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Pro-Convulsant Activity of Progesterone like Compounds in Kainic Acid Induced Convulsions Implications for the Possible Mechanisms

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ABSTRACT

Epilepsy is a very common type of neurological disorder that affects 0.5-1% of the population. The current anticonvulsive drugs therapies are able to satisfy only 70% of patients that too with some side-effects. There are several kinds of epilepsy which are categorized on the basis of affected part of the brain. Among them status epilepsy is a dangerous and much popular to take the life of affected individual. Though the development of anti-epileptics had been rooted since 1990's, still there is much remaining regarding the mechanisms of seizure generation to unravel. Neurosteroids are reported to have marked anti-convulsant activity. They are able to alleviate the seizure frequency in a variety of models. Interestingly, these neurosteroids such as estrogen, progesterone and testosterone are potentiating the seizures induced by kainicacid which resembles status epilepsy in humans. The key findings by several researchers reported that these neurosteroids acted like benzodiazepines in reducing the epileptic scores produced in models such as pentylenetetrazole, Maximal electric shock etc. Some experiments proved that benzodiazepines are also effective in kainicacid induced seizures. If we are able to recognize the other possible actions of these neurosteroids, we could be able to reach the next mile stone in the history of epilepsy especially status epilepsy. The present review article questions that, having a mode of action like benzodiazepines why these neurosteroids are showing proconvulsant activity and, discusses the possible mechanisms behind this.

Keywords: Neurosteroids, Kainicacid, Status epilepsy

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INTRODUCTION

Albeit there are new stratagies and development in the way of convulsive therapy, still some children and old age people are experiencing seizures that do not respond to conventional drug therapies [21]. At times, less conventional therapies like ketogenic diet, immunogloblins and steroids are found to be effective in children who are not suitable for surgery. Although some steroids are reported to be effective against infantile spasms their mechanism of actions are still unknown and need to be elucidated. Marescaux et al studied the role of corticosteroids in treating Landau-kleffner syndrome (LKS) and were experienced good outcome [11]. Lerman et al substantiated the view of Marescaux et al that prednisolone at a dose of 60mg/day [11], Adrenocorticotrophic hormone (80units/day) and Dexamethsone (4mg/day) reduced the seizure frequency in children of age group ranging from 5-9 years [14]. So experiments determining the role of these steroids especially neurosteroids have to be carried out and are essential towards anti-convulsant therapy.

Mechanism of action of neurosteroids

Neurosteroids act manly by enhancing Gamma amino butyric acid receptor type-A ($GABA_A$) and thereby increases the influx of chloride ions. More specifically, the binding of neurosteroid to the $GABA_A$ receptor does not prolong channel opening time but upon activation, increases the chance that the channel will enter long open state. Besides that they have other mechanisms as proposed by Ffrench-mullen and Spence 1991 that they can inhibit voltage gated calcium channels. Wu et al, Irwin et al and Bowlby proposed the other mechanism that they can also mediate N-methyl D-aspartate receptor mediated excitatory amino acid responses [2,10, 27].

Mroz et al studied the role of a neurosteroid Androsterone (AND), A major excreted metabolite of testosterone in various seizure models such as Pentylenetetrazole (PTZ), Maximal electric shock (MES) and Kainic acid (KA) inducing seizures in male adult swiss mice [17]. They found that and is effective in treating PTZ and MES induced convulsions which are reminiscent of human myoclonic seizures and human generalized tonic-clonic seizures respectively. Interestingly, AND potentiated KA induced convulsions which stands for status epilepsy or complex partial seizures in humans. That means AND showed pro-convulsant activity and they are not sure about the mechanism by which it happened.

Nicoletti et al, investigated the actions of an estrogen analogue, estradiol benzoate (EB) and a progesterone analogue, medroxyprogesterone acetate (MPA) on seizures induced by KA. They observed that subcutaneous administration of EB for 10 days at a dose of 10µg/Kg potentiated KA induced convulsions and the effect was more prominent in males. Even though MPA offered some protection against KA induced convulsions in females, it too exacerbated the condition in males by increasing a 30% increase in seizure severity score. Supporting the results obtained by Nicoletti et al, veliskov et al also experienced pro-convulsant activity by estradiol and progesterone in KA induced seizures [20, 27]. Interestingly testosterone also worsened the

convulsions induced by KA in a study carried out by Meijas-Aponte et al on adult Sprague-dawley rats [17]. They noted that male animals were more vulnerable to convulsions and badly affected compared to female rats. To confirm the previous issue they divided the batch of male animals into half and carried out gonadectomy for one half and left the other half untouched. As they proceeded to induce seizures by KA, they noticed that non-gonadectomized animals were more susceptible to and there was increased frequency of seizures compared to gonadectamized animals. Testosterone has a pro-convulsive effect in the KA model of temporal lobe epilepsy and as the testosterone is a male specific hormone it would be the reason why male animals were badly affected in the experiments conducted by Nicolette et al., that means testosterone itself showed pro-convulsing activity along with the estrogen and progesterone analogue [20].

Conventional anti-convulsing agents like benzodiazepines (BDZs) and barbiturates have had the same mode of action as neurosteroids that they selectively binds to $GABA_A$ receptors, enhances the chloride ion influx which hyperpolarises the cell, thereby reducing its excitability [1,3,13].

Heart of the current issue

Kleinork et al., carried out the efficacy testing of various anti-convulsant drugs against convulsions evoked upon intracerebrovascular (ICV) administration of KA. They found phenobarbitol, a conventional barbiturate inhibited seizures where as diazepam, a benzodiazepine found to be most effective among all other classes of drugs tested.

The current issue

Having the mode of action same as that of BDZs and barbiturates, why these neurosteroids are showing pro-convulsant action instead of anti-seizure activity in KA induced status epilepticus or temporal lobe epilepsy.

Gist of the present discussion

Mroz et al., observed proconvulsant action of androsterone, Mejias-Aponte et al., 2002 found the pro-convulsant activity of testosterone and recently veliskova et al., 2010 noticed the pro-convulsant activity of estradiol and progesterone in KA evoked convulsions. All these studies except mejias-aponte et al., were done recently and the authors were not sure to elucidate the mechanism that lying behind [17,18].

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POSSIBLE PREDICTIONS

Importance of the structure

The structural arrangement of neurosteroids has profound importance in exhibiting their efficacy and to their affinity. 3α, 5β-P (3α-hydroxy, 5β-pregnan-20-one) and Co 2-1068 (3β-(4 acetylphenyl) ethynyl-3α, 21-dihydroxy-5β -20-one-21-hemisuccinate) are more effective against NMDA induced convulsions compared to the 3β methylated analogue, Ganaxolone (3α hydroxy, 3β methyl-5α-pregnan-20-one) and 3α hydroxy, 5α-pregnan-20-one. Gasior et al., proposed that 3α, 5β-P and Co2-1068 shared a structural similarity which is absent in other two compounds. The similarity is they both are 5β reduced in which steroid ring-A projects out of the general plane of the pregnane ring system. From this perspective there is a possibility to assume a structural change would have brought to these neurosteroids by KA which might have reversed their action [7].

These neurosteroids would have other mechanisms of action instead of $GABA_A$ potentiation . French mullen et al., proposed a mechanism for neurosteroids that they have other non-genomic membrane effects like voltage gated calcium channel modulation [2]. Prince and simonds 1992 suggested that neurosteroids also have a modulatory effect on glycine activated chloride channels. Veliskova et al proposed that estrogens have promiscuity in binding to various receptors such as neurotrophin receptors [24, 25]. They also share membrane site with dopamine, epinephrine and nor-adrenaline [19]. β-estradiol can also act on neurotransmitter receptors like NMDA, AMPA and kainite [8, 26]. The hidden mechanisms like aforementioned, which are yet to be identified may possibly, mediate their pro-convulsant activity.

Neurosteroids have specific binding site on GABA receptor instead of binding to BDZ site [4]. They found that BDZ antagonist like flumazenil showed no inhibitory effect on neurosteroids when were given together. And also, the binding of (H^3) flunitrazepam was not displaced by neurosteroids but allosterically enhanced its action in study carried out by [9, 16, 23]

Kokate et al., 1996 carried out the efficacy testing of various progesterone and deoxycorticosterone analogues in kainate (KA) induced status epilepticus [12]. They noticed that 5α, 3α and 5β ,3α isomers were effective than respective 3β isomers in delaying the KA induced seizures. Albeit 3α-hydroxy isomers offered protection but was not comparable to 3α-H isomers. The current steroids under discussion Androsterone, testosterone, Estradiol, and progesterone are lacking 3α-H in their structure. So this would have been a cause for their pro-convulsant activity. Frye 2000 tested and compared the efficacy of progesterone and its active metabolite 3α, 5α-THP in alleviating seizures induced by KA in overeictomized animals[6]. They suggested that the anti-seizure effects of progesterone is due to its conversion to active metabolite 3α,5α-THP which has 3α-H in its structure and also has more affinity for $GABA_A$ receptors whereas progesterone does not have affinity for $GABA_A$ receptors [22, 11]. This

finding by Frye 1999 is supporting the perspective of kokate et al., 1994 that 3α-H is necessary for the action of neurosteroids [6, 19]

However, we could not rely upon assumptions and further investigations are needed to uncover the facts that underlying the pro-convulsant action of these neurosteroids.

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