Diet-Induced Obesity Dramatically Reduces the Efficacy of a 2009 Pandemic H1N1 Vaccine in a Mouse Model

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(See the article by O’Brien et al, on pages 252–61, and the editorial commentary by Beck on pages 172–3.)

Background. Obesity, a risk factor for increased severity of diverse diseases, is believed to have negative impact on vaccine efficacy. Recently, mortality has emerged as an outcome of pandemic influenza A virus subtype H1N1, necessitating development of effective vaccine strategies. Here we investigated effects of diet-induced obesity on vaccine-induced immune responses and protective efficacy against pandemic H1N1 influenza virus.

Methods. Diet-induced obese and lean C57BL/6J mice were immunized with commercial monovalent 2009 H1N1 vaccine, and antigen-specific antibody responses and neutralizing activities were observed. Following vaccination, mice were challenged with homologous H1N1 virus, and pathogenesis and mortality were examined.

Results. Vaccine-induced H1N1-specific antibody responses and neutralizing activities were markedly reduced in obese mice. Consistent with antibody responses, lung virus titers were significantly higher in obese mice than in lean controls after challenge. In addition, obese group showed greatly increased expression of proinflammatory cytokines and chemokines in lung tissue, severe lung inflammation, and higher eventual mortality rate (100%) compared with that among lean control mice (14%).

Conclusions. Our results show that prophylactic immune responses and protectiveness induced by 2009 H1N1 vaccine could be extremely compromised in diet-induced obesity. These results suggest that novel vaccination strategies for high-risk groups, including the obese population, are required.

Influenza is a respiratory illness caused by the influenza virus [1], which is spread through airborne transmission, is highly contagious, and is responsible for a great deal of morbidity and mortality worldwide [1, 2]. In the last century alone, we have observed 3 major influenza pandemics: the 1918 Spanish flu, the 1957 Asian flu, and the 1968 Hong Kong flu. Among them, the 1918 pandemic was the most significant, causing an estimated 30–50 million deaths worldwide [2, 3]. In 2009, a new influenza A virus subtype H1N1 emerged in the United States, and the World Health Organization (WHO) declared it the first influenza pandemic of the 21st century [4].

Obesity has become a worldwide epidemic [5]. The WHO has predicted that given the current trends, by the year 2015, 2.3 billion adults will be overweight (body mass index [BMI] ≥25), and 700 million will be clinically obese (BMI ≥30) [6]. Numerous health problems and chronic diseases have been related to obesity (eg, type 2 diabetes) and the hormonal and metabolic changes that are related to an increase in adipose tissue mass [7, 8]. Obesity is a risk factor for infection [9, 10], and it ranks as the most frequently identified underlying condition in fatal cases of 2009 pandemic H1N1 virus (2009 H1N1) infection worldwide [11, 12]. Moreover, the US Centers for Disease Control and Prevention has suggested that obese individuals are at a greater risk of morbidity and mortality from 2009 H1N1 [13]. Recent studies have also indicated that influenza virus–infected obese animals show increased mortality and decreased immune
immune responses [14–16]. However, although obesity has been associated with an increased severity of influenza symptoms, the effects of obesity on influenza vaccine efficacy have not yet been studied to our knowledge in humans or in an animal model.

Inactivated influenza virus is a major component of conventional vaccines for the prevention of human influenza, and monovalent H1N1 vaccines have been widely used to control pandemic H1N1 [17]. Observational studies have suggested that the available vaccines for 2009 H1N1 can induce antigen-specific immune responses and reduce the mortality risk in virus-infected humans [18]. However, the greater part of vaccination strategies have been developed for ordinary people [19, 20]. Furthermore, the health of the vaccinated individual can influence the efficacy of vaccination. For example, seasonal influenza vaccine efficacy is reportedly diminished in high-risk aged populations [21], and poor immune responses to hepatitis B virus vaccine have been observed in obese hosts [22]. With regard to 2009 H1N1 influenza, however, relatively little has been done to study the differences in vaccination efficacy between healthy and vulnerable groups. In this study, we investigated the efficacy of 1 current pandemic vaccine in a high-fat diet (HFD)–induced obese murine model. In obese mice, antibody responses were dramatically reduced, and viral infection caused vigorous lung inflammation and greater mortality. To our knowledge, this is the first report showing that obesity significantly reduces the efficacy of a 2009 pandemic influenza vaccine in a mouse model.

MATERIALS AND METHODS

Virus

The influenza A (H1N1) virus (A/California/04/2009, CA/04) used for challenge was kindly provided by Dr Robert G. Webster at St. Jude Children’s Research Hospital (Memphis, TN). The virus was grown in the allantoic cavities of 10-day-old embryonated chicken eggs for 48 hours at 35°C. The virus-containing allantoic fluid was harvested and stored at −80°C until use. The yield of the H1N1 virus was determined by calculating the 50% egg infectious dose (EID50) per mL of viral stock, using the method described by Reed and Muench [23].

Animal Experiments

Four-week-old male C57BL/6J mice from the Korea Research Institute of Bioscience and Biotechnology (KRIIBB; Daejeon, Korea) were used. All mice were acclimatized to a 12-hour light/dark cycle at 22°C ± 2°C for 2 weeks with free access to food (standard chow diet; Harlan Teklad, Madison, WI) and water in a specific pathogen-free facility (KRIIBB). The mice were fed for 15 weeks with either the normal-chow diet (NCD) or a high-fat diet (HFD), and randomly divided into 4 groups: (1) nonimmunized NCD group (NCD + phosphate-buffered saline [PBS], n = 12); (2) immunized NCD group (NCD + vaccine, n = 13); (3) nonimmunized HFD group (HFD + PBS, n = 12); (4) immunized HFD group (HFD + vaccine, n = 13). The HFD was a modified Western diet containing 31.6% (weight per weight) lard (D12492; Research Diets, New Brunswick, NJ). The NCD was a regular chow diet (2018S; Harlan Teklad). On weeks 10, 12, and 14, mice were immunized intramuscularly with 1.6 μg of pandemic H1N1 split vaccine antigen (CA/07, Green Flu-S; kindly provided by Green Cross, Yong-in, South Korea) or PBS. One week after the third immunization, the mice were challenged intranasally with 10 times the 50% mouse lethal dose (10 MLD50) of wild-type CA/04 virus. Challenges were performed in biosafety level (BSL) 3 + facilities at BioLeaders Cooperation (Daejeon). Thereafter, the mice were observed for body weight changes and mortality for 14 days. Animals that showed signs of severe disease and weight loss of >25% were humanely killed. The used H1N1 antigen was based on the strain that was derived from the CA/07 (H1N1) virus and has been officially recommended by the WHO for the manufacture of vaccines during the current influenza pandemic [24]. All animal experiments were approved by the Institutional Animal Use and Care Committee of the KRIIBB and were performed in accordance with the US National Institutes of Health (NIH) guidelines for animal experiments (NIH Publication 85-23, revised 1996).

Analysis of Blood Parameters

Blood samples were collected from all groups of mice of fed state by retroorbital venous plexus puncture with heparinized capillary tubes (Becton Dickinson, Franklin Lakes, NJ) under isoflurane anesthesia before viral challenge. Plasma was collected by centrifugation, and samples were aliquotted and stored at −80°C until analysis. Plasma glucose levels were determined with an automated blood chemistry analyzer (Hitachi 7150; Tokyo, Japan). Plasma insulin levels were identified using an insulin-specific enzyme-linked immunosorbent assay (ELISA) kit (Insulin Mouse ELISA; ALPCO Diagnostics, Salem, NH), and plasma leptin levels were determined using a leptin-specific ELISA kit (DY498 Mouse Leptin; R&D Systems, MN).

Hemagglutination Inhibition Assay

The collected serum specimens were treated with a receptor-degrading enzyme (RDE; Denka Seiken, Campbell, CA), following the manufacturer’s instructions, and seroreactivity was analyzed using a hemagglutination inhibition (HI) assay performed as described elsewhere [25]. Briefly, the virus was diluted to 4 agglutinating units in PBS, and then incubated at room temperature for 30 minutes with serial 2-fold dilutions of the RDE-treated serum samples, starting with a 1:10 dilution. The hemagglutination activity of the antigen–antibody mixture was assessed by the addition of 0.5% turkey red blood cells, and the HI titers were determined.

Antibody Assays

Antibodies against the CA/04 virus were measured by ELISA. Briefly, microtiter plates (Maxisorp Nunc, Roskilde, Denmark) were coated overnight at 4°C with the split influenza vaccine (CA/07) antigen diluted in calcium-saline solution at a final
concentration of 0.5 µg/mL. The plates were blocked for 2 hours with PBS containing 5% (weight-in-volume [w/v]) skim milk. The plasma was prepared as serial 2-fold dilutions starting with a 1:400 dilution in dilution buffer (PBS containing 1% [w/v] skim milk). The dilutions were added to the plates, which were then incubated at 37°C for 2 hours, whereupon peroxidase-conjugated horse antimouse immunoglobulin G (IgG) (Cell Signaling Technology, Beverly, MA) was added. The plates were washed 4 times with 0.05% Tween 20-PBS. Color was developed using tetramethylbenzidine (BD Biosciences Pharmingen, San Diego, CA) as a substrate, and the reaction was stopped by adding 0.5 N H₂SO₄. Absorbance was read at 450 nm.

**Lung Histopathology**

On day 8 after the viral challenge, some of the infected mice (n = 5–6) were killed, and their lungs were removed, macroscopically photographed, and then fixed in 10% neutral-buffered formalin. The formalin-fixed tissues were paraffinized, sagittal sections of lung tissue (3–4 µm thick) were taken, and the sections were stained with hematoxylin and eosin (H&E). The extent of lung pathology was graded in a semiquantitative manner according to the relative degree (from lung to lung) of inflammatory cell infiltration. Briefly, sections were scored on a scale from 0 to 4 as follows: 0, no inflammation; 1, mild influx of inflammatory cells involving 1%–25% of the lung; 2, increased inflammation with 25%–50% of the total lung involved; 3, severe inflammation involving 50%–75% of the lung; and 4, almost all of the lung tissue containing inflammatory infiltrates.

**Quantitative Real-Time Polymerase Chain Reaction**

The mice were killed at days 0, 3, and 8 postchallenge, and total RNA was extracted from lungs and reverse transcribed using the iScript complementary DNA (cDNA) synthesis kit (Bio-Rad, Hercules, CA). The resulting cDNAs were subjected to real-time polymerase chain reaction (PCR) using an Exicycler 96 (Bioneer, Daejeon, South Korea) and the SYBR Green PCR master mix (TaKaRa Bio, Otsu, Shiga, Japan) along with primers specific for monocyte chemoattractant protein-1 (MCP-1) (forward 5′-CAGCAAGATGATCCCAATGAGTAG-3′, reverse 5′-TCTCTTGAGCTTGGACAAAAAC-3′), regulated on actin expression, normal T-cell expressed and secreted (RANTES) (forward 5′-GACACACTCTCGTCTGTT-3′, reverse 5′-ACAACACAGCTGCAAGATTGG-3′), tumor necrosis factor α (TNFα) (forward 5′-TTGGCCTCTCGTCATCAGTT-3′, reverse 5′-CCTCCATTGTGCGTTTGTG-3′), interleukin (IL)-1β (forward 5′-CTACAGGCTCGAGATGAAAC-3′, reverse 5′-TCCAT TGAGGTTGAGGTCTCCTG-3′), IL-6 (forward 5′-GTGACCTCTC TTGGGACTGATG-3′, reverse 5′-GGGAGTTGATCTCGTGAA GTGCT-3′), and IL-10 (forward 5′-GGGTTGCCAGGCTC TATCG-3′, reverse 5′-TCTGACCCAGGAAATTCGAGAT-3′). All data were normalized with respect to the expression level of the ribosomal 18S cDNA (forward 5′-GACACGGACAGGATTGACAGATTG-3′, reverse 5′-GTTAGCATGCCAGGTCTC GTTGTT-3′)

**Statistical Analyses**

Numerical data are presented as means ± standard error of measurement. Comparisons between groups were performed using a 2-tailed Student t test or 1-way analysis of variance. The threshold of significance was set at P < .05.

**RESULTS**

**Obesity Is Induced in C57BL/6J Mice Fed a High-Fat Diet**

Diet-induced obesity (DIO) is a physiologically relevant animal model of human obesity [26]. To investigate the effects of obesity on vaccine efficacy, we established an obese mouse model by feeding mice ad libitum with a high-fat diet for 15 weeks. As shown in Figure 1A, body weight was dramatically increased in HFD-fed mice compared with lean mice. For further quantitative analysis of DIO, we examined the levels of blood glucose, insulin, and leptin. All of these biochemical indicators were significantly elevated in the HFD-fed group compared with controls (Figure 1B-D). All parameters showed no differences between the nonimmunized and immunized groups (Figure 1). These results confirmed that feeding a HFD for 15 weeks elicited both DIO and obesity-related insulin resistance phenotypes in C57BL/6J mice, validating that this experimental system could be a suitable model for human DIO.

**The Protectiveiveness of the 2009 Pandemic H1N1 Vaccine Is Reduced in Obese Mice**

To identify the effects of DIO on the protective efficacy of pandemic H1N1 influenza vaccine, we challenged mice with a wild-type CA/04 virus a week after the third vaccination. As shown in Figure 2A, the proportion of survivors in the immunized lean group was relatively high (86%) at 14 days after virus challenge. In contrast, none of the immunized obese mice survived beyond 12 days after the virus challenge, suggesting that obesity blocked the induction of the necessary protective immune responses. In terms of body weight, the immunized obese mice showed a continuous decline, whereas the immunized lean group lost weight for 8 days and then recovered to their healthy body weight thereafter (Figure 2B). Meanwhile, in the nonimmunized lean or obese group, none of the mice were alive at 8 or 9 days after the virus challenge, and body weight constantly decreased, although the mice lived (Figure 2).

The pandemic H1N1 influenza virus primarily infects cells in the respiratory system, where it induces vigorous inflammation and damage in the lung tissues, eventually leading to fatality in a murine model. To verify if the higher virus-induced mortality observed in the obese group was accompanied by severe pathogenesis in their lung tissues, we investigated H&E-stained lung sections taken on day 8 postinfection. As shown in Figure 3A, the lung pathology score was significantly higher in immunized obese mice than in
the immunized lean control mice. Moreover, prominent consolidation was observed in the lungs of immunized obese mice, whereas this was rarely seen in immunized control mice (Figure 3B). Upon microscopic examination, obese mice exhibited signs of suppurative bronchopneumonia, including denuding bronchiolitis, apoptosis of airway epithelial cells, accumulation of apoptotic debris within the parenchyma, alveolar hemorrhage, and severe peribronchovascular cuffing in the lungs; in contrast, these symptoms were mild or absent in the lean mice (Figure 3B). Consistent with the higher mortality and more severe inflammation displayed in obese mice, the viral titers of the lungs were significantly higher in vaccinated obese mice (geometric mean titer [GMT] 3.5 ± 0.0 \log_{10} EID_{50}/mL) compared with vaccinated lean mice (GMT 2.4 ± 0.5 \log_{10} EID_{50}/mL) after CA/04 viral challenge. Collectively, these results indicate that DIO conspicuously reduces the protective efficacy of a pandemic 2009 H1N1 vaccine in a mouse model.

A Significant Decrease in Humoral Immunity to the 2009 Pandemic H1N1 Vaccine Is Observed in Obese Mice

As neutralizing antibodies to the influenza virus play critical roles in protection, and split vaccines tend to induce T-helper 2–biased antibody responses [17, 18], we investigated the vaccine-induced antibody responses in the lean and obese groups. Mice were immunized 3 times with an inactivated split CA/07 vaccine (1.6 g HA protein), and the level of antibody production was checked 1 week after the final immunization. As shown in Figure 4A, the amount of HA-specific total IgG was significantly diminished in serial double dilution of serum between 1:400 and 1:25 \times 10^6 of the HFD-fed group. To check the neutralization activity of the generated antibodies, we then performed an HI assay. Both the GMT of HI antibodies and the number of HI-positive serum samples were markedly decreased in immunized obese mice compared with immunized NCD-fed mice (Figure 4B and 4C). These results suggest that the induction of Ag-specific antibody responses is
impaired in DIO mice, implying that the obese group may be more vulnerable to pandemic H1N1 infection even after vaccination.

The 2009 Pandemic H1N1 Virus Induces Exorbitant Inflammatory Immune Responses in Vaccinated Obese Mice

The protectiveness of the pandemic 2009 H1N1 vaccine was impaired in the obese mice, which showed higher viral titers and severe tissue damage following viral challenge. As inflammatory responses are a key part of the innate immune response to influenza virus infection [27], and uncontrolled viral replication in obese mice may be accompanied by prolonged overactivation of innate immunity, which causes tissue damage, we examined the expression level of immune-modulating cytokines and chemokines in virus-challenged immunized obese and control mice. Before challenge, the basal messenger RNA (mRNA) levels of 2 chemokines, MCP-1 and RANTES, were lower in immunized obese mice than in immunized controls. However, the mRNA levels of MCP-1 and RANTES were markedly increased

Figure 2. Mortality and body weight changes in lean and obese mice after pandemic 2009 H1N1 virus challenge. Mice from each group (n = 12–13 per group) were challenged with H1N1 virus, and the survival rates (A) and body weight changes (B) were determined daily during 14 days after challenge. Abbreviations: PBS, phosphate-buffered saline; HFD, high-fat diet.

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at 3 and 8 days after viral challenge in immunized obese mice compared with each corresponding day of immunized healthy weight mice (Figure 5A and 5B). In addition to increased chemokine expression, the levels of 3 proinflammatory cytokines (TNF-α, IL-1β, and IL-6) were dramatically elevated in immunized obese group on days 3 and 8 postchallenge compared with according day of immunized lean controls (Figure 5C-E), which agrees well with the increased lung pathology in this group. Interestingly, the expression of IL-10, an antiinflammatory cytokine, was also significantly increased in the immunized obese group on day 8 postchallenge (Figure 5F), implying that the increased inflammatory response had stimulated an enhanced negative feedback. These data show that vigorous inflammatory responses were induced upon viral infection in the obese group, and these excessive immune responses were not attenuated as much as that of the control group, even though vaccinated.

DISCUSSION

Pandemic strains of influenza have widespread implications for the global economy and worldwide health [19, 20]. Several studies have reported that obesity is associated with an increased death rate among those infected with 2009 H1N1 [11–13], and it has been suggested that obese patients should be prioritized for pandemic influenza vaccine administration and treated promptly upon infection [12, 13]. However, we are not aware of any previous study examining whether obesity influences 2009 H1N1 vaccine efficacy in humans or in an animal model of the disease. Here, we report for the first time to our knowledge that the efficacy of a H1N1 influenza vaccine is significantly diminished in C57BL/6J mice subjected to DIO.

The increased prevalence of obesity has become a worldwide problem [28]; at present, only about a third of adults are considered to be of “healthy” weight in the United States, and similar trends are being observed in many other countries [29, 30]. Obesity is associated with numerous conditions, with insulin resistance being among the most serious [28]. In this study, we found that feeding mice with an HFD for 15 weeks led to DIO as well as evidence of insulin resistance, as reflected in the animals’ blood glucose, insulin, and leptin levels. Obesity and/or insulin resistance results in ineffective immune responses to influenza virus infection and are underlying risk factors for fatal complications of pandemic 2009 H1N1 infection [11, 13]. Moreover, the chronic elevation of leptin in cases of DIO appears to cause a state of leptin resistance [31] that may be disadvantageous to immune responses [32]. Consistent with this, poor antibody responses to tetanus or hepatitis B plasma vaccines have been reported in obese human cases [22, 33]. In the present study, we immunized DIO mice with a monovalent CA/07 vaccine that is currently used to protect humans against pandemic H1N1 influenza [24] and examined the subsequent humoral immune responses. Although normal antigen-specific antibody responses were induced by vaccination of control lean mice, obese mice showed marked suppression of neutralizing activity and antibody production.

During an influenza virus infection, cytokines and chemokines are produced in a coordinated and specific cascade [27], with antiviral and proinflammatory cytokines induced first, followed by IL-6 expression, and finally the induction of chemokines such as MCP-1 and RANTES [27, 34]. These chemokines accelerate the recruitment and activation of other innate and adaptive immune
cells, thereby mediating a more effective immune response to influenza virus infection [35]. Under healthy conditions, these antiviral immune responses are strong enough to control influenza virus replication [36]. Under impaired immune conditions, however, the viral replication is not controlled appropriately, and an excessive and persistent inflammatory response ensues, eventually causing structural damage to the airway [36]. The prophylactic vaccines against the influenza virus are able to induce antigen-specific immune responses and attenuate this uncontrolled immune response by preventing viral infection and/or controlling viral replication [18, 22, 33]. In the present study, obese mice showed greatly increased expression of proinflammatory cytokines (TNFα, IL-1β, IL-6, and IL-10) in their lungs postchallenge compared with corresponding day of control mice. Along with the notable elevation of these cytokines, the lung expression of IL-10, an anti-inflammatory cytokine responsible for maintaining homeostasis by countering the proinflammatory cytokines [37], was also significantly increased in obese mice after 2009 H1N1 challenge, as was the expression of the chemokines MCP-1, and RANTES compared with corresponding day of controls.

In terms of pathology, vaccinated obese mice showed severe airway destruction, with greatly increased inflammatory cell infiltration to the pulmonary parenchyma and higher viral titers in lungs compared with immunized lean control mice. Moreover, the vaccinated obese mice failed to show the rebound of body weight evidenced by control mice by day 8 postchallenge, and none of the vaccinated obese mice survived beyond 12 days after CA/04 virus challenge, whereas the lean mice showed only 14% mortality at 14 days after virus challenge. These results collectively indicate that 2009 H1N1 vaccine-induced precautionary immune responses and protection against viral infection were reduced in the DIO mice.

Impaired immune functions have been observed in many obese animal models as well as the human population. It was reported that dendritic cells (DCs) from the mice fed with a high-fat diet exhibited impaired functions, leading to decreased anti–hepatitis B surface and core antigen-specific immune responses after vaccination [38]. Although DC functions were not directly examined in our experiment, it is plausible that malfunction of DCs in obese mice resulted in disrupted vaccine efficacy. In addition to DCs, it was also shown that obese mice have decreased T-cell population, as well as reduced number of natural killer cells, which may explain vulnerability of obese animals to influenza infection [39–43]. In particular, it was found that memory T-cell responses are significantly abrogated after influenza infection in DIO mice [44], supporting our observation. Thus, further study to understand the detailed mechanism of poor immune responses to influenza vaccine in the obese population may be required.

**Figure 5.** Expression of chemokines and cytokines in lungs from vaccinated lean and DIO mice after 2009 H1N1 virus challenge. The mRNA expression levels of chemokines (MCP-1 and RANTES) and cytokines (TNFα, IL-1β, IL-6, and IL-10) were measured from lung tissues. The data were normalized with respect to the 18S mRNA values, and then to the NCD + vaccine value at day 0 postvirus infection (n = 12–13 per group). Grouped quantitative data are presented as means ± standard error of measurement. Student t test, *P < .05 compared with the NCD + vaccine group on the corresponding day. Abbreviations: DIO, diet-induced obese; mRNA, messenger RNA; MCP-1, monocyte chemoattractant protein-1; RANTES, regulated on activation, normal T-cell expressed and secreted; TNFα, tumor necrosis factor α; IL, interleukin; NCD, normal-chow diet; HFD, high-fat diet.
In sum, we herein showed that DIO mice vaccinated and then challenged with pandemic 2009 H1N1 virus showed impaired immune responses, uncontrolled inflammation, and increased mortality. These results may have significant public health implications in that they suggest that conventional vaccine strategies may be less effective in the increasing obese population, and indicate that we may need to develop more efficacious and individually adjusted strategies for flu vaccination of this high-risk group.

Notes

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References