available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Genetic variance contributes to dopamine and opioid receptor antagonist-induced inhibition of intralipid (fat) intake in inbred and outbred mouse strains

Cheryl T. Dym[a,c], *Veronica S. Bae*[a], *Tamar Kraft*[a], *Yakov Yakubov*[a], *Amanda Winn*[a], *Anthony Sclafani*[b,c,d], *Richard J. Bodnar*[a,c,*]

[a]*Department of Psychology, Queens College, The Graduate Center, City University of New York, Flushing, NY 11367, USA*
[b]*Department of Psychology, Brooklyn College, The Graduate Center, City University of New York, Flushing, NY 11367, USA*
[c]*Neuropsychology, Brain and Behavior, Doctoral Sub-Programs, The Graduate Center, City University of New York, Flushing, NY 11367, USA*
[d]*Cognition, Brain and Behavior, Doctoral Sub-Programs, The Graduate Center, City University of New York, Flushing, NY 11367, USA*

ARTICLE INFO

Article history:
Accepted 8 December 2009
Available online 22 December 2009

Keywords:
Dopamine D1 receptor
Opioid receptors
SCH23390
Naltrexone
Fat Intake

ABSTRACT

Preference for and intake of solid and emulsified fat (intralipid) solutions vary across different mouse strains. Fat intake in rodents is inhibited by dopamine and opioid receptor antagonists, but any variation in these responses as a function of genetic background is unknown. Therefore, the present study compared the ability of dopamine D1-like (SCH23390) and general opioid (naltrexone) receptor antagonism to alter intake of fat emulsions (intralipid) in mice. Two-hour intakes of 5% intralipid were measured (5–120 min) in seven inbred (*BALB/c*, *C57BL/6*, *C57BL/10*, *DBA/2*, *SJL*, *SWR*, *129P3*) and one outbred (CD-1) mouse strains following treatment with vehicle, SCH23390 (50–1600 nmol/kg, ip) and naltrexone (0.001–5 mg/kg, sc). SCH23390 significantly, dose-dependently and differentially reduced intralipid intake at all five (*DBA/2*, *SWR*, CD-1), four (*SJL*, *C57BL/6*), three (*129P3*) and one (*C57BL/10*) of the doses tested, but failed to affect intralipid intake in *BALB/c* mice. Naltrexone significantly, dose-dependently and differentially reduced intralipid intake at all four (*DBA/2*), three (*SWR*, *SJL*), two (CD-1, *C57BL/10*) and one (*C57BL/6*, *129P3*) of the doses tested, and also failed to affect intralipid intake in *BALB/cJ* mice. SCH23390 and naltrexone were respectively 13.3-fold and 9.3-fold more potent in inhibiting intralipid intake in the most sensitive (*DBA/2*) relative to the least sensitive (*BALB/c*) mouse strains. A strong positive relationship ($r=0.91$) was observed for the abilities of SCH23390 and naltrexone to inhibit intralipid intake across strains. These findings indicate that dopaminergic and opioid signaling mechanisms differentially control intralipid intake across different mouse strains, suggesting important genetic and pharmacological interactions in the short-term control of rewarding and post-ingestive consequences of fat intake.

* *Corresponding author*. Department of Psychology, Queens College, City University of New York, Flushing, NY 11367, USA. Fax: +1 718 997 3257.
E-mail address: richard.bodnar@qc.cuny.edu (R.J. Bodnar).

0006-8993/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2009.12.021

1. Introduction

Genetic variance has been observed for many aspects of ingestive behavior in inbred mouse strains (see review: Reed et al., 1997), including the intake of dietary fat (see review: West and York, 1998). Thus, mouse strain differences have been observed in the intake of complete high-fat diets, fat selection in nutrient self-selection paradigms, or intake of fat emulsions (e.g., Alexander et al., 2006; Bachmanov et al., 2001; Glendinning et al., 2008; Sclafani, 2007; Sclafani and Glendinning, 2005; Smith et al., 2000, 2001; Smith-Richards et al., 1999, 2002). Specifically, *AKR* inbred mice consumed moderate amounts of a high-fat diet that promoted weight gain and obesity, whereas carbohydrate-preferring *SWR* mice consumed large amounts of the same diet that was not accompanied by weight gain (Smith et al., 2000, 2001). The different patterns of fat intake and compensatory weight changes observed in *AKR* and *SWR* strains persisted across different types of fat sources and whether the high- and low-fat diets were isocaloric (Smith-Richards et al., 1999). Indeed, whereas fat consumption and accumulation of ependymal fat were correlated in *AKR* and *C57BL/6* mice, fat consumption in *SWR* and *CAST/Ei* strains was inversely correlated with accumulation of ependymal fat (Smith et al., 2000, 2001). Diet-sensitive *AKR* and *DBA/2* strains consumed greater amounts of fat, displayed more adiposity, and displayed elevated levels of leptin and insulin, whereas *C57BL/6* mice showed an equal preference between protein and fat, and displayed normal insulin and leptin levels (Alexander et al., 2006). In contrast, obesity-resistant *SWR* and *A* mice that consumed more fat than carbohydrate displayed lower insulin levels, increased capacity of skeletal muscle to metabolize fat, enhanced paraventricular galanin, and/or reduced arcuate NPY levels (Leibowitz et al., 2005). Finally, chromosomal mapping analyses revealed a series of genetic loci (mob 1–4), located on chromosomes 9 and 15, that appeared to explain some of these genetic variations for fat and obesity (e.g., Bachmanov et al., 2001; Smith-Richards et al., 2002).

Our laboratory has also investigated genetic variance in fat preference and intake (Lewis et al., 2007) using a liquid fat source in the form of intralipid, a stable soybean oil emulsion, which is highly attractive and avidly consumed by rodents (e.g., Higgs and Cooper, 1998). Eleven inbred and one outbred mouse strains, including some (*A, AKR, C57BL/6, DBA/2, SWR*) described in the earlier studies, were given 24-h two-bottle tests with intralipid vs. water over a wide range of lipid concentrations (0.0001–5%). We found significant increases in intralipid intake in *BALB/c* mice at the seven highest concentrations, in *SWR*, *AKR*, *C57BL/6* and *DBA/2* mice at the four highest concentrations, in CD-1, *C57BL/10* and *SJL* mice at the three highest concentrations, and in *A*, *C3H/He*, *CBA* and *129P3* mice at the two highest concentrations, thereby demonstrating a wide degree of genetic variance in the detection sensitivity to consume a fat solution.

Among the multiple pharmacological substrates governing intake of fat in outbred rats are the opioid and dopaminergic receptor systems. Fat intake is significantly reduced in rats by general and selective mu and kappa opioid receptor antagonists (Glass et al., 2000; Higgs and Cooper, 1998; Islam and Bodnar, 1990; Jarosz et al., 2006; Marks-Kaufman et al., 1985; Naleid et al., 2007; Sahr et al., 2008). Chronic mu, mu-1, delta-1, and delta-2 opioid antagonists also significantly decreased weight and intake of a fat source in rats during development of dietary obesity (Cole et al., 1995). Correspondingly, administration of the mu-selective opioid agonist, DAMGO into the nucleus accumbens stimulates high-fat intake in rats (Zhang et al., 1998). Fat intake is also significantly reduced by systemic treatment with dopamine antagonists in rats as well (Baker et al., 2001; Davis et al., 2006; Rao et al., 2008; Weatherford et al., 1988; 1990).

The aforementioned data therefore indicate that control of a critical macronutrient, fat, is influenced by dopamine and opioid receptor systems and by genetic factors. Whether genetic variance plays a role in the opioid and dopaminergic modulation of fat intake is unknown, and is the purpose of this study. Thus, the present study examined whether genetic variance exists in the dose-dependent ability of general opioid (naltrexone) or dopamine D1-like receptor (SCH23390) antagonism to alter intralipid intake in a short-term (2 h) test developed previously for the examination of genetic variance in the pharmacology of sucrose intake (Dym et al., 2007, 2009). A 5% intralipid concentration was selected because it generated substantial intakes in our prior 24-h study (Lewis et al., 2007). We focused on the D1-like antagonist, SCH23390, rather than the D2-like antagonist, raclopride, since the latter drug was relatively ineffective in reducing sucrose intake and/or displaying genetic variance in sucrose intake (Dym et al., 2009). As in our previous studies (Dym et al., 2007, 2009), mouse strains were initially assessed for their ability to display short-term (2 h) intralipid intake at or above a criterion baseline criterion intake (>1 ml) to allow for the reliable observation of short-acting antagonist-induced reductions. Seven inbred (*BALB/c*, *C57BL/6*, *C57BL/10*, *DBA/2*, *SJL*, *SWR*, *129P3*) and one outbred (CD-1) mouse strains met this criterion of short-term intralipid intake, and were used in the pharmacological analyses, while other strains showing genetic variance in fat intake (*AKR, A*) failed to meet this criterion, and were therefore not included.

2. Results

2.1. Strain differences in intralipid intake following vehicle baseline injections

Evaluation of intralipid intake following vehicle baseline injections revealed significant differences among strains ($F(7,70)=7.45$, $P<0.0001$) and for the interaction between strains and test times ($F(35,350)=5.68$, $P<0.0001$). The rank-order of the cumulative 2-h baseline vehicle intralipid intake among the eight strains was: *BALB/c* (2.2 ml), CD-1 (2.1 ml), *SWR* (2.0 ml), *DBA/2* (1.7 ml), *C57BL/10* (1.6 ml), *SJL* (1.4 ml), *129P3* (1.4 ml) and *C57BL/6* (1.4 ml). To account for these baseline differences in intralipid intake, the drug effects were evaluated both on absolute intralipid intakes and on intakes as a percent of baseline levels.

2.2. Strain differences in SCH23390-induced inhibition of intralipid intake

Overall significant differences in intralipid intake following SCH23390 were observed among the eight mouse strains (*F*