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Stress-induced bystander signaling as a possible factor contributing to neuronal excitability and seizure generation/epileptogenesis

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ABSTRACT

We hypothesize that cell stress-caused bystander signaling induced by certain exogenous and endogenous stressors, such as ionizing radiation exposure, chemicals, tumor, or senescent cells, might contribute to neuronal excitability and synchronization, specifically to initiation of hyperexcitability, excessive synchronization and seizure generation in epileptic brain/epileptogenesis. It is suggested that bystanderly induced interconnected variations in cytosolic Ca^{2+}, cytokines, and reactive oxygen/nitrogen species, and in activity of mitogen-activated protein kinases and nuclear factor κB pathways might affect neurotransmitter system, neuronal receptors and ion channels implicated in seizure generation/epileptogenesis, or modulate expression of genes associated with epileptogenesis. The mechanism suggested may, at least partly, explain the emerging evidence of association between exposures to low-dose ionizing radiation and epileptogenesis. The bystander mechanism for the generation of epilepsy might constitute new potential molecular target for the design of antiepileptic drugs.

Introduction

The causative factors for the development of epilepsy, one of the most common serious neurological disorders, are not completely understood. In this paper we consider the possibility that a response to cell stress mediated through the production of reactive oxygen species and pro-inflammatory cytokines might contribute to neuronal excitability and seizure generation/epileptogenesis. We restrict ourselves mainly to such stress factors as ionizing radiation, tumor, and chemicals.

There is evidence that low-dose ionizing radiation may have an impact on epileptogenesis. Complex investigations of participants in the Chernobyl atomic power station clean-up operation and subjects who arrived to the region of the Chernobyl accident later give evidence that exposure to low-dose ionizing radiation may induce paroxysmal electroencephalography patterns and epileptiform activity, such as spikes, polyspikes, spike-waves, acute waves, and high-amplitude slow waves, as well as may significantly increase the frequency of epileptic seizures [1–3]. The mechanisms of these effects are unknown. Lestaevel et al. [4] have shown that sub-chronic low-dose irradiation corresponding to the post-Chernobyl nuclear accident irradiation can result in molecular modifications of pro- and anti-inflammatory cytokines and NO-ergic pathway in the brain (in their study rats were exposed for 3 months to drinking water contaminated with Cs-137 at a dose of 400 Bq/kg which is similar to that ingested by the population living in contaminated areas after the Chernobyl nuclear accident). Epileptogenicity in rats irradiated in utero with 1 Gy (Cs-137 source) has been recently revealed [5]; the study [5] suggests that the extent of cortical lesions induced by irradiation is not always a precursor to epileptogenesis.

Seizures and epilepsy are a frequent neurologic complication associated with cancer [6–11]. Many patients with brain cancer experience seizures or epilepsy. Also, epileptic seizures are a frequent complication in patients with disseminated cancer. The main factors of brain tumor-related epileptogenesis include changes in gene expression, expression of ion channels and receptors, extracellular ion concentrations, extracellular amino acid levels, enzymes, and neurotransmission [9,6,12]. Other, until now unknown factors may be associated with tumor-related epileptogenesis [9].

Epileptic seizures may also be caused by exposure to chemotherapy or radiotherapy to the brain [10,8]. Cancer chemotherapy is a frequent cause of provoked seizures [7,10]. The factors inducing chemotherapy-related seizures include hypomagnesemia, reversible posterior leukoencephalopathy syndrome, hyponatremia, and increased concentration of neurotoxic

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metabolites [7]. Other types of medications may also induce seizures. These include antiemetics, antibiotics, and narcotics [7]. In general, various CNS and non-CNS targeted drugs have been shown to be able to induce seizures [13].

We have substantiated recently that bystander signaling induced by certain exogenous and endogenous stress factors, such as exposure to ionizing radiation, chemicals, or tumor, might contribute to neuronal functioning and pathogenesis of some neurological disorders and diseases [14]. Bystander effects are characterized by biological responses in non-stressed cells in some vicinity to a stressed cell or cells, so that non-targeted (non-stressed) cells are affected by signals from targeted (stressed) cell [15–21]. Bystander responses can be induced by both low as well as high doses of ionizing radiation and also by other stressors such as tumor or chemicals [22–36]. Bystander effects are cell specific and include stress responses, changes in gene expression, gene damage, and apoptosis [15–21,37]. Radiation-induced bystander effects are nearly independent of the fraction of cells targeted by radiation which would imply their relevance to very low doses (~0.1 mGy) and dose-rates (<10 mGy/year) such as those from natural radiation background [38,20]; however, bystander effect can play a significant role even after high doses (>10 Gy) [18]. There is increasing evidence for radiation-driven bystander effects in the brain in vivo, including long range bystander effects occurring outside radiation fields in organisms [20,39–42]. Radiation-induced bystander responses have been shown to occur in the non-irradiated mice brain after exposure of distant tissues with a 3 Gy dose of X-rays [40]. These bystander responses include alteration and loss of genetic material in the brain and tumorigenesis in mice cerebellum [40]. In the study [41], healthy and tumor-bearing rats were exposed to doses beginning from 17.5 Gy applied to the right cerebral hemisphere; strong long-range radiation-induced bystander effect has been found to occur in the non-irradiated contra-lateral brain hemisphere of normal and tumor-bearing rats. Irradiation-induced bystander effect can result in proteomic changes which are linked with reactive oxygen species (ROS)-mediated apoptosis and neurodegeneration [42]. Irradiated with helium ions normal primary human astrocytes and T98G glioma cells have been shown to generate bystander signals that induce γH2AX foci in non-targeted cells; similar effects have been observed for cells irradiated with 0.1 Gy or 2 Gy of X-rays [43].

Mechanisms of bystander effect are not completely clear. In targeted cells, generation of bystander signals can be associated with perturbations of mitochondrial respiratory chain, calcium fluxes, ROS, activity of nitric oxide synthase (NOS), nitric oxide (NO), and cytokines [38,37,19]. Bystander effects are mediated by gap junction intercellular communications or the release of soluble factors that can be transferred through medium to non-targeted cells [16,18,19,37]. For example, the mentioned above bystander response in the non-irradiated mice brain after exposure of distant tissues seems to be mediated by transmission of specific bystander factors through gap-junctional intercellular communication [40]. The soluble bystander factors have been shown to be present in blood samples from persons exposed to radiation from the Chernobyl atomic power station accident [44]. In non-targeted cells, mediators of bystander effect include strong calcium fluxes, variations of ROS, inducible NO synthase (NOS), cytokines, cyclooxygenase-2 (COX-2), mitogen-activated protein kinases (MAPK) and nuclear factor κB (NF-κB) pathways and can induce genetic/epigenetic alterations [19,37,45–49]. Long-range bystander effect can be associated also with immune cells activation; activated immune cells can secrete cytokines and produce NO [18].

As indicated above, in addition to ionizing radiation, other agents can induce bystander effect. These include chemicals, tumor, senescent cells, photodynamic therapy, UV-radiation, heat, mechanical stress, changes in pH [20,22–36]. Various sources of cell stress, including media from cancerous cells, have been revealed to result in a DNA damage response in normal human cells that is reminiscent of radiation-induced bystander effect [25]. Specifically, some chemotherapeutic drugs can induce bystander effect. Thus, chloroethylnitrosourea, chemotherapeutic DNA alkylating agent, may induce bystander effects through soluble factors for melanoma tumor model [24]. The progeny of cells exposed to chemotherapeutic bifunctional alkylating agent mitomycin C has been shown to induce a hyperrecombination phenotype in unexposed neighboring cells [22]. Chemotherapeutic radiomimetic drugs neocarzinostatin and bleomycin can induce bystander responses in different types of human cells [30]. Actinomycin D, a genotoxic chemotherapeutic drug, has been shown to induce bystander effect in Chinese hamster V79 cells through the medium soluble factors excreted from exposed cells [31]. Typically, these bystander responses are associated with DNA damage.

The mechanisms of bystander responses induced by ionizing radiation and other exogenous and endogenous stressors may be similar [23,26–29,32–36]. The bystander responses, induced by damaged normal cells (e.g., cells stressed by DNA lesions or senescent cells) or undamaged tumor cells, have been shown to be abrogated by NOS inhibitors, transforming growth factor-β (TGF-β) blocking antibody and antioxidants [26]. This suggests that bystander response results from exposure of bystander cells to cytokines, ROS or NO released from stressed cells, regardless of stress nature [26]. Similarly, cells undergoing different forms of senescence can induce DNA damage and senescence in normal bystander cells through cytokines (IL-1, IL-6, and TGF-β) and ROS-dependent mechanisms [33]. It has also been shown that tumors of different origin in mice may bystanderly induce oxidative DNA damage in normal tissues distant to tumor sites, with critical contribution of proinflammatory cytokines [27].

As discussed in [14], the magnitudes and time scales of bystanderly induced variations of cytosolic Ca^{2+}, cytokines, and ROS/reactive nitrogen species (RNS) might be sufficient to modulate calcium/calmodulin-dependent signaling molecules, MAPK- and NF-κB-associated signal transduction pathways, transcription factors such as cAMP response element-binding protein (CREB) and NF-κB, and gene expression in the brain. Herein, we hypothesize that bystander signaling, induced by such stressors as ionizing radiation exposure, chemicals or tumor, and corresponding alterations in activity of signal pathways and transcription factors might contribute to excess neuronal excitability and seizure generation/epileptogenesis.

Hypothesis

We hypothesize that cell stress-caused bystander signaling induced by certain exogenous and endogenous stressors, such as low-dose ionizing radiation exposure, chemicals or tumor/tumor microenvironment, might contribute to initiation of hyperexcitability, excess synchronization and seizure generation in epileptic brain/epileptogenesis. It is suggested that interconnected bystander variations in cytosolic Ca^{2+}, cytokines, and ROS/RNS, and in activity of MAPK and NF-κB pathways might affect neurotransmitter system, neuronal receptors and ion channels implicated in seizure generation/epileptogenesis, or modulate expression of genes associated with epileptogenesis.

Some evidence suggests that calcium bystander signaling may be realized in the brain region that receives radiation energy deposition [50]. Bystander cells are characterized by significantly increased intracellular Ca^{2+} levels. For instance, using the method of irradiated cell conditioned medium (ICCM), Lyng et al. [51] have shown that bystander signaling can increase significantly intracellular calcium concentration. In their experiment the medium from