroid function. Particularly critical was finding that TRH reverse pentobarbital sedation and influenced the action of imipramine and L-DOPA.

Breese GR, Cott JM, Cooper BR, Prange AJ Jr, Lipton MA, Plotnikoff NP. (1975) Effects of thyrotropin-releasing hormone (TRH) on the actions of pentobarbital and other centrally acting drugs. J Pharmacol Exp Ther. 193:111-122

Cott JM, Breese GR, Cooper BR, Barlow S, Prange AJ Jr. (1976) Investigations into the mechanism of reduction of ethanol sleep by thyrotropin-releasing hormone (TRH). J Pharmacol Exp Ther. 196:594-604

Kraemer GW, Mueller R, Breese GR, Prange AJ, Lewis JK, Morrison H, McKinney WT Jr. (1976) Thyrotropin releasing hormone: antagonism of pentobarbital narcosis in the monkey. Pharmacol Biochem Behav. 4:709-712

Frye GD, Luttinger D, Nemeroff CB, Vogel RA, Prange AJ Jr, Breese GR. (1981) Modification of the actions of ethanol by centrally active peptides. Peptides. 2 Suppl 1:99-106.

➢ In ensuing years, a variety of investigations utilized Fos to evaluate neural activity associated with varying behavioral and drug challenges associated with adaptation were undertaken. At this point, further discussion of the consequences of giving 6-hydroxydopamine (6-OHDA) to 2-3 day old rats in the 1970's to evaluate catecholamine levels in brain when these animals reached adulthood is reviewed. In one set of these neonate–lesioned rats, L-DOPa was given to these rats reached adulthood. This L-DOPA treatment resulted in severe self-injury in these neonate-lesioned rats—a response to L-DOPA never observed in rats lesioned with 6-OHDA as adults. Somewhat later, a published clinical reported that patients with Lesch-Nyhan (L-N) disease had DA-neurons destroyed. Because a prominent symptom in LN patients was self-injury, a conclusion from this report was that the basis of self-injury to L-DOPA in the rats lesioned as neonates was the early age at which the DA neurons were destroyed.

Breese GR, Baumeister AA, McCown TJ, Emerick SG, Frye GD, Crotty K, Mueller RA (1984): Behavioral differences between neonatal and adult 6-hydroxydopamine-treated rats to dopamine agonists: relevance to neurological symptoms in clinical syndromes with reduced brain dopamine. J Pharmacol Exp Ther 231: 343–354.

Breese GR, Knapp DJ, Criswell HE, Moy SS, Papadeas ST, Blake BL (2004): The neonate 6-hydroxydopamine lesioned rat: a model for clinical neuroscience and neurobiological principles. Brain Res Rev 48: 57–73

➢ In years to follow, a number of important findings concerning adaptation related to repeated withdrawals from chronic alcohol were pursued—a pursuit which related to the hypothesis of Ballenger and Post (1978) that seizures in alcoholics were related to a "kindling" process over time. The first study performed provided direct support for this hypothesis.

McCown TJ, Breese GR. (1990) Multiple withdrawals from chronic ethanol "kindles" inferior collicular seizure activity: evidence for kindling of seizures associated with alcoholism. Alcohol Clin Exp res.14:394-399.

➢ Subsequently, after a move to the UNC Alcohol Center, various seminal studies related to defining the basis of repeated withdrawals from chronic alcohol increasing withdrawal induced anxiety were pursued. Particularly critical was defining CRF involvement in the central amygdala (CeA)--which provided an anatomical link to the stress involvement associated with repeated alcohol withdrawals. These latter findings were subsequently accompanied by finding that cytokines could contribute to withdrawal-induced anxiety—an involvement which also involved CRF. Selected studies related to stress, CRF, and cytokines and withdrawal from alcohol are provided below:

Overstreet DH, Knapp DJ, Breese GR (2002) Accentuated decrease in social interaction in rats subjected to repeated ethanol withdrawals. Alcohol Clin Exp Res. 26:1259-1268.

Qin L, Wu X, Block ML, Yuxin L, Breese GR, Hong J, Knapp DJ, Crews FT. (2007) Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration GLIA 55: 453-462

Breese GR, Knapp DJ, Overstreet DH, Navarro M, Wills TA, Angel RA. (2008) Repeated lipopolysaccharide (LPS) or cytokine treatments sensitize ethanol withdrawal-induced anxiety-like behavior. Neuropsychopharmacology. 33:867-876.

Huang MM, Overstreet DH, Knapp DJ, Angel R, Wills TA, Navarro M, Rivier J, Vale W, Breese GR. (2010) Corticotropin-releasing factor (CRF) sensitization of ethanol withdrawal-induced anxiety-like behavior is brain site specific and mediated by CRF-1 receptors: relation to stress-induced sensitization. J Pharmacol Exp Ther. 332:298-307.

Whitman BA, Knapp DJ, Werner DF, Crews FT, Breese GR (2013) The cytokine-mRNA increase induced by withdrawal from chronic ethanol in the sterile environment of brain is mediated by CRF and HMGB1 release. Alcohol Clin Exp Res. 37:2086-2997

Ming Z, Criswell, HE, Breese GR. (2013) Evidence for TNFα action on excitatory and inhibitory neuro-transmission in the central amygdala—a brain site influenced by stress. Brain Behavior Immunity. 33:102-111.

C. SELECTED-PEER-REVIEWED PUBLICATIONS.

Breese GR,Sinha R, Heilig M. Chronic alcohol neuroadaptation and stress contribute to susceptibility for alcohol craving and relapse. Pharmacol Therap. 129: 149-171, 2011.

Knapp, DJ, Overstreet DA, Huang M, Wills TA, Whitman, BA, Angel, RA, Sinnett SE, Breese GR. Effects of a stressor and corticotropin releasing factor on ethanol deprivation-induced ethanol intake and anxiety-like behavior in alcohol-preferring P Rats. Psychopharmacology 218:179-189, 2011 PMID 21643675

Knapp, DJ, Whitman, BA, Wills TA, Angel, RA, Overstreet DA, Criswell HE, Ming Z, Breese GR Cytokine involvement in stress may depend on corticotrophin releasing factor to sensitize ethanol withdrawal anxiety. Brain, Behavior, Immunity. 25: S146-S154, 2011

Kelm MK, Criswell HE, Breese GR. Ethanol-enhnaced GABA release: a focus of G protein-coupled receptors. Brain Res Rev. 65:113-123, 2011.

Kelm MK, Weinberg R, Criswell HE, Breese GR. The PLC/IP3R/PKC Pathway is required for ethanol enhanced GABA Release. Neuropharmacology. 58:1179-86, 2010.

Wills TA, Knapp DJ, Overstreet DH, Breese GR. Interactions of stress and CRF in ethanol-withdrawal induced anxiety in adolescent and adult rats. Alcohol Clin Exp Res. 34:1603-1612, 2010.