

Gym Of The Living Dead

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People have become jaded to horror movies, as producers have abandoned the well-written script that builds suspense for the low-hanging fruit of gore and slash with a few gratuitous nude scenes. Going back to the original horror films brings about nearly as much humor as fright, as the primitive special effects, makeup and props seem childish compared to today's CGI mapping, blue screens and animation. Yet, there is something gripping about the classics...memories that stay with a viewer for years and raise goose bumps whenever theme music is played. To this day, the final minutes of the 1961 movie, "The Pit and the Pendulum," rank highly on my personal list of movie frights.

Another 1960's

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Another 1960's horror classic is "Night of the Living Dead." In this film, the dead are reanimated by some unexplained energy, wreaking havoc as they amble their way across fields and towns in search of food (the living). Though this movie had its share of memorable quotes, such as: "They're coming to get you, Barbara," its influence may be best understood by the many parodies and imitations it spawned, including "The Simpsons" 1992 Halloween special "Treehouse of Horror III" - Dial Z for Zombies. In this animated classic, Bart accidentally brings the dead to life, infesting the town with hungry corpses calling out, "BRAINS." Certain voices in governmental agencies, academic institutions and the media appear to be intent upon convincing the public that anabolic steroid use will lead to hordes of extremely buff zombies terrorizing retail stores for protein and Lycra.

Scientists involved in research soon realize that in order for a study to be published, it must be innovative, well-designed and agreeable to the editorial staff of a journal. Very little research has been published documenting benefits associated with anabolic steroids. Conversely, a plethora of reports and studies of varying quality and credibility have been published decrying adverse effects related to testosterone and other anabolic steroids.

Approximately one year ago, a study by Yale researchers received a considerable amount of media attention when it pronounced that elevated testosterone killed brain cells. Women, comedians and nonmesomorphs rejoiced, as science seemed to validate their stereotypes that masculine men only think with their little heads, since testosterone was proven to kill off brain cells. Yet, the flaws inherent in the conclusion, detailed in an article published in Muscular Development, went unnoticed. [Note: In the 2006 article in Muscular Development, I miscalculated the normal range for CSF testosterone as 1-3 nm; it is ~50 nm.] The discrepancies between the "brain killer" headlines and other contemporary testosterone-related news were also ignored, as it did not promote the party propaganda to acknowledge that testosterone may protect against Alzheimer's, aid in stroke recovery, improve cognition (thinking), protect against cardiovascular disease and not be associated with an increased risk of prostate cancer.

A more recent study on anabolic steroids and neurotoxicity (brain cell death) was published in the journal Brain Research, which was very well designed and quite eloquent. Though the authors focused on the effect of certain anabolic steroids on (mouse) brain cells when exposed to a drug known to kill brain cells (NMDA), the information contained in this study was quite enlightening.

The researchers, primarily affiliated with the University of Rome, endeavored to study whether testosterone or three other anabolic steroids could make brain cells more vulnerable to the toxic effects of NMDA—a chemical that kills nerve cells by overstimulating them when present in high concentrations. The exact process involved in NMDA toxicity is vital to understand in order to fully evaluate the study's findings. This will be discussed shortly.

To investigate their hypothesis, the authors of the study first created plates lined with mixed cortical cells (brain cells) and astrocytes (cells that support and protect the brain cells), then exposed the brain cells to one of four steroids for four days. The steroids included testosterone, stanozolol (Winstrol), 19-nortestosterone (nandrolone, Deca) and gestrinone (the base steroid for the designer drug THG that initiated the BALCO scandal). Six different concentrations of the anabolic steroids (AAS) were applied to separate groups of the brain cells. The investigators also included groups at the varying concentrations that combined either one of two aromatase inhibitors or an androgen receptor antagonist (blocker). Anastrozole (Arimidex) and aminoglutethimide (Cytadren) were the aromatase inhibitors and flutamide (a drug used to treat prostate cancer) was the androgen receptor antagonist.

Other sets of brain cell cultures were developed and incubated with either estradiol (estrogen) or progesterone (the other female sex hormone). After four days, all the brain cell cultures were exposed to NMDA for 10 minutes at a concentration that was known to kill about 50 percent of the cells. Once the NMDA was washed away, the cells were bathed in a dye that can only stain dead cells and the cultures were then examined to see how many cells survived the assault. Interestingly, one observation noted by the researchers that was not prominently discussed was the fact that none of the steroids, at concentrations up to 10 μm , were toxic to the brain cell cultures before the NMDA was applied. This is strikingly different from the findings of the 2006 study, which found that testosterone at concentrations of 1-10 μm induced

brain cell death. (A μm is a very, very small amount; 0.000001 mol/L. Normally, brain cells are only exposed to 20-80 nm or 1/20th that amount.) In other words, at concentrations approximately 20 to 200 times normal, none of the AAS were toxic to the brain cells. Now, some might take that sentence and decide that it is safe to use AAS at high levels, but that is premature, as the human body does not exist in a sterile lab dish.

While it is somewhat reassuring to see that several AAS do not cause brain cell injury, even at excessively high levels, on their own, the story changed when the brain cells were subjected to NMDA. Testosterone actually protected against brain cell damage when the concentration was in the normal range of men not taking steroids (10-100 nm). However, when the concentration was increased to the μm range (20-200 times normal), the cells became more vulnerable to the toxic effects of NMDA.

The problem was even worse for the other three AAS, as there was no protective effect at all and concentrations that presumably represent athlete use increased NMDA-induced cell death by roughly 20 percent to 80 percent. Working on the assumption that the increased damage is related to the androgen receptor, the investigators then looked at the AAS when combined with the aromatase inhibitors or the androgen receptor antagonist.

When combined with the aromatase inhibitors, testosterone no longer protected against cell damage at normal concentrations and a significantly greater amount of damage was done at the higher concentrations. Neither aromatase inhibitor affected the three AAS (nortestosterone, stanozolol, gestrinone), which is consistent with their being considered nonaromatizable AAS. The androgen receptor antagonist flutamide reduced the damage done at the higher concentrations in all four AAS. The female steroids, estradiol and progesterone, both protected against cell death, though the protective effect of estrogen was lost at higher concentrations. These findings all support the suggestion that the increased vulnerability to NMDA is due to actions involving the androgen receptor. Interestingly, gestrinone actually became less toxic at the highest concentrations. The authors commented that the progesterone-like qualities of gestrinone may become more prominent at those concentrations.

One last experiment was run to see if the effect required a long-term exposure to AAS or if the increased damage was realized immediately. To study this, the researchers exposed another round of brain cell cultures to NMDA, along with the various androgens, for 10 minutes and then looked for cell death. These cultures had not been previously exposed to any of the steroids. Testosterone did not significantly affect brain cell death; stanozolol did so only at the highest concentration; and gestrinone's effects lessened as the concentration increased. Nortestosterone increased cell death at medium to high doses. This aspect of the experiment was relevant, as it supports a hypothesis that the effect is related to AAS activity at the membrane receptors (nongenomic) and not solely dependent upon the classic nuclear receptor complex (genomic). In other words, AAS do have some immediate effect and do not require days to weeks to act on certain parts of a cell's metabolism. The more obvious effect of AAS, muscle growth, occurs over days to weeks and involves activation of specific genes in the muscle cell DNA. Similar effects occurring at the membrane receptors are seen with other hormones, including IGF-1 and insulin, which some users will stack with AAS. This increases the potential for problems in people who stack numerous anabolic agents and makes it difficult to predict the level of risk.

So what is learned? AAS do not appear to be dangerous, even at high doses, in a pristine environment. However, if a chemical challenge is present, certain AAS may make brain cells (in a mouse, at least) more prone to damage and even cell death. The greatest danger appears to come from AAS that do not aromatize or if an aromatase inhibitor is used when AAS concentrations are elevated.

Now, how relevant is this? Even though the study used brain cells from a mouse and those findings cannot always be translated into human physiology, the study was very relevant. First of all, the concentration range included the normal range seen in people not using AAS and extended beyond what is conceivably practiced by athletes and other AAS users. Secondly, the AAS chosen represented some of the most commonly used steroids, as well as one related to the designer drug, THG (the clear). Third, the inclusion of an aromatase inhibitor is important, as many AAS-users include Arimidex or Femara in their stacks to reduce the risk of gynecomastia or other estrogenic side effects. Fourth, the chemical toxin they chose (NMDA) causes cell death by overstimulating a class of glutamate receptor in brain cells. Glutamate receptors are also stimulated by the taste enhancer MSG (commonly used in Oriental cuisine and responsible for the headaches some get from Chinese food), as well as the amino acid L-aspartate. The artificial sweetener aspartame (NutraSweet, Equal) breaks down into three compounds: methanol, L-phenylalanine and L-aspartic acid. Some diet soda drinkers complain of chronic headaches; many of these may be related to caffeine, but L-aspartate could certainly contribute to this effect as well. Fifth, chronic, neurodegenerative disease develops slowly and is usually irreversible once it becomes detectable. Alzheimer's, Parkinson's and many other neurodegenerative disorders are becoming increasingly prevalent in our aging society.

NMDA was a wise choice for the investigators, as it causes cell death by flooding the brain cells with calcium. As an ion, calcium activates many enzymes in cells when its concentration rises. At low concentrations, many of these enzymes are related to cell function, and the calcium can be "flushed away" once it has accomplished its goal. However, high calcium concentrations cause the cell to respond by "committing suicide" because other enzymes are activated that are destructive. NMDA is capable of forcing calcium to reach these "suicidal" levels.

How then do AAS increase the cells' vulnerability to NMDA? It has been shown with nerve cells and muscle cells that androgens are able to stimulate receptors on the cell membrane allowing calcium to enter. At normal concentrations, this effect is beneficial and promotes cell growth and development. However, when concentrations escalate well above normal, the calcium influx continues and the cell is unable to clear out the buildup of the stimulating ion. In mature nerve cells, surrounded by their supporting cast of astrocytes, this buildup does not reach critical levels by itself. In the natural state, testosterone protects against the androgenic stimulation by providing its own antagonist, estradiol, via the aromatase enzyme present in astrocytes. Even nonaromatizing AAS do not cause cell death in a pure environment.

However, note that both AAS and NMDA cause cell damage/death by increasing calcium entry into the brain cell. It is inherently clear that the effect of the two agents combined would be additive, with both attacking the cell via different receptors. The influx and buildup of calcium would occur at a more rapid rate and result in greater damage/death, as the study found. These findings are a bit chilling, as they suggest that common food additives (MSG, aspartame) may cause brain damage that AAS users are especially sensitive to, particularly if they use a nonaromatizing AAS or Arimidex or other aromatase inhibitors. Nortestosterone (Deca), stanzolol (Winstrol) and gestrinone were all associated with greater damage in concentrations that would easily be reached in an anabolic cycle, particularly gestrinone. Testosterone was relatively safe in normal concentrations (assuming no aromatase inhibitor is used) and concentrations used in most recreational cycles (400mg-600mg testosterone enanthate/week). Testosterone enanthate cycles using more than 1,250mg/week may begin to enter the range, wherein the risk for NMDA-induced damage increases. A study published in the Archives of General Psychiatry in 2001 found that subjects administered methyltestosterone at a dose of 240mg/day for four days had CSF concentrations of the steroid approaching 1 μm , though there was a great deal of variability among subjects. In that study, methyltestosterone was found to be present in greater concentration in the CSF than in the blood, which may not be typical of all steroids. Granted, methyltestosterone is not used as an anabolic steroid by athletes or bodybuilders, but the chemistry of the drug is similar to other steroids, particularly oral steroids. Also, 240mg/day is an excessively high dose, as the closely related and more familiar AAS methandienone (Dianabol) is commonly used in the 20mg-25mg/day range.

MSG and aspartame are considered safe by the FDA and they are nowhere near as potent as NMDA at inducing brain cell damage. Further, the concentration of NMDA used in the study was quite high. However, for those wishing to use testosterone or other AAS, it appears to be prudent to avoid those two food additives during a cycle. MSG may be listed as monosodium glutamate, glutamate, umami or by trade names. It is very high in soy sauce and Parmesan cheese. Aspartame is commonly used in numerous food and beverages.

The BALCO scandal created a number of ethical dilemmas, but a graver concern for any users exposed to the gestrinone-like steroid THG is the possibility of brain injury, given the finding that gestrinone increased the vulnerability of brain cells to NMDA damage. Fortunately, in the absence of NMDA, gestrinone did not appear to cause direct harm. Further, the number of athletes to whom THG was made available appears to have been somewhat limited. A responsible move by the government would be to fund a study to examine athletes known to have used THG and determine if any cognitive impairment or structural lesions are present. Further studies looking at the brains of AAS users who undergo autopsy would also be beneficial to see if the possibility for brain cell damage is relevant to non-medical use in humans.

What is the take-home message? If a person is going to use AAS illicitly, be informed of all the possible consequences (medical, psychological, ethical, social and legal) and be prepared to accept whatever outcome may arise. These powerful hormones circulate throughout the body and affect many tissues other than skeletal muscle. As rewarding as being in peak condition is, it does not merit the cost of risking later loss of function or life. Hopefully, findings such as these will continue to be researched. There is a place for testosterone replacement therapy, there is a place for cosmetic/performance enhancement using AAS, but there is not a place for extreme abuse of AAS that places users in jeopardy and sullies the reputation of responsible users.

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