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Med Hypotheses. 1992 May;38(1):20-4.

1. **Eliminating human immunodeficiency virus (HIV) from infected individuals and cells: is it possible?**

O'Brien DR.
Central Institute of Technology, School of Pharmacy, Trentham, New Zealand.

Abstract
The literature from 1984 to 1991 has been searched for reports of patients who have eliminated human immunodeficiency virus (HIV) from their system. While such reports are scarce, it appears that a small number of HIV-positive patients have reverted to a negative state either spontaneously or following radical immunosuppressive regimens for neoplastic disease. Although no carefully planned animal experiments or clinical trials have been reported, it would appear that bone marrow ablation and replacement may eliminate HIV from healthy, asymptomatic HIV-positive individuals. Although much of the clinical experience to date suggests that radical immunosuppression is not indicated in advanced AIDS patients in whom the virus has likely spread beyond the immune system, such cases do not represent evidence that immunosuppression is not indicated in healthy, HIV-positive individuals.

PMID: 1614355 [PubMed - indexed for MEDLINE]

MeSH Terms

Med Hypotheses. 1989 Apr;28(4):277-80.

2. **The effective agent in electroconvulsive therapy: convulsion or coma?**

O'Brien DR.
Central Institute of Technology, School of Pharmacy, Trentham, New Zealand.

Abstract
The ability of electrically-induced convulsions to alleviate at least some symptoms of mental illness was first reported in the literature 50 years ago; however, the cerebral mechanisms responsible for such therapeutic effects have thus far escaped elucidation. It is thus

interesting to note that those seeking explanations for the therapeutic effects of electroconvulsive therapy (ECT) have focused their attention on the convulsion produced by ECT, as opposed to the coma. The present hypothesis emphasizes the coma following the convulsion as a potential explanation of the effectiveness of ECT and other convulsive therapies. It is postulated that the primary effect of the convulsion is to cause the release of adenosine (ARN) from neuronal tissue and that the subsequent depressant effect of ARN on neuronal activity results in the clinical effect observed. Thus hypothesis suggests that chemically-induced coma, particularly coma induced by benzodiazepines, may offer a safe, effective and more acceptable alternative to ECT.

PMID: 2739595 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

Med Hypotheses. 1988 Dec;27(4):281-4.

3. **The adenosine hypothesis of epilepsy.**

O'Brien DR.
Central Institute of Technology, School of Pharmacy, Trentham, New Zealand.

Abstract
The present communication summarizes a variety of diverse observations indicating that adenine ribo-nucleoside (ARN), or adenosine, may play an important role as an endogenous anti-epileptic compound in the central nervous system. From such observations has evolved an hypothesis which states that defects in the synthesis, release, action and/or degradation of ARN may be a causative factor in some forms of epilepsy. Of particular interest is the emerging realization that the adenosine system may be a common factor in the mechanism of action of many otherwise unrelated anticonvulsant compounds. Thus, a more detailed understanding of the ARN system and its role in the control of cerebral activity may lead to rational strategies for the development of efficacious therapeutic agents having greater specificity and fewer side effects.

PMID: 3226359 [PubMed - indexed for MEDLINE]

MeSH Terms, Substances

Med Hypotheses. 1987 Jul;23(3):327-33.

4. **The inverse relationship between drug affinity and**

effectiveness: prediction under rate theory, paradox under occupancy theory.

O'Brien DR.

Abstract

The two major theories of drug action are occupancy theory and rate theory. Although the two theories make a number of predictions that should serve to clearly distinguish one from the other, data generated over the last 25 years in intact muscle or organ systems have failed in this respect because the interpretation of those data has been confounded by unknown and unmeasurable factors such as the rates and extent of drug diffusion, uptake and metabolism. In the present communication rate theory and occupancy theory are discussed in the light of data obtained from a broken-cell system in which uncontrollable factors are minimized, the beta adrenergic-responsive adenylate cyclase of the S49 mouse lymphoma cell line. It is pointed out that rate theory predicts an inverse relationship between the affinity of isoproterenol (INE) for the beta adrenergic receptor and the magnitude of stimulation of adenylate cyclase. On the other hand, occupancy theory predicts that the affinity of INE and the magnitude of its effect will be directly related. By fitting data obtained in this system to the simple equations derived from the two theories it is demonstrated that the available data are in excellent agreement with the predictions of rate theory and diametrically opposed to the predictions of occupancy theory.

PMID: 3039323 [PubMed - indexed for MEDLINE]

MeSH Terms, Substances

Mol Cell Biochem. 1987 Feb;73(2):129-39.

5. ## Accumulation of adenosine 3',5'-monophosphate in slices of rat cerebral cortex induced by alpha-adrenergic agonists. II. Studies on mechanisms underlying the interaction with adenosine.

O'Brien DR, Rall TW.

Abstract

Incubation of slices of rat cerebral cortex with the calcium ionophore A23187 produced small increases in the accumulation of adenosine 3',5'-monophosphate (cyclic AMP). While low concentrations of Ca2+ ions (e.g., 200 microM) were sometimes necessary, the presence of adenosine (e.g., 50 microM) was essential; no effect of ionophore was observed when isoproterenol or isobutylmethylxanthine was substituted for adenosine. These results are consistent with the previously advanced hypothesis that stimulation of alpha-adrenergic

receptors in this issue may cause calcium mobilization and thereby produce a calmodulin-mediated stimulation of adenylate cyclase. However, there is no apparent explanation for the requirement for adenosine. In addition, the possibility that additional mechanisms may be operating was suggested by experiments in which the incorporation of 3H-adenine into cyclic AMP was examined under steady-state conditions. While brief exposure to 3H-adenine after maximal adenosine- or isoproterenol-induced accumulations had been achieved led to small increases in the specific activity of cyclic AMP, the combination of norepinephrine and adenosine (plus propranolol) produced substantial decreases in the specific activity of cyclic AMP. Since the rate of incorporation of radioactivity did not keep pace with the expansion of the cyclic AMP pool, it is possible that norepinephrine also caused some reduction in the rate of cyclic AMP degradation under these conditions. Other interpretations of these results are discussed.

PMID: 2882412 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances, Grant Support

Mol Cell Biochem. 1987 Feb;73(2):117-28.

6. **Accumulation of adenosine 3',5'-monophosphate in slices of rat cerebral cortex induced by alpha-adrenergic agonists. I. Responses to methoxamine and norepinephrine in adult and neonatal tissue.**

O'Brien DR, Rall TW.

Abstract

The effects of adrenergic agonists and adenosine on the accumulation of adenosine 3',5'-monophosphate (cyclic AMP) were examined in cerebral cortical slices from adult and neonatal rats. Methoxamine (10 to 100 microM) produced up to a two-fold increase in tissue from adult animals only in the presence of optimal concentrations of adenosine (40 to 100 microM), but had no effect in neonatal tissue. Such responses were inhibited more readily by prazosin than by yohimbine, but the reverse was true for responses to norepinephrine; when tested without the addition of adenosine, however, responses to norepinephrine were somewhat more sensitive to prazosin. Under the latter conditions, norepinephrine induced about twice as much increase in cyclic AMP as did isoproterenol in adult tissue. While always prevented by alpha-adrenergic antagonists, the greater efficacy of norepinephrine was eliminated by methylxanthines only in some instances, but never in tissue from animals known to be less than 60 days of age. At 11 to 15 days of age, responses to norepinephrine were more than fourfold those to isoproterenol, even in the presence of methylxanthines, and were completely suppressed by propranolol. Responses to isoproterenol were enhanced when tested in the presence of adenosine, especially in neonatal tissue. The results suggest that both endogenous adenosine and age-related phenomena may account for some of the

discrepancies among earlier studies. Moreover, they indicate that several populations of alpha-adrenergic receptors may be involved in responses to adrenergic agonists in rat cerebral cortical tissue.

PMID: 2882411 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

Brain Res. 1986 Jun 18;376(1):140-8.

7. **Effects of D-aspartate on excitatory amino acid-induced release of [3H]GABA from goldfish retina.**

Cha JH, O'Brien DR, Dowling JE.

Abstract

The rate of release of [3H]GABA from isolated intact goldfish retinas was studied. Release of [3H]GABA is markedly stimulated by the inclusion in the incubation medium of the photoreceptor neurotransmitter candidates L-glutamate (L-Glu) and L-aspartate (L-Asp), and the glutamate analogs, kainate and quisqualate. At micromolar concentrations, kainate and quisqualate are effective releasers of [3H]GABA, whereas millimolar concentrations of L-Glu and L-Asp are required to release comparable amounts of [3H]GABA. The D-isomers of aspartate (D-Asp) and glutamate (D-Glu) are able to release [3H]GABA, but only when applied at high concentrations (3-30 mM). In the presence of 5 mM D-Asp, the effect of L-Glu in releasing [3H]GABA was markedly potentiated. This dose-response curve of L-Glu was shifted to the left in the presence of D-Asp, although the maximal amount of release was unchanged. D-Asp at 5 mM only slightly increased the GABA release induced by quisqualate, and it did not increase the GABA release induced by kainate. Finally, low concentrations of L-Asp were potentiated by D-Asp, but higher concentrations of L-Asp (3-10 mM) were clearly inhibited by this agent. This biphasic effect of D-Asp on L-Asp-induced release of [3H]GABA is a possible explanation for previously conflicting reports of D-Asp's effect on L-Asp action. Our data suggest that D-Asp has both pre- and postsynaptic sites of action.

PMID: 2872943 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances, Grant Support

Brain Res. 1985 Dec 23;360(1-2):41-50.

8. **Dopaminergic regulation of GABA release from the intact goldfish retina.**

O'Brien DR, Dowling JE.

Abstract

The rate of release of [3H]GABA from intact goldfish retinas was studied using a modified superfusion technique. Small, significant increases in the rate of GABA release were observed when the retinas were exposed to dopamine (DA) (100-1000 microM); however, when free Ca2+ was removed from the medium, the basal rate of GABA release was increased and DA became inhibitory. Forskolin, a non-specific stimulator of adenylate cyclase in intact cells, also inhibited GABA release in the absence of Ca2+. There was no significant effect of forskolin in the presence of Ca2+; however, (+)-butaclamol, a dopamine antagonist, increased basal GABA release under these conditions. L-glutamic acid (L-Glu) (1-10 mM) causes up to a 10-fold increase in GABA release. In the presence of Ca2+, DA did not significantly alter the effects of L-Glu; however, in the absence of Ca2+ a significant inhibition of the effects of L-Glu by DA was observed. Forskolin, on the other hand, inhibited the effects of L-Glu both in the presence and absence of Ca2+. Finally, EGTA (0.3-1 mM) produced a large release of GABA: this release was inhibited by DA, forskolin, theophylline, and 8-bromo cyclic AMP. These results suggest a model wherein DA stimulates Ca2+-dependent GABA release from one site and inhibits Ca2+-independent GABA release from another site via a cyclic AMP-mediated event.

PMID: 2866828 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances, Grant Support