Exogenous IGF-1 improves tau pathology and neuronal pyroptosis in high-fat diet mice with cognitive dysfunction

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Abstract
Insulin-like growth factor-I (IGF-1) improves obesity-induced cognitive dysfunction, but its mechanism is not fully clarified. The aim of the study was to reveal whether IGF-1 treated cognitive dysfunction by improving tau pathology and neuronal pyroptosis in high-fat diet mice. During in vitro experiment, C57BL/6J mice were fed with high-fat diet, and were treated with PEG-IGF-1, IGF-1 receptor blocker AXL1717, HO-1 blocker Znpp IX or their combinations. Cognitive function was evaluated using Morris water maze. Expression of Nrf2, HO-1, p-tau, NLRP3, caspase-1 and IL-1β in hippocampus was determined using western blotting. Pyroptosis rate in hippocampus was measured using flow cytometry. During in vivo experiment, HN-h cells were treated with palmitic acid, pyroptosis blocker nonecrosulfonamide or their combinations. The expression of the proteins and rate of pyroptosis were also measured using western blotting and flow cytometry. During in vitro experiment, high-fat diet mice showed cognitive dysfunction, significant hyperphosphorylation of tau protein and neuronal pyroptosis in hippocampus compared with the sham mice. After exogenous IGF-1 treatment, these abnormalities were reversed and Nrf2/HO-1 signaling pathway was activated. Inhibition of the signaling pathway using AXL1717 or Znpp IX re-deteriorated cognitive function, tau pathology and neuronal pyroptosis in hippocampus. During in vivo experiment, inhibition of pyroptosis using nonecrosulfonamide improved tau pathology in palmitic acid-treated HN-h cells. Exogenous IGF-1 improved tau pathology induced by high-fat diet through inhibition of neuronal pyroptosis and activation of Nrf2/HO-1 signaling pathway.

Keywords Cognitive dysfunction · Insulin-like growth factor I · Obesity · Pyroptosis · Tau proteins

Introduction
It is well known that cognitive function includes ability of many aspects, such as memory, language, understanding, judgment and so on. Functionally decline of one or several aspects mentioned above is defined as cognitive dysfunction. So, cognitive dysfunction is a group of symptom, and is most commonly manifested in neurological diseases, such as Alzheimer’s disease and vascular dementia. Not only that, an increasing number of evidence has proved that obesity also causes cognitive dysfunction (Wang et al. 2017; Zhang et al. 2020a, b). Due to the huge number of obese population, such type of cognitive dysfunction has received more and more attention all around the world (Hansen et al. 2020; Zhang et al. 2020a, b). However, its pathogenesis and therapeutic strategy are still not fully elaborated.

The pathogenesis of cognitive dysfunction is complicated and is associated with a variety of factors. Of them, tau protein is a matter of great concern to academia. Such protein is originally one type of microtubular protein. Hyperphosphorylation causes its physiological dysfunction, and lets it accumulate and form neurofibrillary tangle. The latter has neurotoxic effect and is considered to be an important pathological change in Alzheimer’s disease (Abu-Rumeileh...
Interestingly, tau pathology is also discovered in animal models of high-fat diet (HFD) or metabolic disorders (Puigoriol-Illamola et al. 2020; Zhou et al. 2020). These findings give us a hint that tau pathology might also contribute to the development of obesity-induced cognitive dysfunction.

There are many factors which are associated with the hyperphosphorylation of tau protein. For example, one study suggests that NLRP3 inflammasome activation drives tau pathology in Alzheimer’s disease (Ising et al. 2019). Another study reports that IL-1β and IL-18 induced by inflammasome signaling increased hyperphosphorylation of tau protein in the same model (Li et al. 2020). Because NLRP3 inflammasome is one of the main upstream signaling of pyroptosis, neuronal pyroptosis might be related to tau pathology in Alzheimer’s disease. Meanwhile, previous studies reveal that obesity and HFD not only cause tau pathology, but also elevate the expression of pyroptosis-related proteins (i.e. NLRP3 and IL-1β) and rate of neuronal pyroptosis in nervous system (Xu et al. 2019a, b; Guo et al. 2020; Wang et al. 2021). Therefore, we speculated that neuronal pyroptosis might also play an important role in hyperphosphorylation of tau protein in obese model.

At present, many substances have been provided against neuronal pyroptosis. Insulin-like growth factor-1 (IGF-1) is a widely distributed polypeptide in human body, and plays a protective role in cognitive dysfunction (Farias Quipildor et al. 2019; Yang et al. 2019). Our previous study reveals that exogenous IGF-1 inhibits neuroinflammation induced by HFD in mice, and up-regulation of endogenous IGF-1 alleviates NLRP3/caspase-1 signaling and improves cognitive function in the same model (Wang et al. 2020; Wang et al. 2021). In addition, Nrf2/HO-1 signaling is activated by IGF-1 in brain tissue (Kim et al. 2012; Niu et al. 2020), and HO-1 is an important regulator for pyroptosis (Al Mamun et al. 2020; Ryter 2021). So, we speculated that IGF-1 might alleviate neuronal pyroptosis partly through activation of Nrf2/HO-1 signaling in obese model.

Taken together, the present study treated HFD mice with exogenous IGF-1, and tried to reveal whether IGF-1 improved tau pathology and neuronal pyroptosis through activation of Nrf2/HO-1 signaling pathway. Then, the study adopted a palmitic acid (PA)—treated human neurons-hippocampal (HN-h) cell line, and tried to explore whether inhibition of neuronal pyroptosis contributed to the improvement of tau pathology.

Materials and methods

The study was approved by the ethics committees of Tianjin Anding Hospital and Tianjin Medical University General Hospital.

Grouping, modeling and intervention in mice

Flow chart of the in vivo experiment was shown in Fig. 1a. Fifty male C57BL/6 J mice (four weeks old) were purchased from laboratory animal center of the academy of military medical sciences (Beijing, China). The mice were supplied with normal, balanced and adequate diets, and were kept at room temperature with a light/dark cycle (12 h/12 h) for seven days before the experiments.
Then, the animals were divided into five groups according to randomization principle: sham group, HFD group, IGF-1 treatment group (IGF group), IGF-1 receptor inhibition group (IGFR_I group) and HO-1 inhibition group (HO_I group). Each group contained 10 mice.

After grouping, the mice in the HFD, IGF, IGFR_I and HO_I groups were treated with HFD (D12492, Research Diets) for 12 weeks. Its energy composition was fats (60%), carbohydrates (20%) and proteins (20%). During the same period (12 weeks), the sham mice were fed with normal diet (D12450B, Research Diets). Their body weights were measured weekly, and their fasting blood glucose and lipids were determined at the end of the modeling process. Briefly, fasting blood was obtained from caudal vein of each mouse, and an automatic biochemical analyzer (Hitachi 7170, Hitachi, Japan) was adopted to measure these biochemical markers.

In the next step, the mice in the IGF, IGFR_I and HO_I groups were treated with polyethylene glycol—IGF-1 (PEG-IGF-1) by intraperitoneal injection for four weeks (1 mg/kg, twice a week) (Sama et al. 2018). Meanwhile, the mice in the IGFR_I and HO_I groups were separately treated with IGF-1 receptor blocker AXL1717 and HO-1 blocker Znpp IX by intraperitoneal injection for four weeks (AXL1717: 20 mg/kg, once a day; Znpp IX: 20 mg/kg, twice a week) (Yao et al. 2018). Necrosulfonamide (4 μmol/l) was added with specific neuronal medium (NM, Cat. #1521) to form the concentration of 800 μmol/l. Necrosulfonamide was dissolved and diluted using DMSO (0.1%) to produce the concentration of 4 μmol/l.

**Cognitive function test in mice**

After modeling and intervention, cognitive function was evaluated using Morris water maze. Detailed steps were described in a previous literature (Barnhart et al. 2015). During a day of adaptive training, the mice were arranged to familiarize themselves with an experimental pool with a platform in it. Subsequently, navigation test was conducted on day 2 to day 5. The mice were randomly placed any quadrant in the pool, and their trajectories were recorded using a video-tracking system (TSE Systems, Bad Homburg, Germany). “Escape latency” was defined as the length of time a mouse took from being placed in the pool to climbing the platform. If the “escape latency” of one mouse was longer than 60 s, its “escape latency” was recorded as 60 s. This mouse was also guided to the platform and placed on it for another 30 s. After the navigation test, the platform was removed in order to perform spatial probe test on Day 6. Each mouse was placed in the pool again, and let it swim in the pool for 120 s. The length of time each mouse spent in the target quadrant (i.e. “Time in target quadrant”) and the number of times it went through the platform area (i.e. “Times crossing the platform area”) were recorded. The “target quadrant” was defined as the quadrant where the platform was originally located.

**Specimen collection and preparation in mice**

After the cognitive evaluation, the mice were humanely euthanized under anesthesia. Cerebrospinal fluid specimen was obtained from cisterna magna using a glass capillary tube (Liu and Duff 2008). Hippocampus tissue was collected and cleaned using double distilled water. The fresh tissue was cut as small as possible and digested with trypsin (0.2%) for about 30 min until the tissue was dispersed. The tissue suspension was filtered through a 100 mesh nylon filter. The obtained cell suspension was centrifugated at 1000 rpm for 5 min, and was mixed with phosphate buffer saline to form a hippocampus neuron suspension for further experiments.

**Tau protein in cerebrospinal fluids**

Cerebrospinal fluid levels of p-tau (Ser 181) and p-tau (Thr 205) were determined using a Singulex Erenna immunoassay.
platform (USA) (Hastings et al. 2017). HT7 was adopted as capture antibody. AT270 and AT8 which separately recognized p-tau (Ser 181) and p-tau (Thr 205) served as detection antibodies. In the process, the measurement was performed in the presence of HalTr Protease and Phosphatase Inhibitor Cocktail (Thermo Fisher). Briefly, in 96-well plate, each well contained 10 mg capture beads, 50 μl Singulex assay buffer and 50 μl cerebrospinal fluids (or standard peptide), which was diluted in PBS-T (0.2% Tween 20 in PBS). The plate was incubated at 25°C for 4 h, and was washed using a Biotek 405™ TS microplate washer. Then, 20 μl AT270 or AT8 antibody (50 ng/ml) was added into the plate, and was incubated and shaken overnight at 25°C. The cerebrospinal fluid specimen was developed according to the instruction, and the result was analyzed using Sgx link software (Singulex Erenna).

Protein expression in hippocampus tissue and HN-h cells

Expression of Nrf2, HO-1, p-tau (Ser 181), p-tau (Thr 205), t-tau, NLRP3, cleaved caspase-1, IL-1β and GAPDH in the hippocampus tissue and HN-h cells were determined using western blotting.

Briefly, RIPA lysis buffer (Thermo Fisher Scientific, MA, USA) was adopted to extract the protein from the specimens, and Pierce™ modified Lowry protein assay kit (Thermo Fisher Scientific, MA, USA) was used to measure the total protein levels. A certain amount of protein (50 μg) was separated using 12% sodium dodecyl sulfate–polyacrylamide gel electrophoresis, and then were transferred onto a Bio-Rad’s nitrocellulose membrane (Hercules, CA, USA). After 2-h blocking with 5% skimmed milk at 25°C, the membrane was incubated anti-Nrf2 (Ser 9) (CST, #12721, 1:1000 dilution), anti-HO-1 (CST, #82206, 1:1000 dilution), anti-p-tau (Ser 181) (CST, #12721, 1:1000 dilution), anti-p-tau (Thr 205) (CST, #49561, 1:1000 dilution), anti-t-tau (CST, #46687, 1:1000 dilution), NLRP3 (CST, #15101, 1:1000 dilution), anti-cleaved caspase-1 (CST, #89332, 1:1000 dilution), IL-1β (CST, #31202, 1:1000 dilution) and anti-GAPDH (CST, #5174, 1:1000 dilution) at 4°C overnight. Subsequently, the membrane was incubated with an anti-rabbit IgG, HRP-linked secondary antibody (#7074, CST). Chemiluminescence detection was adopted to visualize the immunoreactive bands (Immolilon Western, USA). Image J software was used to measure the intensity of the bands.

Pyroptosis rate in hippocampus tissue and HN-h cells

Pyroptosis rate in the specimens was determined using a FAM-FLICA Caspase-1 detection kit (ImmunoChemistry) (Zeng et al. 2019). Briefly, the prepared cells were stained with FAM-FLICA (10 μl) and PI (5 μl) at 26°C for 20 min. Then, fluorescence intensity of the specimens was measured by a Coulter Epics XL flow cytometer. Pyroptosis rate was calculated using a formula: number of double-positive cells / number of total cells × 100%.

Statistical analysis

Continuous variable in the study was expressed using mean ± standard deviation. Variable comparison between two groups was conducted by independent sample t test, and the comparison among more than two groups was performed using variance analysis (ANOVA) with LSD test. P value less than 0.05 was regarded as statistically significant. All statistical analysis was performed using Statistical Product and Service Solutions (SPSS) version 19.0.

Results

Metabolic markers in mice

Body weight and three metabolic markers in serum (i.e. fasting glucose, total cholesterol and triglycerides) were measured immediately at the end of modeling (before intervention). Because the mice in the HFD, IGF, IGFR_I and HO_I groups were treated with HFD, all of them combined into a large group. The large group was then compared with the sham group. As a result in Fig. 1c, the levels of body weight, fasting glucose, total cholesterol and triglycerides in the large group were higher than that in the sham group (t = 11.961, P < 0.001; t = 5.298, P < 0.001; t = 11.177, P < 0.001; t = 14.191, P < 0.001, respectively). After that, the levels of body weight, fasting glucose, total cholesterol and triglycerides were separately compared among the HFD, IGF, IGFR_I and HO_I groups, and the results did not show any difference in these metabolic markers among the groups (F = 0.108, P = 0.955; F = 1.289, P = 0.293; F = 1.199, P = 0.324; F = 0.535, P = 0.661, respectively).

Cognitive function in mice

In Fig. 2, “escape latency”, “time in target quadrant” and “times crossing the platform area” were reported in Morris water maze. As a result, “escape latency” differed significantly among the sham, HFD, IGF, IGFR_I and HO_I groups (F = 54.380, P < 0.001), as did “time in target quadrant” and “times crossing the platform area” (F = 63.916, P < 0.001; F = 15.424, P < 0.001, respectively).

Briefly, compared with the sham group, “escape latency” was extended and the other two markers (i.e. “time in target quadrant” and “times crossing the platform area”) were shortened in the HFD group (P < 0.001,
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**Nrf2/HO-1 signaling pathway in hippocampus**

In Fig. 3, there was significant difference in activities of Nrf2 and HO-1 among the five animal groups \((F = 16.356, P < 0.001; F = 49.245, P < 0.001)\).

Briefly, compared with the sham group, the expression of Nrf2 and HO-1 were significantly decreased in the HFD group \((P < 0.001, P < 0.001\), respectively). In the IGF group, PEG-IGF-1 was able to elevate the expression of the proteins \((P = 0.004, P < 0.001\), respectively). In the IGFR_I and HO_I groups, IGF-1 receptor blocker inhibited the expression of Nrf2 and HO-1 \((P = 0.010, P < 0.001\), respectively), while HO-1 blocker only inhibited the expression of HO-1 \((P < 0.001)\).

**Neuronal pyroptosis in hippocampus**

In Fig. 4, expression of pyroptosis-related proteins \(\text{i.e. NLRP3, caspase-1, IL-1β}\) and rate of pyroptosis were significant different among the five animal groups \((F = 35.776, P < 0.001; F = 66.098, P < 0.001; F = 21.195, P < 0.001; F = 14.831, P < 0.001)\).

Briefly, compared with the sham group, the expression of NLRP3, caspase-1 and IL-1β were up-regulated in the HFD group \((P < 0.001, P < 0.001, P < 0.001\), respectively). In the IGF group, PEG-IGF-1 inhibited the expression of the three proteins \((P < 0.001, P < 0.001, P = 0.002\), respectively). In the IGFR_I and HO_I groups, both IGF-1 receptor and HO-1 blockers up-regulated the expression of NLRP3, caspase-1 and IL-1β than that in the IGF group \((\text{IGFR}_I: P = 0.004, P = 0.001, P = 0.008\), respectively; \text{HO}_I: P < 0.001, P < 0.001, P = 0.018\), respectively).

Meanwhile, pyroptosis rate was increased in the HFD group than in the sham group \((P < 0.001)\). PEG-IGF-1
treatment in the IGF group decreased the rate compared with the HFD group ($P = 0.002$). In the IGFR_I and HO_I groups, pyroptosis rate was re-increased, again ($P = 0.014$, $P = 0.006$, respectively).

**Tau protein in cerebrospinal fluid and hippocampus**

In Fig. 5a, b, cerebrospinal fluid levels of $p$-tau (Ser 181) and $p$-tau (Thr 205) significantly differed among the five animal groups ($F = 21.799$, $P < 0.001$; $F = 20.714$, $P < 0.001$, respectively). Briefly, compared with the sham group, cerebrospinal fluid levels of $p$-tau (Ser 181) and $p$-tau (Thr 205) were increased in the HFD group ($P < 0.001$, $P < 0.001$, respectively). In the IGF group, the levels of two proteins were lower than that in the HFD group ($P = 0.005$, $P = 0.001$, respectively). In the IGFR_I and HO_I groups, IGF-1 receptor and HO-1 blockers again elevated the levels of $p$-tau (Ser 181) and $p$-tau (Thr 205) in cerebrospinal fluids (IGFR_I: $P = 0.024$, $P = 0.005$, respectively; HO_I: $P = 0.022$, $P = 0.007$, respectively).

In Fig. 5c–e, expression of $p$-tau (Ser 181) and $p$-tau (Thr 205) in hippocampus also differed among the five groups ($F = 12.571$, $P < 0.001$; $F = 26.466$, $P < 0.001$, respectively). Briefly, expression of $p$-tau (Ser 181) and $p$-tau (Thr 205) were higher in the HFD group than in the sham group ($P < 0.001$, $P < 0.001$, respectively). In the IGF group, PEG-IGF-1 treatment significantly inhibited the expression of the proteins ($P = 0.020$, $P = 0.003$, respectively). In the IGFR_I and HO_I groups, both blockers up-regulated the expression of $p$-tau (Ser 181) and $p$-tau (Thr 205), again (IGFR_I: $P = 0.040$, $P = 0.018$, respectively; HO_I: $P = 0.042$, $P = 0.031$, respectively).

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Fig. 4 Neuronal pyroptosis in the mouse groups. Expression of NLRP3, caspase-1 and IL-1β in the hippocampus was determined using western blotting. Pyroptosis rate in the hippocampus was measured using flow cytometry. “*” indicated $P < 0.05$ compared with the sham group. “†” indicated $P < 0.05$ compared with the HFD group. “‡” indicated $P < 0.05$ compared with the IGF group.

Fig. 5 Expression of tau proteins in the mouse groups. Cerebrospinal fluid levels of $p$-tau (Ser 181) and $p$-tau (Thr 205) were determined using a Singulex Erenna immunoassay platform. Expression of $p$-tau (Ser 181), $p$-tau (Thr 205) and total-tau in the hippocampus was determined using western blotting. “*” indicated $P < 0.05$ compared with the sham group. “†” indicated $P < 0.05$ compared with the HFD group. “‡” indicated $P < 0.05$ compared with the IGF group.
Pyroptosis in HN-h cells

In Fig. 6, there was significant difference in expression of pyroptosis-related proteins (i.e. NLRP3, caspase-1 and IL-1β) and rate of pyroptosis in the control, PA and PYR_I groups (\(F = 28.960, P < 0.001; F = 27.915, P < 0.001; F = 30.489, P < 0.001; F = 21.366, P < 0.001\), respectively). Briefly, the expression of the proteins (i.e. NLRP3, caspase-1 and IL-1β) and rate of pyroptosis were higher in the PA group than the control group \((P < 0.001, P < 0.001, P < 0.001\), respectively). In the PYR_I group, pyroptosis blocker necrosulfonamide significantly decreased the expression of IL-1β and rate of pyroptosis compared with the PA group \((P = 0.001, P < 0.001, P < 0.001, \) respectively), but can not affect the expression of NLRP3 and caspase-1 \((P = 0.388, P = 0.156\), respectively).

Fig. 6 Neuronal pyroptosis in the cell groups. Human neurons-hippocampal (HN-h) cells were randomly divided into three groups, and each group contained ten wells. The cells in the PA and PYR_I groups were treated with palmitic acid, and the cells in the PYR_I group were also treated with pyroptosis blocker necrosulfonamide.

Expression of NLRP3, caspase-1 and IL-1β in the HN-h cells was determined using western blotting. Pyroptosis rate in the HN-h cells was measured using flow cytometry. “†” indicated \(P < 0.05\) compared with the control group. “‡” indicated \(P < 0.05\) compared with the PA group.

Tau protein in HN-h cells

In Fig. 7, the expression of p-tau (Ser 181) and p-tau (Thr 205) was quite different among the three HN-h cell groups (\(F = 46.187, P < 0.001; F = 35.654, P < 0.001\), respectively).

Briefly, the expression of the two p-tau proteins were higher in the PA group than in the control group \((P < 0.001, P < 0.001\), respectively). In the PYR_I group, necrosulfonamide significantly inhibited the expression of p-tau (Ser 181) and p-tau (Thr 205) compared with the PA group \((P = 0.005, P = 0.002\), respectively).

Fig. 7 Expression of tau proteins in the hippocampal neuron groups. Expression of p-tau (Ser 181), p-tau (Thr 205) and total-tau in the HN-h cells was determined using western blotting. “†” indicated \(P < 0.05\) compared with the control group. “‡” indicated \(P < 0.05\) compared with the PA group.
Discussion

In 2016, nearly 40% of the population in the United States was affected by obesity (Hansen et al. 2020). In China, obesity rate also exceeded 12% in the same year (Zhang et al. 2020a, b). More importantly, previous studies confirmed that obesity not only caused cardiovascular disease, stroke and type 2 diabetes, but also affected cognitive function (Wang et al. 2017; Zhang et al. 2020a, b). Thus, with the dramatic increase in obese prevalence, obesity-related cognitive dysfunction was becoming an important health threat globally. However, the pathogenesis and therapeutic strategy of such cognitive dysfunction were still unclear. Therefore, the present study focused on the pathogenic effect of tau protein and neuronal pyroptosis on obesity-related cognitive dysfunction, and further explored whether IGF-1 could be a potential therapy against the disease.

It was well known that hyperphosphorylated tau protein impaired cognitive function, and was confirmed to be an crucial pathological change in Alzheimer’s disease (Abu-Rumeileh et al. 2018). Recently, tau pathology was found in studies which focused on high-fat or metabolic models (Puigoriol-Illamola et al. 2020; Zhou et al. 2020). Based on the results mentioned above, the present study further suggested that hyperphosphorylated tau protein was significantly up-regulated both in the hippocampus obtained from the HFD mice and the HN-h cell line which was treated with PA. Therefore, high-fat intervention can cause hyperphosphorylation of tau protein in central nervous system (especially hippocampus), which is likely to be one of the potential mechanisms of HFD-induced cognitive dysfunction.

Meanwhile, the present study reported that high-fat intervention increased the rate of neuronal pyroptosis both in the neuronal and animal models. More importantly, the study found that inhibition of neuronal pyroptosis using specific blocker significantly improved tau pathology in the PA treated HN-h cells. Thus finding was consistent with previous studies focusing on Alzheimer’s disease (Ising et al. 2019; Li et al. 2020). Therefore, we concluded that neuronal pyroptosis may contribute to the hyperphosphorylation of tau protein, which should be one of the important ways in which neuronal pyroptosis was involved in the pathogenesis of obesity-induced cognitive dysfunction.

In addition, pyroptosis was one kind of inflammatory process of death (McKenzie et al. 2020). A great number of evidence had proved that obese people suffered from sub-clinical inflammation in whole body including brain tissue (Miller and Spencer 2014). Furthermore, neuroinflammation contributed to a series of pathophysiological disorders, such as apoptosis and oxidative stress (Guillemot-Legris and Muccioli 2017). So, neuronal pyroptosis might also be related to these pathophysiological disorders. Tsuchiya et al. suggested that caspase-1 initiated apoptosis in a certain condition, which revealed the potential relationship between pyroptosis and apoptosis, and partly confirmed this speculation (Tsuchiya et al. 2019). Eventually, all the disorders combined to impair cognitive function in obese models (Miller and Spencer 2014). Therefore, neuronal pyroptosis may be involved in the development of obesity-induced cognitive dysfunction through a variety of mechanisms, but not only tau pathology.

Our previous study revealed that IGF-1, one type of polypeptide which was structurally similar to insulin, improved cognitive dysfunction in a vivo model of HFD, but its protective mechanism was not clear (Wang et al. 2020). However, effect of IGF-1 on tau pathology in many other models had widely been explored. One study suggested that astrocytic IGF-1 inhibited neuronal death and hyperphosphorylated tau in an in vitro model of neurodegeneration (Chen et al. 2019). Another study revealed that exogenous IGF-1 attenuated acute ischemic stroke induced memory impairment via modulating inflammatory response and tau phosphorylation (Yang et al. 2020). So, the present study adopted exogenous IGF-1 to treat the HFD mice, and found that the polypeptide alleviated the hyperphosphorylation of tau protein, and also inhibited the neuronal pyroptosis. Combined with the results of the in vitro experiment, such protective effect on tau protein might be partly performed through inhibiting neuronal pyroptosis. To our best knowledge, this was the first published article focusing on this topic, and the results was helpful to the therapeutic strategy of obesity-related tau pathology.

In addition, the present study found that exogenous IGF-1 played its protective role by activation of Nrf2/HO-1 signaling pathway. The latter was an antioxidant stress signaling pathway, and was also involved in the regulation of inflammation, apoptosis and energy metabolism (Luo et al. 2017; Ali et al. 2018; Ma et al. 2020). Our study updated the knowledge about the regulative effect of the signaling pathway on tau pathology and neuronal pyroptosis in the HFD model.

During the in vivo experiment, we adopted long-term HFD to induce a mouse model of obesity. The reason why we chose HFD to do the modeling was that the strategy was much closer to the reality than surgery, genetic modification and other modeling methods (Heydemann 2016). During the in vitro experiment, we treated HN-h cells with PA, one type of saturated fatty acids, to establish a cell model of high-fat, which has been successfully adopted in previous studies (Yi et al. 2008). Both the strategies well simulated the high-fat condition and ensured the reliability of the conclusion.
The study adopted PEG-IGF-1, but not free IGF-1 to treat HFD mice. PEG extended half-life of the regent and reduced the frequency of injection, which may help to ensure efficacy and reduce animal suffering (Kletzl et al. 2017). In addition, Morris water maze was a cognitively assessment method, which was introduced for rats. However, there were three explanations why we chose it for mice in the present study. First, Morris water maze had been used by many scientific teams in several mouse models of brain trauma and neurodegenerative disease (Brody and Holtzman 2006; Bromley-Brits et al. 2011). Second, our team had used Morris water maze successfully to evaluate the cognitive function in HFD mice, and obtained satisfactory results (Yang et al. 2021). Third, C57BL/6 J mice, but not rats, were ideal for the establishment of HFD models, and was widely used in the study of related metabolic diseases (Brito-Casillas et al. 2016).

In conclusion, the present study confirmed that exogenous IGF-1 significantly improved HFD-induced cognitive dysfunction partly through down-regulation of hyperphosphorylated tau protein in hippocampus. The study also provided some interesting evidence that such protective effect of IGF-1 on tau pathology was associated with the inhibition of neuronal pyroptosis and activation of Nrf2/HO-1 signaling pathway.

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Authors’ contributions Sui Guanghong, Wang Lu, Chen Zheng and Wang Feng conduct study design, literature research and manuscript preparation. Yang Caixia, Guo Mengtian and Xiong Xiangyang carry out experiment and performed data analysis.

Availability of data and material The data cannot be shared because this is an ongoing study.

Code availability All analysis is performed by Statistical Product and Service Solutions 19.0.

Compliance with ethical standards

Conflict of interest The author declare that they have no conflict of interest.

Ethics approval The study is approved by the ethics committees of Tianjin Anding Hospital and Tianjin Medical University General Hospital.

Consent to participate This is an in vivo and in vitro study, and no human subjects are included.

Consent for publication All authors agree to submit this article to your journal.

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