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Original article

Pharmacological melioration by Selenium on the toxicity of tellurium in neuroendocrine centre (Pituitary Gland) in male wistar rats: A mechanistic approach

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ABSTRACT

Purpose: The present research was designed to evaluate the toxicity of tellurium and its prevention by selenium on the pituitary gland in male Wistar rats.
Methods: 30 rats were used weighing 200–250 gm, and randomly divided them into five groups. Each group contained an equal number of animals. Group-1 was nominated as control group. Group-2 received an intraperitoneal dose of selenium 0.3 mg per kg body wt. Group-3 was administered with tellurium 4.15 mg per kg body wt. Group-4 was given low-dose (L) of both selenium 0.15 and tellurium 2.075, Group-5 was given High-dose (H) of both selenium 0.3 and tellurium 4.15 mg/kg body wt. orally once in a day. After 15 days of dosing, the behavioral activities- motor co-ordination rotarod and grip strength test were measured. On 16th-day animals were sacrificed and activity of LPO, GSH, caspase-3, caspase-9, GPx, GR, SOD, catalase, and AChE were performed on the pituitary gland as per standard method reported.
Results: Se when given together with Te, significantly protects the motor coordination up to 32.5%, and also protects the grip strength up to 75% in group 4 and 5 respectively as compared to group- 3. Se + Te treatment protects the activity of TBARS up to 48.68% and GSH is 58%. As compared to control, it protects caspase-3 up to 118% and caspase-9 up to 83%. The level of AChE was also observed to be modulated by the administration of Se in Group- 4 and 5. Se + Te protected AChE up to 28.6%. Similar findings were observed for the biochemical activities of GPx (140% protection), SOD (458%), GR (159%), and catalase (95%) activities that were protected significantly Se + Te in Group- 4 and 5.
Conclusion: Selenium dose-dependently protects behavioral activities. It also protects apoptosis, oxidative stress, and AChE activities in the pituitary gland.

1. Introduction

The neuroendocrine center consists of the hypothalamus, pituitary, and pineal gland. Out of these, the pituitary gland is a neuroendocrine center secreting various hormones responsible for the control of energy management in the human body, blood pressure, thyroid level, metabolism, and fertility, etc. Many hormones responsible for the growth of the various organs and involved in various pathways and metabolic processes are secreted by the pituitary gland (Melmed et al., 2002). There are several reports of toxicity of elements on the neuroendocrine system (Rana, 2014; Iavicoli et al., 2009). Some trace elements have a beneficial effect on the pituitary gland and thyroid gland like selenium and iodine (Basalaeva, 2013).

Tellurium is a trace element that has many industrial applications like rubber compounding, electronic microchip industries,
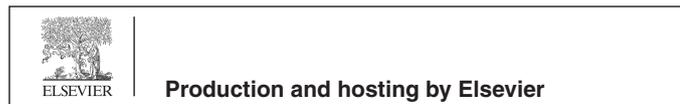
glass industries to name a few. Tellurium is a known poison and is characterized by nausea, garlic odor in urine and breath (Taylor, 1996). This element is also known to interfere with cholesterol synthesis (Laden and Porter, 2001) and have toxic effects on the nervous system suggesting symptoms like peripheral neuropathy (Harry et al., 1989). Gajkowska et al., 1995 suggested the neurotoxic effect of sodium tellurite in the rat temporal lobe and neurotoxic effect of sodium tellurite in the central nervous system of the adult rat was studied by Smialek et al. (1994). Accordingly, Widy-Tyszkiewicz et al. (2002) suggested the cognitive deficits in rats following sodium tellurite at two different doses. It is reported that oral dose i.e. LD50 of sodium tellurite is 83 mg/kg for rat model (Lewis, 1996).

Selenium on the other hand belonging to the same group is a micronutrient and essential element for animals and humans (Lockitch, 1989). It works as an excellent antioxidant for them. Selenium has the ability to incorporate the enzymes including glutathione peroxidase (Maggini et al., 2007; Zeng, 2009; Yao et al., 2013). At least 25 mammalian proteins have Se in their structure to form selenoproteins (Kryukov et al., 2003) to boost the biological functions with various degrees (Ferguson et al., 2012; Burk and Hill, 2005). It protects neurodegenerative diseases like cerebral stroke (Ansari et al., 2004), Parkinson's disease (Zafar et al., 2003), traumatic brain injury (Yeo and Kang, 2007), Alzheimer's disease (Zheng et al., 2016). An optimal concentration of selenium has been reported beneficial for male and female reproduction (Mistry et al., 2012) and autoimmune thyroid disease (Beckett and Arthur, 2005). The reported oral LD50 values of sodium selenite in rats ranged between 3 and 12 mg selenium/kg body weight (Morss and Olcott, 1967; Cummins and Kimura, 1971).

As Se and Te belong to the same group in the periodic table, they have similar chemical properties. Selenium, as discussed above, is the essential trace element and is required for many physiological processes but Te, on the other hand, is not an essential micronutrient and have properties close to the elements that represent a potential danger to human health (Larner, 1995; Taylor, 1996). There are reports that Se is involved in the thyroid function and has a beneficial effect on the pituitary gland no data have been available related to the effect of Te on the pituitary gland. This study is designed to elicit the mechanisms of action of Te only, Se only, and Se + Te together on the pituitary gland of rats by understanding the behavioral activities, oxidative stress, and apoptosis marker. The underlying hypothesis of this study is to understand the toxic effect of Te on the pituitary gland and its prevention by Se and elucidating the mechanism of action.

2. Materials & methods

Sodium selenite (Na_2SeO_3), sodium tellurite (Na_2TeO_3), sodium carbonate, sodium hydroxide, sodium potassium tartrate, copper sulphate, Folin-Ciocalteu reagent (FCR), Trichloroacetic acid (TCR), Thiobarbituric acid (TBA), sulfosalicylic acid, 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB), β - Nicotinamide adenine dinucleotide phosphate (NADPH), ethylene di-amine tetra acetic acid (EDTA), sodium azide, Glutathione Reductase, H_2O_2, Oxidised Glutathione, Glutathione reduced, (-)-epinephrine. Kits for Caspase-3, - 9 Assay were obtained from Abcam (U.S.A.) with catalog number ab39401 and ab65608 respectively.

2.1. Animals and drug dosage

Thirty male Wistar rats (200–250 gm) were procured from Animal House, run and managed by Jazan University, Jazan KSA under animal ethical clearance number is 108/2508/1438.

In this study, we divided animals randomly into five groups each having six animals. In the present study, groups were defined as -

Group – 1: The Control group.
Group – 2: Selenium high (H) dose (0.3 mg per kg body weight, i.p.) was given as reported (Islam et al., 2002).
Group – 3: Tellurium high (H) dose (4.15 mg per kg body weight, oral) was given to rats.
Group – 4: Selenium low (L) dose (0.15 mg per kg body weight, i.p.) and Tellurium low (L) dose (2.075 mg per kg body weight, oral) was given to rats.
Group – 5: Selenium high (H) dose (0.3 mg per kg body weight, i.p.) and Tellurium high (H) dose (4.15 mg per kg body weight, oral) was given to rats.

All the above doses were given for 15 days to all groups as reported (Safhi et al., 2018). After 1 h of the drug administration on the last day, the behavioral activities were assessed systematically. On day 16th of the study, we have sacrificed the animal and dissected out the pituitary gland from the brain of the animals of all groups. It is also hereby declared that the aforesaid study was performed with a strong consideration of the ethical guidelines issued by the institution, national and international bodies of animal experiments studies rights.

2.2. Behavioral studies

The animals of all groups underwent for the rotarod training, and grip tests training for the duration of five days, before performing the dosing. Further behavioral studies were continued parallel to dosing until the sacrifice of the animals. Both behavior studies were performed at a temperature of 25 ± 2 °C and relative humidity 45–50%. In this study, every behavioral test was executed by the persons completely blind to the experiment.

2.2.1. Motor co-ordination by rotarod test
We used Omni Rotor Rotamex (Columbus Instruments, Columbus, OH, USA) for the evaluation of motor co-ordination behavioral activity. Rotarod was reported to evaluate muscular coordination after 24 h we followed the same (Kelly et al., 1998). The available apparatus was capable to test four rats simultaneously; there was a 75 cm diameter rotating rod. Apparatus used in this study automatically record the time in 0.1 s as soon as the animal falls from the rotating rod. Animals were trained at the speed 8 rpm for the first two days followed by 10 rpm for the next three days and subsequently, the experiment was started. We performed daily two trials each of 280 s during the training period. We adjusted the rotating speed exactly 10 rounds per minute while cut off time limit was adjusted to 280 s during motor co-ordination test on the selenium treated group.

2.2.2. Grip strength test
This test was performed in our research laboratory with the help of the available apparatus, according to the grip strength test reported in (Moran et al., 1995). Grip test apparatus was equipped with a 50 cm string properly stretched between two vertical bars of height 1 m, with 40 cm string elevation from the base. Rats were allowed to put on the string and grip strength was measured on (0–5) categorical scale as; category 0: falls off from the string; category – 1: animal hangs on the string by two forepaws; category – 2: almost as category −1 but attempts and tried to climb on the string; category -3: animal hangs onto string by two forepaws in addition to one or both hind limbs; category- 4: animal hangs onto string by all forepaws in addition to tail wrapped around string; category – 5: animal escapes from the string. All animals used in

this study were testifying in the aforementioned six categories and results were recorded.

2.3. Tissue preparation

As mentioned above on day 16th, rats were sacrificed and brains were taken out to dissect the pituitary gland. The pituitary glands of each group were homogenized in Tris-HCl buffer (10 mM, pH 7.4) and centrifuged at 3000 rpm at 4 °C to separate the supernatant-1 (S-1). The S-1 was used for LPO, SOD, caspase-3, and caspase- 9. The remaining S-1 was again centrifuged at 15,000 g for 20 min at 4 °C which yields the post mitochondrial supernatant (PMS) which was used for the assays of GSH, protein , GPx, GR, catalase, and Acetylcholine esterase (AChE).

2.4. Biochemical studies

2.4.1. Assay for LPO content as thiobarbituric reactive substances (TBARS)

We had performed Assay for the LPO on the supernatant-1. We used the standard method of Utley et al., 1967 further modified by Islam et al., 2002. This is the most suitable procedure for lipid peroxidation estimation. The result of LPO was calculated in nmol TBARS/mg protein.

2.4.2. Assay for reduced glutathione (GSH)

In this study estimation of GSH was carried out by the method reported (Jollow et al., 1974) and the results were calculated in nmol/mg protein.

2.4.3. Glutathione reductase (GR) activity

The method given in (Carlberg and Mannervik, 1975) further modified by (Mohandas et al., 1984) was used for the activity of GR and the result was calculated in nmol NADPH oxidized/min/ mg protein.

2.4.4. Glutathione peroxidase (GPx) activity

We used the method described in (Mohandas et al., 1984) for the activity of GPx and the result was calculated in nmol NADPH oxidized/min/mg protein.

2.4.5. Superoxide dismutase (SOD) activity

In this study, we measured SOD activity by the procedure described in (Stevens et al., 2000).

2.4.6. Assay of catalase (CAT)

We measured the CAT activity by the method given in (Claiborne, 1985) and results were calculated in nmol H_2O_2 consumed/min/mg protein.

2.4.7. Acetylcholinesterase (AChE) activity

AChE activity was evaluated by the procedure given by (Ellman et al., 1961). Our results of this activity were calculated in micro mol thiocholine formed/min/mg protein.

2.4.8. Caspase-3 and -9 activities

The Company standard procedure guidelines (Caspase -3, -9 Assay Kit) were followed. The assay Kit (abcam, US) was purchased from the supplier for the assays of caspase-3, and -9.

2.4.9. Protein estimation

In this study, protein estimation was carried out by the procedure given in (Lowry et al., 1951).

2.5. Statistical analysis

The results were expressed as mean ± S.E.M. Statistical analysis named as one-way analysis of variance (ANOVA), followed by Turkey's-test was carried out for the significance of the data. For statistical analysis of the readings, Origin software was used. The values which had $p < 0.05$ were considered statistically significant.

3. Result

3.1. Selenium administration improves motor coordination in Te intoxicated animals

The motor coordination was 37.8% decreased in the Group-3 in comparison to the control Group-1. We observed in our findings that selenium protects the motor coordination in Group-4 with 9.7% and Group-5 with 32.5% in comparison to the Group-3. Group-2 Se(H) has no significant changes as compared to the control group. The values in results are expressed as mean ± S.E.M. (n = 6). [#]$p < 0.001$ control group compared to Te(H) group, ***$p < 0.001$ Te(H) group compared to Se + Te-(L) group, ***$p < 0.001$ Te(H) group compared to Se + Te-(H) group. (Fig. 1).

3.2. Tellurium toxicity protection in grip strength test by selenium

The tellurium is toxic and it reduced 44.9% grip strength in comparison to the control group. Selenium ameliorated the grip strength by 31% on the lower dose (Group-4) and 75% on the higher dose (Group-5). Group-2, Se(H) and the control group do not have significant changes. The data were expressed as mean ± SEM (n = 6), [#]$p < 0.001$ Control group compared to Te(H) group, *$p < 0.05$ Te(H) group compared to Se + Te-(L) group, ***$p < 0.001$ Te(H) group compared to Se + Te-(H) group. (Fig. 2).

3.3. Tellurium toxicity protection by selenium on the caspase-3 activity

It can be observed from bar-chart (Fig. 3) that, caspase-3 activity was notably increased ([#]$p < 0.001$, 128%) in Group-3 i.e. sodium tellurite (high dose) administered group compared to the control Group-1. Se + Te protected the toxicity of the tellurium because caspase-3 activity gradually declined in the Group-4 (*$p < 0.05$, reduction by 85% as compared to Group-3) and Group-5 (**$p < 0.01$, reduction by 118% as compared to Group-3). There was no significant changes between Group-2 Se(H) and control Group-1.
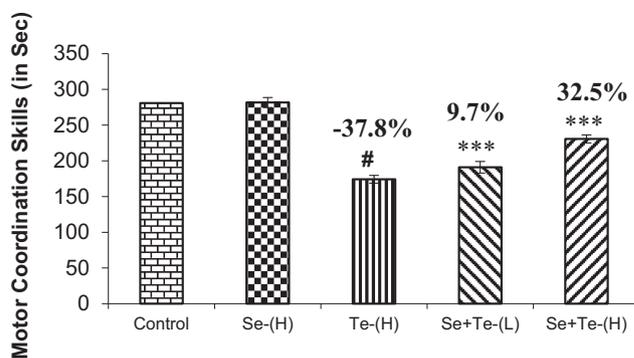

Fig. 1. **Motor co-ordination protection by Tellurium + Selenium**. Motor co-ordination behavioral activity was significantly declined in Te administered group that was protected by the treatment of Se + Te dose dependently. Values are represented as mean value ± S.E.M. Significance expressed as [#]$p < 0.001$ Control group vs. Te(H) group, ***$p < 0.001$Te(H) group vs. Se + Te(L) group, ***$p < 0.001$ Te(H) group vs. Se + Te(H) group.
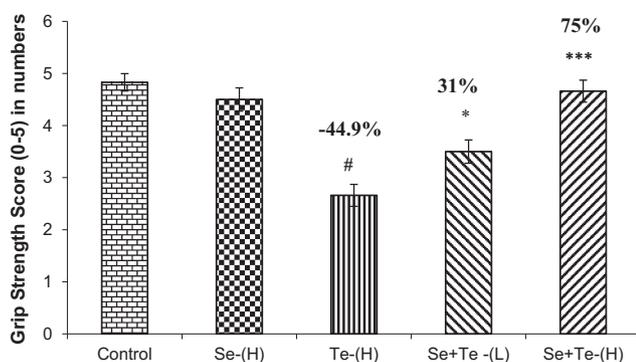
Fig. 2. Grip strength protection by Tellurium + Selenium. Grip strength behavioral activity was declined significantly in Te administered group that was protected by the treatment of Se + Te dose dependently. Values are represented as mean value ± S.E.M. Significance expressed as [#]p < 0.001 Control group vs. Te(H) group, [*]p < 0.05 Te(H) group vs. Se + Te(L) group, [***]p < 0.001 Te(H) group vs. Se + Te (H) group.
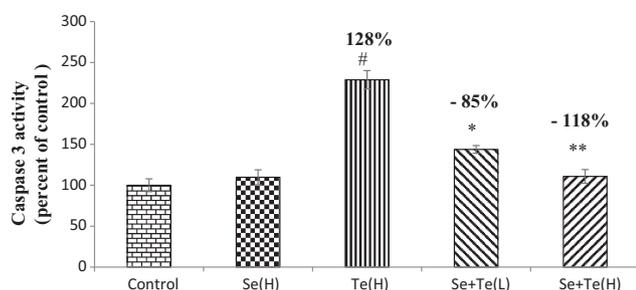

Fig. 3. Caspase-3 activity and protection by Tellurium + Selenium. Caspase-3 activity was activated significantly in Te administered group that were protected by the treatment of Se + Te dose dependently. Values are represented as mean value ± S.E.M. Significance expressed as [#]p < 0.001 Control group vs. Te(H) group, [*]p < 0.05 Te(H) group vs. Se + Te(L) group, [**]p < 0.01 Te(H) group vs. Se + Te(H) group.

3.4. Tellurium toxicity protection by selenium on the caspase-9 activity

It can be observed from bar-chart (Fig. 4) that, caspase-9 activity was notably increased ([#]p < 0.001, 104%) in Group-3 i.e. sodium tellurite (high dose) treated group compared to the control Group-1. Se and Te combination protected the toxicity of the tellurium because caspase-9 activity was gradually decreased in the Group-4 ([*]p < 0.05, reduction by 49% compared to Group-3) and Group-5 ([**]p < 0.01, reduction by 83% as compared to Group-3). There was no significant changes between Group-2 Se(H) and control Group-1.
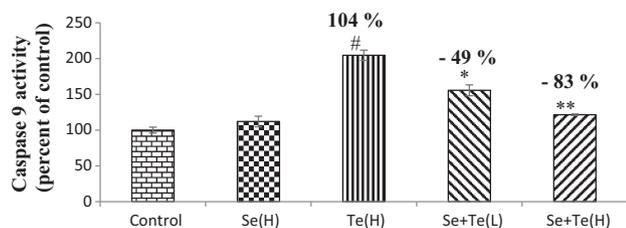

Fig. 4. Caspase-9 activity and protection by Tellurium + Selenium. Caspase-9 activity was significantly activated in Te administered group that were protected by the treatment of Se + Te dose dependently. Values are represented as mean value ± S.E.M. and significance [#]p < 0.001 Control group vs. Te(H) group, [*]p < 0.05 Te (H) group vs. Se + Te(L) group, [**]p < 0.01 Te(H) group vs. Se + Te(H) group.

3.5. Tellurium toxicity protection by selenium on the Acetylcholinesterase activity

It can be observed from bar-chart (Fig. 5) that, Acetylcholinesterase activity was notably increased ([#]p < 0.001, 63.2%) in Group-3 i.e. sodium tellurite (high dose) administered group compared to the control Group-1. Se and Te combination protected the toxicity of the tellurium because Acetylcholinesterase activity was gradually decreased in the Group-4 ([**]p < 0.01, reduction by 19.6% compared to Group-3) and group- 5 ([***]p < 0.001, reduction by 28.6% compared to Group-3). There was no significant changes between Group-2 Se(H) and control Group-1.

3.6. Tellurium toxicity protection by selenium on the contents of TBARS

TBARS is a product of lipid peroxidation and can be assayed by reacting the sample with thiobarbituric acid. In this study, we found that there was a significant rise in the content of TBARS (149%) in Group-3, Te(H) administered rats compared to the control Group-1. We also found that the pretreatment with Selenium and Tellurium in Group-4 Se + Te-(L) rats has protected its content significantly (18%) as compared to the Group-3 rats (Table 1). Further, the pretreatment with Se + Te in Group-5 Se + Te-(H) rats has protected its content significantly (48.68%) compared to the Group-3 rats. No significant change was observed in Group-2 Se (H) as compared to the control Group-1. In this study, it was found that the Se + Te combination protected the contents of TBARS dose-dependently.

3.7. Tellurium toxicity protection by selenium on the contents of GSH

In the present study, we found that the GSH level was significantly decreased (50%, p < 0.001) in Group-3 Te(H) administered compared to the control Group-1. Further, the pretreatment of Group-3 rats with Se + Te has significantly (29.6%, p < 0.001) protected the content of GSH in Group-4 and (58%, p < 0.001) in Group-5 as compared to Group-3 rats. There was no significant changes between Group-2 Se(H) and control Group-1 (Table 1).

3.8. Tellurium toxicity protection by selenium on GPx, GR, SOD, and catalase activities

It is clear from Table 2 that, selenium when given together with tellurium, has shown protection on GPx, GR, SOD, and Catalase activities. These activities were decreased significantly (p < 0.001) in Group-3 Te(H) compared to the control Group-1. The activities of these enzymes have shown significant protection
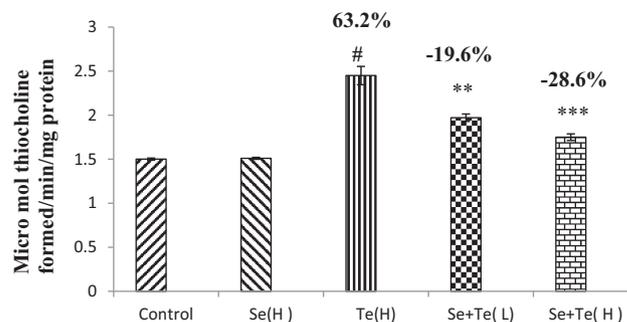

Fig. 5. Acetylcholinesterase activity and protection by Tellurium + Selenium. Acetylcholinestrase activity was significantly activated in Te administered group that were protected by the treatment of Se + Te dose dependently. Values are represented as mean value ± S.E.M. Significance expressed as [#]p < 0.001 Control group vs. Te(H) group, [**]p < 0.01 Te(H) group vs. Se + Te(L) group, [***]p < 0.001 Te(H) group vs. Se + Te(H) group.

Table 1
Tellurium toxicity protection by selenium when given together with tellurium on the contents of GSH.

Biomarkers	Group-1 Control	Group-2 Se(H)	Group- 3 Te(H)	Group- 4 Se + Te (L)	Group- 5 Se + Te (H)
Lipid peroxidation (nmol TBARS/mg protein)	426.82 ± 21.77	464.39 ± 18.0 (8.8%)	1064.19 ± 14.8# (149%) {p < 0.001}	869.155 ± 12.42***(-18%) {p < 0.001}	546.16 ± 17.77*** (-48.68%) {p < 0.001}
GSH (nmol/mg protein)	1345.28 ± 109.15	1375.18 ± 33.87 (2.2%)	671.57 ± 27.448# (-50%) {p < 0.001}	870.67 ± 35.556*** (29.6%) {p < 0.001}	1061.65 ± 28.659*** (58%) {p < 0.001}

Results of TBARS and GSH written in this table are expressed as mean value ± S.E.M of 6 animal leads to significant alterations in Te(H) Group-3 as compared to Control group (#p < 0.001, Te(H) vs. Control group). Significance was ascertained in Te(H) group as compared to Se + Te (L) and Se + Te (H) group as *p < 0.05, **p < 0.01, ***p < 0.001. No significant difference in control group vs Se(H) group. Round brackets are used to express the percentage decrease/increase with respect to the control, while values written in the curly brackets, expressed the significance p values.

Table 2
Tellurium toxicity protection by selenium when given together with tellurium on GPx, GR, SOD, and Catalase activities.

Biomarkers	Group-1 Control	Group-2 Se(H)	Group- 3 Te(H)	Group- 4 Se + Te (L)	Group- 5 Se + Te (H)
GPx (nmol NADPH oxidized/min/mg protein)	103.75 ± 2.64	105.54 ± 2.74 (1.7%)	44.50 ± 2.66# (-57%) {p < 0.001}	51.83 ± 2.87** (16%) {p < 0.01}	107.07 ± 4.57*** (140%) {p < 0.001}
GR (nmol NADPH oxidized/min/mg protein)	64.96 ± 3.59	68.41 ± 6.38 (5.3%)	23.71 ± 1.932 # (-63.5%) {p < 0.001}	33.36 ± 2.49*** (40.7%) {p < 0.001}	61.46 ± 4.28*** (159%) {p < 0.001}
SOD (nmolepinephrineprotected from oxidized/min/mg protein)	194.66 ± 9.67	203.37 ± 9.78 (4.5%)	33.08 ± 1.75 # (-83%) {p < 0.001}	55.92 ± 2.52*** (69%) {p < 0.001}	184.7 ± 2.73*** (458%) {p < 0.001}
CAT (nmol H_2O_2 consumed/min/mg protein)	14.01 ± 0.53	14.84 ± 0.85 (5.9%)	5.94 ± 0.58# (-57.6%) {p < 0.001}	7.66 ± 0.64*** (28.9%) {p < 0.001}	11.59 ± 0.84*** (95%) {p < 0.001}

Results in this table are expressed as mean value ± S.E.M of 6 animal leads to significant alterations in Te(H) Group-3 as compared to Control group (#p < 0.001, Te(H) group vs. Control group). Significance was ascertained Te(H) group as compared to Se + Te (L) and Se + Te (H) group(*p < 0.05, **p < 0.01, ***p < 0.001. No significant different in control group vs Se(H) group. Round brackets are used to express the percentage decrease/increase with respect to the control group, while values written in the curly brackets, expressed the significance p values.

when the rats of Group- 3 were pretreated with two different doses of selenium and tellurium i.e. Group-4 and Group-5. There was no significant changes between Group-2 Se(H) and control Group-1 (Table 2).

4. Discussion

Selenium, it is an antioxidant element incorporates in variety of neuronal function mediated by the central nervous system. Role of selenium profoundly indicated in various neurological disorders including Alzheimer's and Parkinson's disease (Solovyev 2015). However, Tellurium is reported to involve in neurotoxicity such as demyelination, oxidative stress and neuronal death (Gajkowska et al., 1995; Smialek et al., 1994; Widy-Tyszkiewicz et al., 2002). Our findings indicated the toxic effect of Tellurium on the pituitary gland of male Wistar rats and its amelioration by Selenium. The pituitary gland is responsible for the secretion of hormones to control the growth of the various organs and also involved in various pathways as well as a metabolic process (Melmed, 2011). Toxicity to the pituitary gland can lead to various hormonal imbalances and oxidative stress in the gland. This study also observed elevation in oxidative stress parameters by 4.15 mg/kg body weight of sodium tellurite in accordance with Kaur et al., 2003a and Kaur et al., 2003b. Whereas Selenium has prevented the Tellurium toxicity which is in agreement with the previous reports (Zafar et al., 2003; Yeo and Kang, 2007).

Rotarod was used to assess the motor performance of animals walk on the rotating drum whereas grip strength measure by string test in Selenium and Tellurium treated animals. Behavioral data indicated that tellurium caused severe behavioral deficits in rats which were significantly restored with the treatment of Selenium. The reduced neurological dysfunction hampers the motor performance in the pituitary gland of Tellurium treated Group-3 rats in comparison to control Group-1 rats. Our findings perfectly correlate with earlier studies (Rayman,2002; Ahmad et al., 2011) in which motor deficits using the animal model of Parkinson's disease and cerebral ischemia were attenuated by treatment with Selenium (Ansari et al., 2004). The novelty of the present study is that there is no previous work reported on neuroendocrine (pituitary gland) with the same drug.

ACh is an important cholinergic enzyme involved in the learning and memory process. AChE is a membrane-bound enzyme responsible for the breakdown of cholinergic neurotransmitter ACh into choline and acetate. During the course of the toxicity, AChE increases and the availability of ACh decreases which impairs neuron to neuron communication. In the present study, we found a significant elevation in AChE activity in the tellurium treated group. A hypothesis stating that this elevation is mediated by oxidative stress in the pituitary gland can be considered. Several antioxidants can be used to combat this elevation as is in this case by Selenium which is a strong antioxidant. Oxidative stress causes membranous damage leads to an elevation in AChE activity (Kaizer et al., 2005). Selenium treatment significantly ameliorates the AChE activity in the Se + Te group when compared with Te.

Antioxidants and pro-oxidant implicated in several disease progression. Free radicals produced can cause major instabilities in the

normal functioning of the cells by damaging the lipid membranes, proteins, and nucleic acids leading to cell death (Glozman et al., 1998). As reported by Khan et al., 2010, the brain is highly susceptible to oxidative damage due to high ingesting molecular oxygen and polyunsaturated fatty acids content. Rapid generation of free radical causes membrane damage which leads to the oxidation of lipid. Lipid peroxidation in terms of TBARS is a measure of oxidative stress and glutathione depletion accounts for the susceptibility of any xenobiotic in the brain (Black and Wolf, 1991). This study also indicated the deleterious effect of Te treated animals showed significantly increased content of the TBARS which was significantly and dose-dependently restored by Se co-treatment. The findings of this study are in accordance with the previous reports by Safhi et al., 2018.

Reduced glutathione is a well known endogenous antioxidant found in high concentration inside cells. The GSH is a tripeptide having –SH group. The Selenium as well as Tellurium reacts with –SH group and produces a highly toxic compound known as selenotrisulfide and telenotrisulfide respectively (Safhi et al., 2018). Formation of protein-glutathione mixed disulfide and decreased concentration of GSH have resulted in membrane dysfunction leading an increase in lipid peroxidation. The most toxic molecules present in the cell is H_2O_2. Glutathione peroxidase and Catalase does detoxify H_2O_2. The decrease in the content of glutathione will decrease its dependent enzymes too. It is reported many times that Selenium restores the level of GSH, GPx, GR and CAT (Jotty et al., 2013; Peng et al., 2007). A well-known selenoenzyme, GPx has a predominant role as anti-oxidant which has the capability to scavenge the harmful peroxides produced as a result of oxidative stress. It is one of the major protective systems in the brain against oxidative stress (Imam and Ali, 2000). The free radical formation is scavenged by catalase whereas superoxides are scavenged by SOD, originated from stressed mitochondria's electron transport chain. The product of SOD is H_2O_2 (Freeman and Crapo, 1982). H_2O_2 is then catalyzed by catalase to form water, but its activity is very low in the pituitary gland. Here, Selenium treatment augmented the activities of all these enzymes (GPx, GR, SOD, and CAT) in the pituitary gland that protected the brain from free radicles and superoxide-induced injury. We have observed that Selenium has protected the activities of antioxidant enzymes in Wistar rats. Our findings of GPx, GR, SOD, and CAT are in harmony with our previous studies reported earlier (Zafar et al., 2003; Safhi et al., 2018; Islam et al., 2002).

The treatment with Selenium has suppressed the increased activities of caspase-3 and -9 in the pituitary gland. Caspase-3 is activated by Caspases-8 and -9, which cleaves vital cellular proteins which in turn lead to cell death (Thornberry and Lazebnik, 1998). There are several reports suggesting oxidative stress has a direct relationship with Caspases. The activities of caspase-3 and -9 are accelerated by oxidative stress (Rayman, 2002; Vaibhav et al., 2013a; Vaibhav et al., 2013b) but this activation by Te toxicity was never reported. This will be the first report suggesting the increase in caspase-3 and -9 activities on the pituitary gland by Te toxicity. In this study, the Tellurium administration has significantly increased caspase-3 and 9 in Group 3 as compared to control. Further Se protects the caspase -3 and caspase-9 activation.

Toxicity of tellurium can be a cause of hypopituitarism and hyperpituitarism. On one hand, hypopituitarism is a rare disorder where the function of the pituitary is lost and it is unable to produce one or more hormones, or the hormones produce are in insufficient amount. Hyperpituitarism, on the other hand, is a condition due to more production of hormones by increased activity of the pituitary gland especially higher secretion of growth hormone which can result in acromegaly or gigantism. Further research in this area with a proper understanding of hormone profiles would be required to widen the understanding of the toxic effects of Te.

5. Conclusion

With the help of findings and discussion of the present study, we concluded that Sodium Tellurite noticeably increases the TBARS content, expression of caspases and AChE enzyme activities while GSH, GPx, SOD, GR, and CAT were decreases in the pituitary gland of male Wistar rats. However, Selenium treatment significantly protects these changes in the pituitary gland. Selenium was quite effective in the improvement of behavioral activities, suppresses apoptosis and oxidative stress (Enzymatic, and Non-Enzymatic). Hence, we have found that Selenium is very useful for the treatment of Tellurium toxicity in the neuroendocrine center (pituitary gland).

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