



# Topics in the Neurobiology of Aggression: Implications to Deterrence

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## Chapter 6: Oxytocin and the reduction of aggression

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Aggression by humans has a variety of neurologic causes, including brain lesions especially in the orbitalfrontal cortex and amygdala; genetic variants, for example in monoamine oxydase A (MAOA) combined with an adverse developmental history; and variations in neurotransmitters and neuroactive hormones such as serotonin, testosterone and arginine vasopressin (Meht, Goetz & Carrè, 2012). More generally, episodes of aggression, especially repeated aggression by the same individual, are due to combinations of, and interactions between, genes, brains, history, and environments. Indeed, aggression on the field of play, or among soldiers toward enemy combatants, is promoted and acceptable, while abuse of spouses or random killing is inappropriate. This shows the situation-specific role of aggression that determines if it is warranted and acceptable or not.

While many social scientists view aggression (physical or with resources) as the norm, neuroscientific studies of human behavior--many from my lab--suggest the opposite: aggression is a useful but costly strategy and most people have a strong bias to cooperate in many situations. While aggression, and its cousin fear, are fairly easy to induce in laboratory settings, paradigms to study the neurobiology of cooperation began to emerge in the early 2000s. Many studies have used a neuroeconomic approach in which money could be sent to a stranger in the lab in a variety of settings to measure virtuous behaviors such as trust, trustworthiness, and generosity, as well as their absence, distrust, a lack of reciprocation, and greed. Understanding the positive side to human nature is valuable, these studies have shown, because it provides a richer neural and behavioral depiction of why neurologically healthy humans can alter their behavior from cooperation to conflict. Conflicts could be as minor as yelling at a colleague at work, but may also encompass violent mass actions such as terrorist attacks. My own work on the neurobiology of moral behaviors has focused on the role of the neuroactive hormone oxytocin (OT). As I'll discuss below, OT appears to function as a chemical regulator that mediates prosocial behaviors by signaling that another person is safe or familiar, even if the other person is a stranger. While OT interacts with a host of other neurochemicals to affect behavior, its value in explaining human cooperation has recently been appreciated as evidenced by the number of recent books on the subject (Zak, 2012; Young & Alexander, 2012; Kuchinskas, 2009; Taylor, 2002).

OT, perhaps due to its ancient mammalian lineage, has several peculiar properties.

It is one of the few hormones that is directly synthesized in the brain (like a neurotransmitter). It functions both as a hormone (has effects on the peripheral nervous system) and a neurotransmitter (is released into synapses in the brain). It is synthesized within a second or less of a stimulus, and has an approximately three-minute half-life, functioning much like an on-off switch signal safety. Lastly, and conveniently for experimentation, under physiologic stress animal studies have shown that the synthesis of OT by hypothalamic neurons coordinate central (brain) and peripheral (body) OT release. This means that an acute change in OT in the body is correlated with such an acute change in central OT. Yet, until a decade ago, OT was only studied in humans for its role as a hormone in reproduction (sex, birth, and breastfeeding).

There are several reasons OT was not studied in humans outside of reproduction. First, there is no medical disorder other than preterm labor known to be associated with too much or too little OT to prompt its study. Based on recent findings, though, there are now clinical trials for OT examining its role in the impaired social behaviors found in autism, social anxiety disorder, and schizophrenia. Second, OT is a "shy" molecule in that it has a short half-life and degrades rapidly at room temperature. When I began these studies in 2001, I had to develop tight handling protocols to capture the OT signal when it appeared and to minimize signal degradation. Third, although findings for the role of OT in promoting social behaviors in animals began to accumulate in the 1990s, most scientists had not found a behavioral task that would allow a test of the presumed prosocial effects of OT in humans.

Because humans appear to have more OT receptors in the forebrain than other mammals (Loup et al., 1991), and forebrain OT receptors modulate mid-brain dopamine circuits that reinforce and reward behavior (Zak, 2012; Donaldson & Young, 2008), one can make the case that cooperative behaviors are just as "natural" as aggressive ones. That is, the brain reinforces prosocial behaviors, revealing its value to the organism. Further, because recent studies have shown that OT is released even when strangers signal that they are safe and want to cooperate, a case could be made that cooperation with strangers is a typical human behavior, and that conflict among strangers may not be the norm.

## Trust

The first nonreproductive stimulus in humans shown to induce OT release was a monetary transfer task known as the "trust game." In this task, strangers are seated in partitioned computer stations and all participants receive a \$10 endowment for volunteering to be in an experiment. Identities are masked by using alphanumeric codes, and there is no deception of any type. Participants log in to computers and are randomly matched with another participant in the lab. The software randomly assigns participants to the role of decision-maker 1 (DM1) or decision-maker 2 (DM2). All DMs receive by computer the following instructions: DM1 will be prompted to transfer from

\$0-10 from his or her account to the DM2's account. Whatever is transferred is removed from DM1's account but is tripled in DM2's account. DM2 will receive a message through the software identifying the amount sent and the total in his/her account. DM2 is then prompted to send some amount of money, from zero to the total in her/his account to the DM1 who initially sent money.

This task had been designed by experimental economists (Hoffman, Dickhaut & McCabe, 1995; Smith, 1998) and had been run for both small and large stakes around the world. The consensus view in economics was the transfer from DM1 to DM2 was a measure of trust. Note it is not altruism or fairness that motivates a transfer since both DMs have the same amount of money initially. Yet, once DM1 transfers money to DM2 (about 90% of DM1s do this), DM2 now has entered into an implicit contract with DM1 that states "I trusted you because I believe you will reciprocate." Indeed, 95% of DM2s who receive money in this laboratory paradigm show they are trustworthy by reciprocating (Zak et al., 2004, 2005; Zak 2005). On average in these experiments, DM1s earn approximately \$14 and DM2s earn \$17, so their model of human beings as reciprocating creatures is, on average, correct. But why?

By taking blood after participants made decisions, my collaborators and I found that the more money someone received denoting trust, the larger the spike in OT. Further, OT in DM2s predicted how much money would reciprocate (Zak et al., 2004; 2005). The trust game captures in an objective way the notion of the Golden Rule: if you are nice to me, I'll be nice to you. Among the hundreds of people I have tested over the last decade in a number of variants of this task in a variety of cultures, roughly 95% of individuals reciprocate trust (Zak, 2012). The Golden Rule exists in every culture on the planet and reveals our essential social nature. It appears that OT is largely responsible for reciprocation by sending a safety signal motivating nice with nice (additional details in Zak, 2011).

One way to think about OT is that this molecule that evolved to facilitate live birth and motivate care for offspring in mammals is hyperactive in humans so that we often treat strangers like family. Since this is true for safe and stable environments for most people, the OT system allows us to quickly size up strangers and when appropriate derive value from relationships by cooperating with them. This also builds one's reputation as a cooperator which is valuable for future interactions. Because synthetic OT is available and safe to give to humans, we tested whether if we manipulated the OT brain circuit pharmacologically we could induce greater trust in the monetary transfer task. Not only was trust increased for those infused with OT (via the nose), but we more than doubled the number of people who showed maximal trust by transferring all their money to a stranger in these experiments (Kosfeld et al., 2005).

These two sets of studies taken together showed that i) being trusted causes the brain to release OT and motivates reciprocation, and ii) exogenously increasing OT in people causes trust to increase. We showed the causal circle was complete. Nine other neuroactive hormones tested for their effect on trusting behaviors or OT release did not mediate these effects (Zak et al., 2005).

You will note that the trust game provides a win-win opportunity for participants, both can be made better off. In experiments with a win-lose task (more for you means less for me), OT increased generosity but only when the decision-maker had to take the perspective of the other person (Zak, Stanton & Ahmadi, 2007). OT also substantially increased donations to charity when the cause is made highly (Barraza & Zak, 2009) or minimally (Barraza, McCullough, Ahmadi & Zak, 2011) salient.

## Pathology

Among the large number of studies my lab has run on OT, we consistently find that five percent of participants do not release OT when others do for a variety of stimuli. Investigating these individuals, we found they had some of the traits of psychopaths: sexual promiscuity, job instability, deception, and even self-deception (Zak, 2005). Because they do not release OT for positive social stimuli, I have coined the term Oxytocin Deficit Disorder (ODD) to describe them. Interestingly, their baseline OT is often very high. This indicates that their OT system is not processing social information in a safe/nonsafe way that others do. It also suggests a possible dysfunction with their OT receptors that regulate OT synthesis through a feedback loop. A recent study showed that those with diagnosed social anxiety disorder also appear to have ODD (Hoge, Pollack, Kaufman, Zak, & Simon, 2008). We have recently begun studying a large set of diagnosed psychopaths to explore the functioning of their OT systems in more detail.

Most psychopaths are identifiable as children or young adolescents (Kiehl, 2006), suggesting a strong genetic component. But we have also studied an acquired pathology due to repeated and severe sexual abuse suffered during childhood in a female clinical population. In a small sample of these patients that we intensively studied, we found roughly half of them do not release OT when shown trust. They also have impaired social behaviors, and particular difficulty modulating their behavior to the people or situation they are around. The majority of these patients were diagnosed with borderline personality disorder, were clinically depressed, and had psychosomatic medical symptoms (Zak, 2012). A sample of psychiatrically healthy women who had only suffered a few episodes of sexual abuse as children had intact OT systems and healthy social behaviors, for example, the ability to sustain fulfilling romantic relationships and family relationships. In the clinical sample, the severity and degree of abuse did not predict if they had acquired ODD. Resilience to abuse was predicted weakly by the presence of several genes, including genes that affect synaptic serotonin levels, though the sample was too small to have confidence in this finding.

## Environment.

Multiple neurotransmitters activate multiple brain circuits to guide appropriate social behaviors as situations change from safe to unsafe. To simplify the discussion, I will focus on three, OT, testosterone, and epinephrine. Epinephrine (also called

adrenaline) is the body's fast-acting stress signal. If something important, threatening, or difficult is occurring, epinephrine release will increase heart rate and respiration and prepare the organism to engage. Epinephrine is also an effective OT inhibitor (Jezová, Juránková, Mosnářová, Kriska, & Skultétyova, 1996).

Testosterone is also an OT inhibitor (Arsenijevic & Tribollet, 1998). If instead of "you are playing nice, so I'll play nice", the social environment shows that "you are playing bad", then testosterone increases to result in "I'll play bad back." This effect tends to be stronger in men who have five to ten times more testosterone than do women. We first found that men reciprocate bad with bad by turning the trust game on its head and asking what happens physiologically when people are distrusted, i.e. when they receive a small or no monetary transfer as DM2 in the trust game. We could not find a neural signal of distrust in women. But, in men the greater the signal of distrust, the higher the level of the "high octane" version of testosterone known as dihydrotestosterone (DHT). DHT levels spiked with distrust, and men with high DHT reciprocated little or no money to the DM1 who distrusted them. Women, on the other hand, were proportional reciprocators whether as DM2s they received small transfers or large ones (Zak, Borja, Matzner, Kurzban, 2005). Women did not have the "hot" physiologic response associated with distrust that men did. Note that in these experiments all DMs are anonymous so the gender of the DM1 is unknown.

To confirm this finding, we administered synthetic testosterone or placebo to 25 men and had them come to the lab twice in a blinded within-subjects design (once to receive testosterone, once to receive placebo). Using a zero-sum variant of the trust game that includes a costly punishment option, we found that men on testosterone, compared to themselves on placebo, were less generous in sharing resources with strangers, but more demanding of generosity from others (Zak et al., 2009). Indeed, these "alpha males" were more likely than their unenhanced selves to burn their own resources in order to punish others who had not cooperated. This could be the basis for establishing reputation or dominance in social relationships. Other studies have found that even the threat of punishment substantially increases cooperation (Boyd & Richerson, 1992). Men appear to bear the burden of punishment more than do women.

Environments that are unsafe, new, competitive, aggressive, or unpredictable can induce greater epinephrine and/or testosterone release and thereby inhibit prosocial behaviors, especially such behaviors towards strangers. Conversely, in environments that are familiar and safe, people have the luxury of releasing OT more often, possibly improving their family relationships, friendships, and opportunities to engage with strangers. I have collected evidence in my book *The Moral Molecule: The Source of Love and Prosperity*, that such environments can sustain a virtuous cycle of OT release, empathy, trustworthiness, and happiness. Countries that are trustworthy have increased private investment in new businesses, creating jobs and reducing poverty (Zak, 2008; Zak & Knack, 2001). This permits a greater number of people to enjoy social connections and the OT release it potentiates, may stimulate greater virtue, mostly peaceful social relationships, benign international relations, and



prosperity (Zak & Kugler, 2010). Quite a neat trick for an ancient molecule that was until recently largely ignored.

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